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## THE INDUCTION OF PAIN: AN INTEGRATIVE REVIEW

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**Abstract**—The highly disagreeable sensation of pain results from an extraordinarily complex and interactive series of mechanisms integrated at all levels of the neuroaxis, from the periphery, via the dorsal horn to higher cerebral structures. Pain is usually elicited by the activation of specific nociceptors ('nociceptive pain'). However, it may also result from injury to sensory fibres, or from damage to the CNS itself ('neuropathic pain'). Although acute and subchronic, nociceptive pain fulfils a warning role, chronic and/or severe nociceptive and neuropathic pain is maladaptive. Recent years have seen a progressive unravelling of the neuroanatomical circuits and cellular mechanisms underlying the induction of pain. In addition to familiar inflammatory mediators, such as prostaglandins and bradykinin, potentially-important, pronociceptive roles have been proposed for a variety of 'exotic' species, including protons, ATP, cytokines, neurotrophins (growth factors) and nitric oxide. Further, both in the periphery and in the CNS, *non*-neuronal glial and immunocompetent cells have been shown to play a modulatory role in the response to inflammation and injury, and in processes modifying nociception. In the dorsal horn of the spinal cord, wherein the primary processing of nociceptive information occurs, *N*-methyl-D-aspartate receptors are activated by glutamate released from nociceptive afferent fibres. Their activation plays a key role in the induction of neuronal sensitization, a process underlying prolonged painful states. In addition, upon peripheral nerve injury, a reduction of inhibitory interneurone tone in the dorsal horn exacerbates sensitized states and further enhance nociception. As concerns the transfer of nociceptive information to the brain, several pathways *other* than the classical spinothalamic tract are of importance: for example, the postsynaptic dorsal column pathway. In discussing the roles of supraspinal structures in pain sensation, differences between its 'discriminative-sensory' and 'affective-cognitive' dimensions should be emphasized. The purpose of the present article is to provide a global account of mechanisms involved in the induction of pain. Particular attention is focused on cellular aspects and on the consequences of peripheral nerve injury. In the first part of the review, neuronal pathways for the transmission of nociceptive information from peripheral nerve terminals to the dorsal horn, and therefrom to higher centres, are outlined. This neuronal framework is then exploited for a consideration of peripheral, spinal and supraspinal mechanisms involved in the induction of pain by stimulation of peripheral nociceptors, by peripheral nerve injury and by damage to the CNS itself. Finally, a hypothesis is forwarded that neurotrophins may play an important role in central, adaptive mechanisms modulating nociception. An improved understanding of the origins of pain should facilitate the development of novel strategies for its more effective treatment. © 1998 Elsevier Science Ltd. All rights reserved

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**ABBREVIATIONS**

A	Adenosine receptor	ININ	Inhibitory interneurone
[Ca <sup>2+</sup> ] <sub>i</sub>	Intracellular concentration of Ca <sup>2+</sup>	LIF	Leukaemia inhibitory factor
5-HT	Serotonin	LTD	Long-term depression
AC	Adenyl cyclase	LTP	Long-term potentiation
cAMP	Cyclic adenosine monophosphate	MDVC	Mediodorsal ventrocaudal thalamus
AMPA	DL- $\alpha$ -NH <sub>2</sub> -2,3-dihydro-5-methyl-3-oxo-4-isoxazolepropanoic acid	MGLU	Metabotropic
AP	Action potential	NAD	Noradrenaline
AR	Adrenoceptor	NGF	Nerve growth factor
ATP	Adenosine triphosphate	NI	Neurogenic inflammation
B	Bradykinin receptor	NK	Neurokinin
BDNF	Brain derived neurotrophic factor	NMDA	<i>N</i> -methyl- <i>D</i> -aspartate
BK	Bradykinin	NO	Nitric oxide
CAM	Cell adhesion molecule	NON-N	Non-nociceptive
CBV	Cerebral blood vessel	NPY	Neuropeptide Y
CCK	Cholecystokinin	NS	Nociceptive-specific
CGMP	Cyclic guanosine monophosphate	P	Purinoceptor
CGRP	Calcitonin-gene related peptide	PACAP	Pituitary adenyl cyclase activating protein
CNS	Central nervous system	PAD	Primary afferent depolarization
CREB	Ca <sup>2+</sup> /cAMP response element binding protein	PAF	Peripheral afferent fibre
COX	Cyclooxygenase	PAG	Periaqueductal grey
CRF	Corticotropin releasing factor	PBN	Parabrachial nucleus
CSF	Cerebrospinal fluid	PG	Prostaglandin
DA	Dopamine	PK	Protein kinase
DCN	Dorsal column nuclei	PLA	Phospholipase A
DAG	Diaminoglycine	PLC	Phospholipase C
DH	Dorsal horn	PN	Projection neurone
DLF	Dorsolateral funiculus	PSDC	Postsynaptic dorsal column
DRG	Dorsal root ganglia	RF	Receptor field
DRP	Dorsal root reflex	S I/II	Somatosensory area I/II
DRP	Dorsal root potential	SP	Substance P
DYN	Dynorphin	STT	Spinothalamic tract
EAA	Excitatory amino acid	TNF	Tissue necrosis factor
EPSP	Excitatory postsynaptic potential	TRK	Tyrosine kinase
EP	PGE <sub>2</sub> receptor	TTX	Tetrodotoxin
EXIN	Excitatory interneurone	VDCC	Voltage-dependent calcium channel
GABA	Gamma-amino-butyric acid	VH	Ventral horn
GAL	Galanin	VIP	Vasoactive intestinal peptide
GAP	Growth associated protein	VLF	Ventrolateral funiculus
GDNF	Glial cell-line derived neurotrophic factor	VMPO	Ventromedial posterior
GLU	Glutamate	VPI	Ventroposterior inferior
IEG	Immediate early gene	VPL	Ventroposterior medial
IL	Interleukin	VPM	Ventroposterior lateral
IN	Interneurone	WDR	Wide-dynamic range
		Y	Neuropeptide Y receptor

## 1. INTRODUCTION: AIMS AND SCOPE OF REVIEW

The exposure of the skin and other organs to damaging, or potentially-damaging, 'noxious' stimuli elicits the intensely unpleasant sensation of pain, an experience which is ultimately integrated in cortico-limbic centres of the brain. Intervening between this initial exposure to a noxious stimulus and the conscious appreciation of pain is an extraordinarily complex and interactive series of mechanisms whereby the noxious stimulus is encoded as a nociceptive message and is progressively transmitted to, and processed in, higher nervous centres. Such modulatory events occur in the periphery, in the dorsal horn (DH) of the spinal cord ('primary processing'), supraspinal relay centres such as the thalamus ('secondary processing'), as well as in corticolimbic structures themselves. Further, under certain pathological conditions, such as peripheral nerve injury or damage to the central nervous system (CNS), pain can be engendered downstream, and independently, of sensory nerve endings.

The purpose of the present article is to provide an integrative account of:

1. neuronal pathways involved in the receipt and transmission of nociceptive information from the periphery to higher CNS centres; and
2. the cellular and molecular bases of mechanisms underlying the induction of pain.

Special emphasis is afforded to processes underlying the prolonged pain provoked by peripheral nerve injury, the unravelling of which has progressed considerably in recent years.

Endogenous mechanisms for the attenuation of nociception, which are engaged at all levels of transfer and processing, have been extensively reviewed elsewhere and do not comprise the focus of the present article (Basbaum and Fields, 1984; Besson and Chaouch, 1987; Fields and Basbaum, 1994; Hammond, 1997; Hayashi and Maze, 1993; Le Bars,

1988; Millan, 1986, 1997; Ossipov *et al.*, 1997; Picard *et al.*, 1997; Stamford, 1995).

Since the present review is directed not only towards those active in pain research, but also—and primarily—towards those less familiar with this field, no expert knowledge is assumed and several explanatory diagrams have been incorporated. In addition, Table 1 outlines several technical terms frequently encountered in the experimental and clinical literature. The reference list (completed early in 1998), though comprehensive, has no pretensions to exhaustivity. It is compiled from a selection of key papers, reviews and, in particular, recent articles as yet to be covered by reviews. The latter assume particular importance in view of the astonishing rapidity with which this field is developing. Details on many of the specific subjects discussed herein may be found in several books and authoritative review articles, of which the following are particularly useful sources of information (Belemonte and Cervero, 1996; Besson and Chaouch, 1987; Besson *et al.*, 1994; Carli and Zimmerman, 1996; Carstens, 1995; Cervero, 1994, 1995b;Coderre *et al.*, 1993; Coggeshall and Carlton, 1997; Coyle, 1996; Dickenson and Besson, 1997; Dray and Urban, 1996; Dubner and Bennett, 1983; Gebhart, 1995; Handwerker and Kobal, 1993; Hökfelt *et al.*, 1994; Koltzenburg, 1995; Melzack and Wall, 1965; Mense, 1993; Pairet and Engelhardt, 1996; Rang *et al.*, 1991; Ruda *et al.*, 1986; Schaible and Grubb, 1993; Tracey and Walker, 1995; Treede *et al.*, 1992b; Wall and Melzack, 1994; Willis, 1985; Willis and Coggeshall, 1991; Wilson and Kitchener, 1996; Woolf, 1994; Woolf and Doubell, 1994).

The article is organized as follows. Section 2 considers the origins and pathophysiological significance of pain from an evolutionary perspective. Sections 3–6 outline pathways for the peripheral receipt, central transfer and supraspinal passage of nociceptive information: the modulatory role of pathways descending from the brain to the DH is also outlined. These sections provide a neuronal

Table 1. Explanation of technical terms [see also Merskey (1986); Merskey and Bogduk (1994); Millan (1993)]

1.	<i>Pain</i> : an unpleasant sensory and emotional experience associated with actual or potential tissue damage
2.	<i>Nociceptive pain</i> : pain due to (excessive) stimulation of nociceptors localized in the skin, viscera and other organs
3.	<i>Neurogenic pain</i> : pain reflecting damage to neuronal tissue in the periphery or CNS ('central' pain). Neuralgia refers to the pain localized to a region innervated by a specific nerve, or group of nerves
4.	<i>Neuropathic pain</i> : pain due to a dysfunction of, or damage to, a nerve or group of nerves. Primarily peripheral nerves, although pain due to CNS damage ('central' pain) may share these characteristics
5.	<i>Psychogenic pain</i> : pain not due to an identifiable, somatic origin and which <i>may</i> reflect psychological factors
6.	<i>Noxious stimulus</i> : a damaging, or potentially damaging, stimulus
7.	<i>Nociceptor</i> : a peripherally-localized receptor sensitive and responding to noxious stimuli
8.	<i>Analgesia (antinociception)</i> : a reduction in 'spontaneous' pain, or the pain elicited by a noxious stimulus. Operationally-defined in terms of a reduced response to, or an increase in the threshold to respond to, a noxious stimulus
9.	<i>Hyperalgesia</i> : an increase in the pain elicited by a noxious stimulus. Operationally-defined in terms of an increased response to, or a decrease in the threshold to respond to, a noxious stimulus. 'Spontaneous' pain occurs in the apparent absence of extraneous stimulation
10.	<i>Primarily and secondary hyperalgesia</i> : pain in the region of tissue damage (primary), or in the region surrounding this area (secondary). Mediated by different mechanisms
11.	<i>Allodynia</i> : pain evoked by a normally innocuous stimulus. Operationally-defined in terms of a response to an innocuous stimulus which is normally only evoked by a noxious stimulus. (Some authorities consider allodynia an 'extension' of hyperalgesia at the left of the stimulus-response function.)
12.	<i>Paresthesia</i> : an abnormal sensation—if unpleasant, referred to as dysaesthesia—which is either spontaneous or evoked

framework for an understanding of peripheral and central mechanisms underlying 'nociceptive' and 'neuropathic' pain (Table 1). Thus, Sections 7 and 8 deal with peripheral processes triggered by inflammatory tissue damage/nociceptor stimulation and sensory nerve injury, respectively. Section 9 discusses the roles of various classes of sensory nerve in mediating and maintaining painful states, and considers evidence that central mechanisms are involved in their induction. Section 10 discusses spinal mechanisms of sensitization elicited both by tissue inflammation and by peripheral nerve injury. Section 11 outlines processes involved in the regeneration of injured peripheral nerves and in the reorganization of their input to the DH, together with the consequences for nociception. Section 12 summarizes adaptive processes occurring in supraspinal structures. Section 13 is specifically concerned with the 'central' pain provoked by damage to the CNS itself, including several processes resembling these initiated by peripheral nerve injury. In Section 14, a hypothesis is developed according to which nerve growth factors (neurotrophins) may play a role in modulating central, synaptic events underlying prolonged, painful states. Finally, Section 15 concludes with a summary of several major themes and a brief consideration of how an improved understanding of mechanisms underlying the induction of pain may contribute to the development of novel analgesic agents.

The present account concentrates on our knowledge of *cutaneous* sensory input inasmuch as the skin has been the most intensely-studied of organs as concerns pain elicited both by nociceptor stimulation and by peripheral nerve damage. In general, the mechanisms discussed are pertinent to other tissue types, though several major differences to other organs, in particular the viscera, are mentioned. Specific aspects concerning mechanisms of nociception in non-cutaneous tissue have been reviewed in detail elsewhere (Cervero, 1994, 1995b; Gebhart, 1995; Guilbaud, 1988; Meyer *et al.*, 1994; McMahon *et al.*, 1994; Mense, 1993; Meller and Gebhart, 1992; Ness and Gebhart, 1990; Schaible and Grubb, 1993; Willis and Coggeshall, 1991).

Throughout the text, it has been attempted to keep duplication of material to a minimum. To this end, in view of the interdependent nature of many issues discussed, extensive reference is made to other Sections. Nevertheless, in order to avoid the need for incessant consultation of other parts of the review, individual sections are intended to be self-sufficient in information.

## 2. ACUTE AND CHRONIC PAIN: ORIGINS AND PATHOPHYSIOLOGICAL SIGNIFICANCE FROM AN EVOLUTIONARY PERSPECTIVE

### 2.1. The Adaptive Significance of Acute Vs Chronic Pain

The persistent pain which accompanies—and can outlast—inflammatory tissue damage and/or nerve injury is generally characterized by its spontaneous

nature (not elicited by extrinsic stimuli) and by the presence of hyperalgesia (an increase in the pain elicited by a noxious stimulus) and/or allodynia (pain elicited by normally innocuous stimuli) (Table 1). Prolonged, chronic pain is regarded as fulfilling no physiological purpose (Table 2). This lack of adaptive value may be contrasted to the protective function of the motor withdrawal (integrated via a reflex arc in the ventral horn) elicited by phasic, acute exposure to noxious stimuli, and the recuperative, protective behaviour associated with subchronic, painful states (Table 2). Thus, it is reasonable to speak of 'pathological' vs 'physiological' for chronic vs acute/subchronic pain, respectively. The alerting function of acute pain reflects the phasic activation of sensors (nociceptors) by potentially dangerous stimuli exceeding the physiological range. This warning purpose of pain is most evident as concerns the skin, which is exposed to external dangers. Acute, cutaneous pain evokes, thus, motor withdrawal and/or a 'flight' reaction, protective responses intended to discontinue exposure to the noxious stimulus and, thereby, to terminate the pain. On the other hand, under certain conditions, actual pain, or the threat of pain, may elicit a generalized behavioural arousal, endocrine responses (such as corticosterone secretion) and sympathetic activation (leading to elevations in blood pressure and heart rate, etc) which, together with a transient *antinociception*, improve the performance of behavioural repertoires permitting successful disengagement from aggressive encounters or other situations potentially leading to serious tissue damage (Millan, 1986; Wiertelak *et al.*, 1994c; Traub, 1997).

Under most conditions, an adaptive association between dangerous, tissue-damaging (internal) stimuli and pain is likewise apparent for skeletal muscle and, probably, the joints (Mense, 1993; Schaible and Grubb, 1993) (Section 3.1.2). This relationship is, however, less evident for the viscera (Section 3.1.2). For example, pain is seldom, if ever, experienced from the liver or lung, even when they are severely diseased or damaged, possibly since a network of sensory nerves for the transmission of nociceptive information to the CNS is absent in these organs (Cervero, 1994). Further, whereas *global* distension of the hollow viscera (gut and urinary tract) elicits pain, their *local* perforation may *not* necessarily be painful, despite its potentially more dramatic consequences (Cervero, 1994, 1995b; Mailiani *et al.*, 1984; McMahon, 1994; Meller and Gebhart, 1992). Although ischaemic tissue damage, inflammation and distension clearly can elicit visceral pain and hypersensitivity (for example, cystitis), one striking illustration of a dissociation between damage to internal organs and pain (a 'failure to warn') is provided by the phenomenon of 'silent ischaemia'. That is, painless heart attacks which, despite their apparent innocuousness, are predictive of subsequent heart failure. Contrariwise, angina-like thoracic pain in the apparent *absence* of a somatic cause may also be observed (Arnim and Maseri, 1987; Casey, 1996; Casey *et al.*, 1996b; Cervero, 1994; Meller and Gebhart, 1992). These differences to cutaneous pain possibly reflect the fact that visceral and deep pain is often 'inescapable': protective behaviour can be

Table 2. A general, pathophysiological classification of some major features of pain

Type	Duration	Temporal features relationship to cause	Major characteristics	Class	Source of pain	Adaptive value	Adaptive response	Examples
Phasic Acute.	Seconds	Instantaneous Simultaneous	'Proportional to cause'	Noiceptive	Transient nociceptor activation	High Preventative	Withdrawal Escape	Contact with hot surface
Prolonged Subchronic	Hours to days	Resolves upon recovery	1° and 2° Hyperalgesia Allodynia Spontaneous pain	Principally nociceptive. But also neuropathic.	See Tables 5 and 6	Protective Recovery	Quiescence Avoidance of contact with injured tissue	Inflamed wound
Chronic Clinical	Months to years	Persistent Long-term disease May exceed resolution of tissue damage	1° and 2° Hyperalgesia Allodynia Spontaneous pain Parasthesias/ dysthesias Pronounced affective component	Neuropathic Nociceptive	See Tables 5 and 6	None Maladaptive	Psychological and cognitive	Arthritis PAF or CNS injury Metastatic disease

1° and 2°, Primary and secondary, respectively.



less easily engaged in response to internal as compared to external threats. Evolutionary pressure will, thus, have been less intense for the development of an alerting system for internal pain. Notwithstanding these observations, deep visceral- and somatic-pain, when severe, tends to evoke a reaction of quiescence, disinterest, hyporeactivity, hypothermia and bradycardia. Such *temporary* responses may be adaptive inasmuch as they reduce discomfort, accelerate recovery and limit the risk of deleterious encounters. Further, visceral pain, in particular from the peritoneal region, via a series of reflex pathways, can lead to muscular contractions or spasms which rigidify the abdominal wall. This may protect ('guard') the viscera from further trauma, thereby encouraging recuperation. Further, sensations of overdistension and gastric irritation from the gut may also elicit appropriate behavioural responses.

In addition to their protective-sensory, afferent (orthodromic) role, the antidromic stimulation of fine calibre, nocisponsive fibres is associated with '*efferent*' functions in the periphery. That is, the peripheral release of neuropeptides and other substances elicits a constellation of local responses involving actions at neighbouring nocisponsive fibres, the vasculature and immunocompetent cells etc. This phenomenon, which is often termed 'neurogenic inflammation' (NI) (Holzer, 1988; Kilo *et al.*, 1994, 1997; Maggi, 1991a,b) (Section 7.9), may fulfil a beneficial role in, for example, combatting tissue infection and accelerating wound healing. Further, the release of neuropeptides and other molecules from damaged primary afferent fibres (PAFs) may facilitate mechanisms allowing for their regeneration and functional recovery (Hökfelt *et al.*, 1994; White and Maasfield, 1996) (Sections 8.2.5 and 11.3.4.5). However, the antidromic activation of sensory terminals, via a feedback mechanism, further increases their activity and potentiates nociception (Section 7.4.9). Further, where unrestrained and/or prolonged, the efferent excitation of nocisponsive fibres may have other deleterious consequences: for example, an enhancement of those neurogenic and vascular events in dural blood vessels which underlie migraine headaches (Section 7.9), and an exacerbation of pathological processes of arthritic inflammation and joint degeneration (Schaible and Grubb, 1993; Murphy, 1993).

## 2.2. Lack of Endogenous Mechanisms for the Effective Control of Chronic Pain

As mentioned above, temporary inactivity and protective behaviour in response to subchronic pain may be adaptive. However, *persistent* pain may lead to a *long-term* state of withdrawal, anhedonia and environmental indifference. This response resembles depressive-like states ('defeat', 'helplessness' and/or 'despair') triggered by inescapable stress, and cannot, as such, be considered adaptive (Bloom and Kupfer, 1995; Craig, 1994; Millan and Gobert, 1997). Indeed, although the evolution of acute (and subchronic) pain may be attributed to its protective (adaptive) function, the question arises as to why pathological, chronic pain has 'evolved'? In fact, the

question should probably be inverted. Why have specific mechanisms *not* evolved allowing for the counteracting of chronic, painful states, inasmuch as endogenous processes involved in the moderation of shorter-term pain are manifestly inadequate for its suppression?

This may reflect an absence of sufficient selective pressure for their evolution under the circumstances in which chronic pain is generally encountered. Thus, afflicted individuals are frequently old and/or infirm. For example, the pain associated with degenerative tissue diseases (such as rheumatoid arthritis), metabolic disorders (such as late-stage, insulin-dependent diabetes), severe injury (such as limb fracture) or terminal disease (such as cancer). Correspondingly, the probability that affected individuals will survive is meagre, and they probably do not comprise a part of reproductive populations. Genes favouring a moderation of chronic pain under these conditions are unlikely to possess major adaptive value and likely show limited 'penetration' (transmission to succeeding generations). Indeed, even the alleviation of pain would not necessarily be adaptive, since the pathological state would persist and perhaps even be aggravated.

In addition, several processes contributing to chronic pain may be secondary consequences of the adaptive, efferent functions of sensory fibres involved in palliating the effects of tissue damage and/or nerve injury (Sections 2.1 and 8.2.5). Thus, stimulation of, or damage to, PAFs is associated with the induction and *peripheral* release of several trophic factors, in particular neuropeptides. These exert a diversity of actions on local tissues, the vasculature and PAFs themselves which collectively encourage wound healing and *facilitate* the recovery of injured nerves (Section 11.3.4.5). However, upon their peripheral and/or *central* release, certain neuropeptides potentiate the transmission of nociceptive information (Section 8.2.5). Similarly, although immunocompetent and glial cells exert beneficial actions following injury, they also secrete cytokines and other mediators which aggravate nociception associated with inflammation or PAF injury (Sections 7.7 and 8.2.1). Under some conditions—probably of limited duration—the adaptive value of these restorative actions may offset the negative consequences of the pain thereby engendered. However, ultimately, chronic pain becomes deleterious to the organism.

## 3. RECEIPT, ENCODING AND TRANSMISSION TO THE DH OF PRIMARY AFFERENT, NOCICEPTIVE INFORMATION

### 3.1. Sensory Properties of PAFs: Detection of Noxious Stimuli

#### 3.1.1. Cutaneous C, A $\delta$ and A $\beta$ Fibres Encoding Noxious and Innocuous Information

The nature and organization of primary afferent input to the DH has been comprehensively and expertly reviewed elsewhere (Belemonte and Cervero, 1996; Besson and Chaouch, 1987; Cervero, 1994; Laem *et al.*, 1993; Lawson, 1992; Mense,

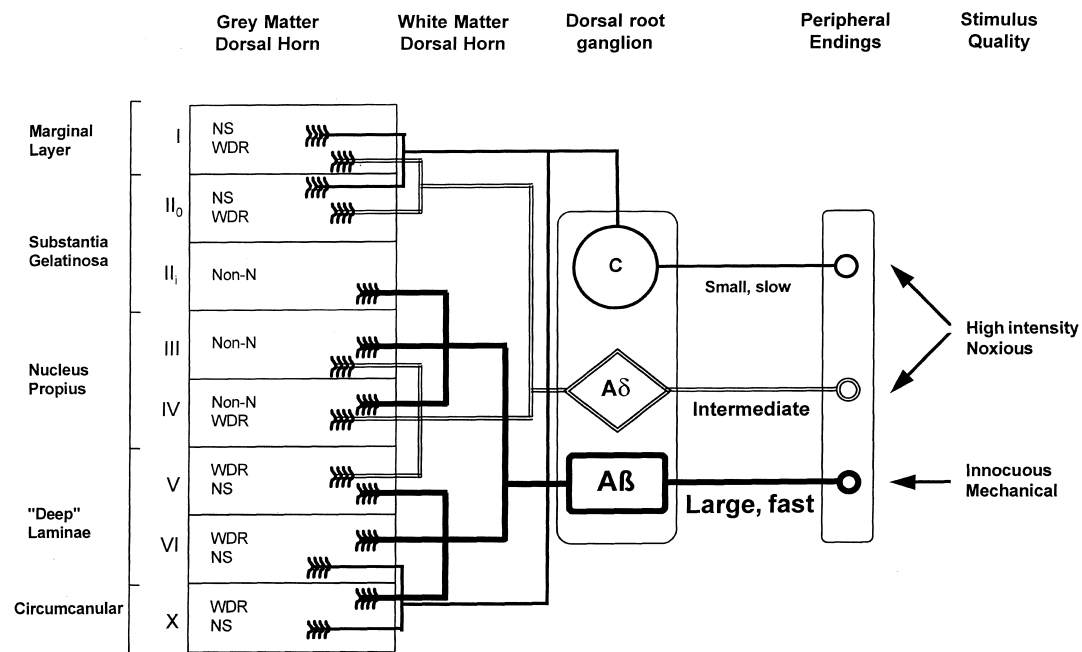


Fig. 1. Organization of cutaneous, primary afferent input to the dorsal horn of the spinal cord. Abbreviations are as indicated in the general list. This schema does *not* quantitatively differentiate between various laminae as concerns PAF input. For example, the density of Aδ fibres innervating lamina I is considerably greater than that projecting to lamina II<sub>0</sub>, a principal target of C fibre input. Unmyelinated fibres from muscle, viscera and joints appear to preferentially innervate laminae I and IV/V/IV rather than II. Cell types (NS, WDR or NON-N) are also qualitatively—rather than quantitatively—indicated in terms of the major class encountered in various laminae. Laminae VI, which functionally complements lamina V, is clearly identifiable only at the level of the cervical and thoracic cord. Lamina X corresponds to the grey matter surrounding the central canal (Sections 3 and 4).

1993; Meyer *et al.*, 1994; Raja *et al.*, 1988; Schaible and Grubb, 1993; Treede and Magerl, 1995; Treede *et al.*, 1992b; Willis and Coggeshall, 1991). Cutaneous PAFs can be classified into essentially three types on the basis of their diameter, structure and conduction velocity (Fig. 1, Table 3).

1. C: thin (0.4–1.2  $\mu\text{m}$  in diameter), unmyelinated and slowly-conducting (0.5–2.0  $\text{m sec}^{-1}$ ).
2. Aδ: medium (2–6  $\mu\text{m}$ ), myelinated and of intermediate velocity (12–30  $\text{m sec}^{-1}$ ).

3. Aβ: large (> 10  $\mu\text{m}$ ), myelinated and fast (30–100  $\text{m sec}^{-1}$ ).

In skin, they are typically present in proportions of ca 70, 10 and 20%, respectively, though their ratios may vary. Each of these classes of PAF encodes sensory information, but they are differentially sensitive to noxious and innocuous stimuli. Thus, although *all* three classes of cutaneous fibres can transmit *non-nociceptive* information, under normal circumstances, only C and Aδ, but *not* Aβ, fibres transmit *nociceptive* information (Table 3) (Section 9.1.2).

Table 3. Comparative properties of primary afferent C and Aβ fibres

Fibre class	Threshold for activation	Principal transmitters*	Receptors engaged*	DH Laminae innervated†	Neurone types targeted	Sensation mediated	
						Physiological	Pathological
C	High	SP/NKA CGRP EAA	NK <sub>1/2</sub> CGRP <sub>1/2</sub> NMDA/ AMPA mGlu	I/II <sub>0</sub> IV/V, X	NS WDR	Noxious (pain)	Highly noxious (hyperalgesia) Cold allodynia (pain)
Aβ	Low	EAA	AMPA	III–VI	NON-N WDR	Innocuous (no pain)	Mechanical allodynia (pain)

\*Partial list. Further, under conditions of nerve injury, PAF phenotype may change, for example, VIP is induced in C fibres and substance P is induced in Aβ fibres (Section 8.2).

†Under conditions of nerve injury, the organization of PAF projections in the DH may change, for example, Aβ fibres sprout to more superficial (II<sub>0</sub>) laminae wherein they may contact NS neurones (Section 11).

Generally-speaking, upon exposure of the skin to a noxious stimulus, myelinated A $\delta$  fibres elicit a rapid, first phase of pain, which is 'sharp' in nature, whereas unmyelinated C fibres evoke a second wave of 'dull' pain (Belemonte and Cervero, 1996; Handwerker and Kobal, 1993; Meyer *et al.*, 1994; Torebjörk and Hallin, 1973; Treede *et al.*, 1992b). A further difference, recently quantified by Yeomans and Proudfit (1996) and Zachariou *et al.* (1997), is that, for cutaneous thermosensitive units, low and high noxious skin heating rates preferentially engage nocisponsive C and A $\delta$  fibres, respectively. One further distinction is that the C fibres responsive to intense and painful, cold stimuli are located along vein walls, whereas thermosensory A $\delta$  fibres responsive to cooling are localized cutaneously (Chen *et al.*, 1996; Craig *et al.*, 1996; Klement and Arndt, 1992; LaMotte and Thalhammer, 1982).

Multiple classes of both C and A $\delta$  fibre exist. However, their characterization and description is complicated by several factors including terminological inconsistencies, species differences, contrasting properties of nocisponsive fibres in various tissues—for example, hairy vs non-hairy ('glabrous') skin—and the methods employed for their detection (Belemonte and Cervero, 1996; Handwerker and Kobal, 1993; Koltzenburg *et al.*, 1997; Meyer *et al.*, 1994; Treede *et al.*, 1990a, 1992b; Willis and Coggeshall, 1991). The following paragraphs provide a simplified overview.

As concerns C fibres, chemospecific nociceptors, thermoreceptors responsive to warming or cooling, as well as low threshold mechanoreceptors responsive to pressure, have all been described (Meyer *et al.*, 1994). The role of cold-sensitive C fibres in mediating cold allodynia is discussed in Sections 9.2.4 and 13.4. Of particular pertinence in the present context are those high threshold receptors localized on C fibres which encode nociceptive information pertaining to noxious thermal and/or mechanical stimuli. Of these, there is an abundance which respond to both mechanical and heat stimuli and the term 'polymodal' or 'CMH' is generally reserved for the population which also responds to irritant, chemical stimuli. The crucial role of polymodal, nocisponsive C fibres in triggering the sensitization of spinal neurones, a process underlying chronic painful states, is described in Sections 10.2, 10.3 and 10.4. A specific class of C fibre nociceptor which exclusively (or primarily) responds to noxious, heat stimuli (and which is coupled to a cation-permeable ion channel) has been detected in primates (including man), but is rare in rodents. Together with polymodal C fibres, this C fibre class is likely involved in mediating the 'axonal flare response' (a component of NI) following tissue damage (Belemonte and Cervero, 1996; Lynn *et al.*, 1996; Meyer *et al.*, 1994; Reichling *et al.*, 1997; Schmidt *et al.*, 1995) (Section 7.9). Collision studies have revealed a minor degree of bidirectional coupling between polymodal C fibres terminals, a process which may be involved in expansion of the flare response. Recently, a micro-neurography approach in human skin permitted the identification of a very thin and slowly-conducting, histamine-responsive class of mechano-insensitive C fibres which showed extensive terminal arborization:

a role of these PAFs in the mediation of itch was suggested (Meyer *et al.*, 1994; Schmeltz *et al.*, 1997b).

As regards A $\delta$  fibres, one class is activated by high intensity, mechanical stimuli in the noxious range (for example, pinch). These so-called 'Type I', high threshold, rapidly-conducting mechanoreceptors, are weakly responsive to high intensity heat, cold (and chemical) stimuli (Handwerker and Kobal, 1993; Meyer *et al.*, 1994; Simone and Kajander, 1997; Treede and Magerl, 1995). However, repetitive thermal stimulation may sensitize them to further stimulation and, following tissue damage, they become heat-responsive and show sustained responses to thermal stimuli of long duration and slow (sec) latency. This increase in responsiveness has been contrasted to the decrease in responsiveness displayed by polymodal C fibres in glabrous skin upon repetitive heat stimulation or injury (Meyer *et al.*, 1994). A further, less common and less rapidly-conducting class of A $\delta$  fibre ('Type II') has principally been examined in the hairy skin of primates. Type II A $\delta$  fibres display a lower threshold to noxious heat stimuli than their Type I counterparts, and respond thereto more rapidly (Beydoun *et al.*, 1996; Treede *et al.*, 1990a,b). A $\delta$  fibres more responsive to cooling than mechanical stimuli, and capable of encoding stimulus intensity, also exist (Craig *et al.*, 1996; Simone and Kajander, 1997).

For cutaneous populations, receptive fields (RFs) may be quite small (2 mm diameter) and homogenous for nocisponsive C fibres: for example, as concerns mechanical, noxious stimuli in the rat (Belemonte and Cervero, 1996; Lynn and Carpenter, 1982). Others may be large ( $\approx 10$  mm) and heterogeneous (containing islands of responsive areas): for example, for mechanical and thermal stimulation of primate and human, hairy skin. Similarly, nocisponsive, high threshold, mechanosensitive A $\delta$  fibres display complex RFs with multiple sites of sensitivity (Belemonte and Cervero, 1996; Treede *et al.*, 1992b).

In the *absence* of tissue or nerve injury, cutaneous A $\beta$  fibres are responsive *only* to touch, vibration, pressure and other modes of *non-noxious*, low intensity mechanical stimuli—although it has been suggested that a sub-population of rapidly-conducting A fibres, of ambiguous A $\delta$ - or A $\beta$ -like characteristics, may contribute to nociceptive transmission from muscle (Mense, 1993; Woolf *et al.*, 1994; Willis and Coggeshall, 1991; Wilson *et al.*, 1996b).

Microneurographic recordings of the activity of cutaneous sensory nerves in man, in parallel with psychophysical assessments of pain intensity, suggest that nociceptors can encode the intensity of noxious thermal (and mechanical) stimuli (Bromm *et al.*, 1984; Brown and Culbertson, 1981; Dubner *et al.*, 1989; Gybels *et al.*, 1979; Handwerker and Kobal, 1993; Meyer *et al.*, 1994; Treede *et al.*, 1992b). They also encode information concerning the spatial localization of noxious, cutaneous stimuli and, for the performance of this function, overlapping territories of individual nociceptive C fibres in skin may be a prerequisite (Schmidt *et al.*, 1997). Generally, a single discharge of an individual nocisponsive fibre is *not* perceived as noxious and many nocisponsive

units need to be recruited over a period of time for 'pain' to be experienced. Further, actual pain thresholds are higher in man than the thresholds for activation of individual nociceptors. These observations suggest the existence of central mechanisms for both spatial and temporal summation for pain signalling (Vierck *et al.*, 1997) (Sections 10 and 12). Nevertheless, the 'instantaneous' function of nociceptors in signalling exposure to acute, noxious stimuli corresponds to the 'alerting' role of pain (Section 2) and likely occurs with little intervention from modulatory (inhibitory) peripheral or central mechanisms (Handwerker and Kopal, 1993). As mentioned above, in the *absence* of tissue damage, repetitive noxious stimulation (like other modes of sensory input) may be associated with a *decreased* response of some polymodal C-fibres. However, under conditions of tissue damage, this phenomenon is greatly outweighed by both peripheral and central processes of sensitization, such that the sensation of pain will be intensified and prolonged. These mechanisms of sensitization comprise a major part of this review and are described in detail in Sections 7, 10 and 12.

### 3.1.2. Nocisponsive Fibres in Other Organs

There is an extensive literature, authoritatively reviewed elsewhere, which exemplifies several similarities, and certain differences, between mechanisms involved in the receipt and processing of nociceptive information from non-cutaneous tissues as compared to the skin (Cervero, 1994, 1995a; Gebhart, 1995; Marchettini *et al.*, 1996; McMahon, 1994; Mense, 1993; Meyer *et al.*, 1994; Schaible and Grubb, 1993; Svensson *et al.*, 1997; Willis and Coggeshall, 1991). Certain of these aspects were evoked above and the following paragraphs summarize several, other distinctive features of nociceptive input from non-cutaneous tissues.

The above-mentioned differentiation between temporally-distinct components of 'sharp' and 'dull' cutaneous pain is not easily recognised for other organs. For example, both 'A $\delta$ ' fibre and 'C' fibre-mediated muscular pain (see below), irrespective of the time-scale, tends to present with a dull, aching and/or cramp-like quality (Marchettini *et al.*, 1996; Mense, 1993). Further, a distinguishing feature of deep somatic and visceral—as compared to cutaneous-pain is the pronounced and intensely-unpleasant, autonomic component (hypotension, nausea, perspiration, etc); this reflects the excitation of sympathetic and parasympathetic pathways. In addition, deep and visceral pain is often diffuse (poorly-localized) and frequently referred to other intact tissues (Section 9.1.4).

The majority of the uncapsulated terminals which innervate skeletal muscle correspond to small 'group III' myelinated fibres (equivalent to A $\delta$  fibres) and to 'group IV' unmyelinated fibres (equivalent to C fibres). Group III fibres, which are engaged by mechanical stimuli, are responsive to muscle stretch, contractions and innocuous pressure. However, they can be sensitized by thermal and chemical stimuli and about one third may be classified as nocisponsive, typically being activated by ischaemia/hypoxia

and localized, noxious increases in pressure (Abrahams *et al.*, 1984; Marchettini *et al.*, 1996; Mense, 1986, 1993; Mense and Meyer, 1985). Group IV fibres share several characteristics of group III fibres and they may also respond to thermal stimuli. Indeed, almost 50% of group IV fibres are nociceptive and, like group III fibres, they respond to ischaemia/hypoxia and localized, noxious increases in pressure. This population also mimics group III fibres in their polymodal-like response to, and sensitization by, chemical stimuli (Mense and Meyer, 1988; Mense, 1993). In line with the above observations, it has been suggested that 'polymodal-like' A $\delta$  (group III) fibres are more prominent in muscle than in skin and that their stimulation, in analogy to polymodal, cutaneous C fibres, plays an important role in initiating processes of sensitization in the spinal cord (Handwerker and Kopal, 1993; Marchettini *et al.*, 1996; Mense, 1993). The intense discharge of nocisponsive, group III and IV skeletal fibres in response to excessive increases in pressure and local ischaemia (Mense and Stahnke, 1983; Mense, 1993) may be considered as fulfilling a 'warning' function analogous to the protective role of cutaneous nociceptors inasmuch as the onset of muscular pain leads to the discontinuation of excessive muscle contraction. Although, clinical, muscular pain is usually diffuse, it can be reasonably well-localized under certain conditions (Marchettini *et al.*, 1996).

Many group III and IV fibres (free nerve endings) innervating joint capsules—as well as a small proportion of large, *corpuseular*, myelinated A $\delta$ -like fibres—discharge only upon extremes of movement beyond the normal range (Grigg *et al.*, 1986; Schaible and Grubb, 1993). Thus, in analogy to muscle group III and IV afferents, one may consider their triggering of pain under these circumstances as fulfilling a 'warning' function.

Pain is an all-too-familiar and prominent sensation from the teeth. It likely reflects the activation of polymodal C and A $\delta$  fibres preferentially transmitting nociceptive information from the tooth pulp and the dentin, respectively (Meyer *et al.*, 1994).

Cerebral blood vessels (CBVs) are surrounded by a dense plexus of sensory nerves, many of which branch extensively. A recent description of nocisponsive PAFs innervating dural vessels suggested that this network constitutes an homogeneous population of polymodal (C) nociceptors (Bove and Moskowitz, 1997). These observations are of evident pertinence to the pathology of migraine and other forms of intracranial pain (Section 7.9).

Although less well-characterized than nociceptors in the skin, there is evidence for the existence of (polymodal) C and A $\delta$  fibres in internal organs such as the heart and gut (Cervero, 1982, 1994, 1995a; Gebhart, 1995; McMahon, 1994; Meller and Gebhart, 1992; Willis and Coggeshall, 1991). Nociceptive information from the viscera reaches the CNS via the sympathetic chains (for example, from the thorax and upper abdomen) and pelvic, parasympathetic chains (notably from the bladder and lower gut) (Cervero, 1994; Meyer *et al.*, 1994). Interestingly, Meller and Gebhart (1992) have suggested that both sympathetic and vagal (para-

sympathetic) afferents contribute to myocardial pain. The generally diffuse nature of deep and visceral pain, notably from the intestinal tract, and its frequent referral to other tissues, may be distinguished from the focal quality of cutaneous pain (Section 9.1.4). Indeed, the density of visceral afferents, for example in the gut, is low as compared to the skin. This sparse innervation, together with the large, weakly-defined, multiple and complex RFs of visceral nocisponsive units, accounts for the poor localization of noxious stimuli in the gut and other visceral tissues: it also explains why extensive stimulation of large tissue areas may be required to elicit pain, presumably via spatial summation (Cervero, 1995b; Handwerker and Kobal, 1993; Mense, 1993; Schaible and Grubb, 1993). Further, the absence of genuine A $\beta$  fibres in the viscera suggests that non-noxious information from the viscera must be transmitted by A $\delta$  and C fibres, leading to a controversy as to whether visceral pain is either:

1. mediated by specific nociceptors (the 'specificity theory'); or
2. more probably, intensity-encoded by 'non-specific' fibres likewise responsive to innocuous stimulation ('pattern theory') (Cervero, 1994, 1995b; Handwerker and Kobal, 1993; Mailiani *et al.*, 1984; McMahon *et al.*, 1994).

### 3.1.3. 'Silent' Nociceptors

There is one further class of nociceptor which has attracted much recent interest within the context of prolonged pain: so-called 'silent' or, perhaps more appropriately, 'sleeping', nociceptors (Cervero, 1994; Koltzenburg, 1995; McMahon and Koltzenburg, 1990a,b; Schaible and Grubb, 1993; Treede *et al.*, 1992b). Although *no* class of nociceptor actually shows spontaneous activity, the term 'silent' refers to a subset (perhaps 10–20%) of unmyelinated C fibres in the skin, joints and viscera—though see Cervero (1994)—which are normally irresponsive to acute noxious stimuli. Under conditions of inflammation and tissue injury, these 'silent' nociceptors are sensitized and activated by a variety of chemical mediators (Dmitrieva and McMahon, 1996; Koltzenburg, 1995; Reeh *et al.*, 1987; Sengupta and Gebhart, 1994). Silent receptors have also been identified in human skin (Schmidt *et al.*, 1995). This recruitment of otherwise-silent, chemosensitive PAFs under pathological states may contribute to temporal and spatial summation and considerably enhances the C fibre afferent barrage to the DH. For example, PAFs in arthritic joints develop both spontaneous activity and emit signals in response to previously-ineffective joint movements, and inflammation of the viscera may enormously enhance their sensitivity to otherwise, innocuous mechanical stimulation (Cervero, 1995a; Coutinho *et al.*, 1996; Clément *et al.*, 1996; Gebhart, 1995; Grigg *et al.*, 1986; Schaible and Grubb, 1993; Schaible and Schmidt, 1988). Treede and Magerl (1995) have pointed out that some types of PAF may be regarded as 'partially silent' as concerns effective stimulus qualities. Thus, some high threshold (Type I), mechanosensitive A $\delta$  fibres only respond to ther-

mal stimuli following their sensitization (Section 3.1.1). Further, an expansion of the RFs of PAFs following tissue injury may reflect the engagement of previously-silent branches. The activation of silent nociceptors underlines the distinctive nature of prolonged, inflammatory painful states as compared to the acute exposure to phasic noxious stimuli. Indeed, the recruitment of silent nociceptors likely makes an important contribution to the sensitization and central adaptive changes which underlie primary hyperalgesia due to tissue inflammation (Sections 7, 9 and 12).

### 3.1.4. 'Ectopic' Functions of Damaged PAFs and 'Central' Pain

As described in Section 8.2, injured peripheral nerves may form structures termed neuromas. These neuromas and/or their dorsal root ganglia (DRG) develop spontaneous electrical activity and become sensitive to inflammatory mediators, noxious stimuli and sympathetic input. Thus, orthodromic impulses conducted to the spinal cord are initiated independently and downstream of terminal-localized nociceptors. The induction of pain by damage to, or a dysfunction of, specific regions of the CNS itself is considered in Section 13.

## 3.2. Role of Neurotransmitters and Neuromodulators in the Transmission of Nociceptive Information by PAFs to the DH of the Spinal Cord

### 3.2.1. Multiple Mediators of Nociceptive Information in PAFs: Interaction with Intracellular Transduction Mechanisms

In Section 3.1.1, various types of PAF were classified on functional grounds according to the mode of sensory information which they encode and transfer to the DH. In this regard, several subtypes of C and A $\delta$  fibre were recognized. A complementary, neurochemical system of PAF categorization may be based upon the nature of the molecules which they contain and release. Indeed, nocisponsive PAFs synthesize a diversity of substances potentially involved in the central transmission and modulation of nociceptive information. These include glutamate (GLU) and other excitatory amino acids (EAAs); neuropeptides, such as substance P (SP) and calcitonin gene related peptide (CGRP); the universal, cellular energy source, adenosine triphosphate (ATP); the diffusible gas, nitric oxide (NO); the phospholipid metabolites, prostaglandins (PGs) and neurotrophins (growth factors). These potential transmitters, a diversity of other neuropeptides, various enzymes, several lectins and a miscellany of other molecules display a complex pattern of colocalization, comodulation and corelease in PAFs (He *et al.*, 1990; Hunt and Rossi, 1985; Kashiba *et al.*, 1996; Lawson, 1992; Lawson *et al.*, 1997; Levine *et al.*, 1993; Lynn, 1997; Mense, 1993; Merighi *et al.*, 1991; Salt and Hill, 1983; Schaffar *et al.*, 1997; Schaible and Grubb, 1993; Willis and Coggeshall, 1991; Yaksh and Malmberg, 1994). In principle, each specific, functional subclass of PAF might possess a characteristic complement of markers, but this remains to be demonstrated. In any case, the neuro-

chemical composition of PAFs varies both qualitatively and quantitatively as a function of several factors.

Thus, differences are apparent:

1. amongst various tissue types—skin, muscle, joints and the viscera (De Groat, 1986; McMahon, 1994; Gebhart, 1995; Lawson, 1992; Lawson *et al.*, 1997; Marchettini *et al.*, 1996; Mense, 1993; Salt and Hill, 1983; Schaffar *et al.*, 1997; Schaible and Grubb, 1993);
2. between the intact state vs peripheral tissue inflammation and PAF injury (Goff *et al.*, 1998; Hökfelt *et al.*, 1994) (Sections 7.6 and 8.2.5); and
3. amongst various classes of PAF, for example, C fibres as compared to A $\beta$  fibres (Hökfelt *et al.*, 1994; Lawson, 1992; Salt and Hill, 1983; Willis and Coggeshall, 1991; Xu and Wiesenfeld-Hallin, 1997).

In addition, differences have been documented *within* a specific class of PAF, and 'peptidergic' and 'non-peptidergic' subpopulations of small calibre PAFs have been recognized for some years (Hunt and Rossi, 1985). A substantial percentage of C fibres are sensitive to the pungent ingredient of hot peppers and vanilloid, capsaicin (Section 7.4.5) and, of these, at least two major subpopulations may be identified (Averill *et al.*, 1995; McMahon and Bennett, 1997; Molliver *et al.*, 1997; Vulchanova *et al.*, 1996; Willis and Coggeshall, 1991). The first contains CGRP and SP and is developmentally dependent upon the neurotrophin, nerve growth factor (NGF) (Section 7.6.1). The second, which is defined by presence of the lectin, IB-4, possesses a subclass of excitatory receptor for ATP on their peripheral terminals and is dependent upon glial cell derived nerve growth factor (GDNF) (Sections 7.4.4 and 11.3.4.3). Each of these classes of C fibre fulfils a key role in nociceptive transmission in the DH. Peptidergic populations of C fibres can be further sub-divided into additional subclasses based on supplementary, neurochemical criteria (Hökfelt *et al.*, 1994; Kashiba *et al.*, 1996; Lawson, 1992; Willis and Coggeshall, 1991).

Of particular interest, a recent study found that SP was more prominent in C fibres emanating from the muscle and other deeper, subcutaneous (s.c.) tissues than in C fibres innervating the skin, while cutaneous A $\delta$  fibres contained little of no SP (Lawson *et al.*, 1997; Lynn, 1997) (Section 4.7). Thus, although SP may be the most familiar and comprehensively-characterized, pronociceptive transmitter in PAFs, these observations draw attention to the fact that nocisponsive PAFs do *not* necessarily contain this tachykinin. Correspondingly, the presence of SP in PAFs is *not* indispensable for the central transmission of nociceptive information (Hunt and Rossi, 1985; Lawson, 1992; Lawson *et al.*, 1997; Lynn, 1997; Willis and Coggeshall, 1991).

Evidently, the neurochemical characterization of specific classes of PAF in relationship to their functional properties is far from complete and remains the topic of intensive study (Coggeshall and Carlton, 1997; Hökfelt *et al.*, 1994; Hunt and Rossi, 1985; Liedtke and Edelmann, 1996; Lynn, 1997;

Todd and Spike, 1993; Yajiri *et al.*, 1997; Yaksh and Malmberg, 1994).

In analysing the roles of PAF mediators in the central transmission of nociceptive information, it is essential to take account of their coupling to intracellular transduction mechanisms inasmuch as the nature of their influence upon ionic fluxes and soluble second messengers determines their impact upon cellular excitability. The opening of cation-ion permeable channels depolarizes neurones. Further, via a cascade of intracellular signals detailed in Section 10.4, activation of phospholipase C (PLC) and adenylyl cyclase (AC) also triggers mechanisms leading to an increase in neuronal excitability and sensitivity. Correspondingly, for a diversity of transmitters released from PAF terminals onto intrinsic, nocisponsive DH neurones, where their receptors are positively or negatively coupled to cation ion flux, PLC and/or AC, they exert pronociceptive or antinociceptive properties, respectively (Sections 3.2.4 and 3.2.6).

The following paragraphs summarize the role of PAF-localized mediators in the transmission of nociceptive information to the DH in relation to their interaction with intracellular transduction mechanisms. Notwithstanding the above comments concerning multiple, neurochemical classes of nocisponsive fibre, the ensuing discussion focuses on the synergistic roles of colocalized EAAs, SP and CGRP in view of the abundance of information available concerning their cooperative actions and influence upon intracellular transduction mechanisms involved in the sensitization of DH neurones, a process playing a key role in the induction of long-term painful states. Thereafter, the potential significance of other neuropeptides contained in PAFs is outlined (Section 3.2.6). The functional roles of ATP, NO and PGs in the DH are discussed in Section 3.2.8.

Molecular and intracellular mechanisms underlying the excitation and sensitization of DH neurones by nociceptive input from PAFs are discussed in detail in Sections 10.2 and 10.3.

### 3.2.2. Role of Colocalized EAAs, Tachykinins and CGRP in Small Calibre PAFs Projecting to the DH

As mentioned earlier, EAAs, tachykinins and CGRP are colocalized in a subset of capsaicin-sensitive, nocisponsive, small calibre fibres projecting to the DH from the skin and other tissues (Battaglia and Rustioni, 1988; Kashiba *et al.*, 1996, 1997; Lawson, 1992; Merighi *et al.*, 1991; Willis and Coggeshall, 1991).

The pronociceptive tachykinins, SP and neurokinin (NK) A, act at NK<sub>1</sub> and NK<sub>2</sub> receptors, respectively—although NKA may also exert actions at NK<sub>1</sub> sites, and SP at NK<sub>2</sub> sites. Both NK<sub>1</sub> and NK<sub>2</sub> receptors are positively coupled to PLC (Bentley and Gent, 1995; Chapman *et al.*, 1996; Hoheisel *et al.*, 1997; Maggi and Schwartz, 1997; Mantyh *et al.*, 1997; Nagy *et al.*, 1994; Radhakrishnan and Henry, 1997; Rupniak *et al.*, 1996; Seguin *et al.*, 1995; Sluka *et al.*, 1997a,b; Tao *et al.*, 1997; Traub, 1996).

A further, pronociceptive neuropeptide, CGRP, exists as two ( $\alpha$  and  $\beta$ ) isoforms. CGRP exerts its

actions via (at least) two receptor types, CGRP<sub>1</sub> and CGRP<sub>2</sub>, both of which are positively coupled to AC, although their respective roles in mediating the actions of CGRP on intrinsic neurones in the DH remain to be characterized (Brain and Cambridge, 1996; Edvinsson *et al.*, 1997; Wimalawansa and El Kholy, 1993; Olesen and Janssen-Olesen, 1997; Woolf and Wiesenfeld-Hallin, 1986; Yu *et al.*, 1996).

EAAAs, such as GLU and aspartate, act at both metabotropic (mGlu) receptors (coupled via G-proteins to soluble *second* messengers) and ionotropic receptors (coupled directly to cation-permeable ion channels): these receptors show a complex pattern of localization on various neuronal classes in the DH (Chaplan *et al.*, 1997; Coggeshall and Carlton, 1997; Conn and Pin, 1997; Dickenson, 1997; Dougherty *et al.*, 1992b,c; Fletcher and Lodge, 1996; Grubb *et al.*, 1996; Haley *et al.*, 1990; Lerea, 1997; Thompson *et al.*, 1995; Valerio *et al.*, 1997; Yoshimura and Nishi, 1992). As outlined in Section 3.2.3, based on the nature of their coupling to intracellular transduction mechanisms and pharmacological properties, three major classes of mGlu receptor—and at least eight subtypes—have been recognized (Conn and Pin, 1997; Valerio *et al.*, 1997). The major types of ionotropic receptor involved in transmitting nociceptive messages in the DH are termed DL- $\alpha$ -NH<sub>2</sub>-2,3-dihydro-5-methyl-3-oxo-4-isoxazolepropanoic acid (AMPA) and *N*-methyl-D-aspartate (NMDA). The significance of NMDA and AMPA receptor isoforms is summarized in Section 3.2.3. Ionotropic, kainate receptors are present in the DH, but the lack of selective, pharmacological tools has hitherto hampered analysis of their putative role in the spinal transmission of nociceptive information (Fletcher and Lodge, 1996). Nevertheless, a selective, high affinity ligand at kainate receptors, SYM 2081, was recently described. SYM 2081 rapidly desensitizes kainate receptors and attenuates the mechanical allodynia and thermal hyperalgesia provoked by PAF injury. However, it is unclear whether the kainate receptors involved are engaged by small and/or large calibre PAFs (Sutton *et al.*, 1997; Zhou *et al.*, 1997a). Further, it is uncertain whether they are localized on intrinsic DH neurones or on the central terminals of small calibre PAFs (Bettler and Mulle, 1995; Coggeshall and Carlton, 1997; Dickenson, 1997; Fletcher and Lodge, 1996; Huettner, 1990) (Sections 3.2.4 and 9.1.4.2).

### 3.2.3. Multiple Isoforms of NMDA, AMPA and mGlu Receptor

The cloning of NMDA and AMPA receptors has identified a multiplicity of subunits allowing for the assembly of a variety of heteromultimeric isoforms (subtypes) in each case (Dickenson, 1997; Hollmann and Heinemann, 1994). The various isoforms may display contrasting properties: for example, differences in their affinity for GLU and in their threshold for activation. The putative roles of individual isoforms in the transmission of nociception in the DH (and elsewhere) is the focus of much current interest. Multiple classes of mGlu subunits have also been cloned. The functional properties of multiple

NMDA, AMPA and mGlu receptor subtypes may be briefly summarized as follows.

NMDA receptors are composed of heteromultimeric subunits and comprise several, distinct classes. These are differentially distributed in the CNS, with the 'NMDA NR<sub>1</sub>' component predominant throughout the DH. Although NMDA receptor isoforms may show contrasting pharmacological properties, they *all* display slow channel kinetics, a certain degree of voltage-dependent Mg<sup>2+</sup>-block and marked permeability to Ca<sup>2+</sup> (Conti *et al.*, 1997; Dickenson, 1997; Hollmann and Heinemann, 1994; Liu *et al.*, 1997d; Momiyama *et al.*, 1996; Sucher *et al.*, 1996) (Section 10.3.1). In addition to the recognition site for NMDA itself, NMDA receptors bear a modulatory (glycine B) site for glycine, the occupation of which is essential for functioning of the coupled, ion channel (Dickenson, 1997; Heppenstall and Fleetwood-Walker, 1997a,b; Hollmann and Heinemann, 1994; Leeson and Iversen, 1994; Seguin *et al.*, 1995). In the DH, glycine is apparently present in a concentration sufficient to saturate these sites.

Like NMDA receptors, AMPA receptor isoforms are composed of several subunits: of these, the 'Glu R-B' (or 'Glu R2') moiety plays a major role in determining Ca<sup>2+</sup>-permeability, conductance and certain other properties. Several post-transcriptional variants of AMPA receptors may also exist (Bettler and Mulle, 1995; Pellegrini-Giampietro *et al.*, 1997; Washburn *et al.*, 1997). AMPA receptor isoforms are differentially distributed within the spinal cord (Dickenson, 1997; Fletcher and Lodge, 1996; Furuyama *et al.*, 1993; Pellegrini-Giampietro *et al.*, 1997; Tachibana *et al.*, 1994; Tomiyama *et al.*, 1996). In contrast to NMDA receptors, the conductance of AMPA receptors localized on nociceptive neurones in the DH is predominantly to Na<sup>+</sup> rather than to Ca<sup>2+</sup>. Further, in distinction to NMDA receptors, AMPA receptors display lower affinity for GLU, low voltage-dependence and rapid kinetics (Furuyama *et al.*, 1993; Tachibana *et al.*, 1994; Tomiyama *et al.*, 1996). Moreover, AMPA receptors can rapidly desensitize upon their selective stimulation (Fletcher and Lodge, 1996). Like NMDA receptors, AMPA receptors possess several allosteric site(s). Actions at these sites modulate the activity and sensitivity of AMPA receptors, in particular the kinetics of desensitization. However, in contrast to the glycine<sub>B</sub> site of NMDA receptors, 'co-agonist' occupation of allosteric sites on AMPA receptors does not appear to be obligatory for activation of the coupled ion channel (Bettler and Mulle, 1995; Fletcher and Lodge, 1996). The ionic and functional properties of kainate receptors are similar to those of their AMPA counterparts (Fletcher and Lodge, 1996).

Numerous (8) types of mGlu receptor have been identified, of which splice variants may also exist. They are divided into three groups. Group I (mGlu<sub>1</sub> and mGlu<sub>5</sub>) receptors, which are concentrated in the superficial DH, are positively coupled to PLC—and possibly, NO synthase. Group II (mGlu<sub>2</sub> and mGlu<sub>3</sub>) receptors and group III mGlu receptors (mGlu<sub>4</sub> and mGlu<sub>6-8</sub>), in contrast, are both negatively coupled to AC, but show differences in their

pharmacological profiles (Conn and Pin, 1997; Valerio *et al.*, 1997). Thus, specific mGlu receptor types differentially modify intracellular calcium concentrations ( $[Ca^{2+}]_i$ ) and the activity of several transduction mechanisms, including various protein kinases (PKs). As described in Section 10.4,  $[Ca^{2+}]_i$  and PKs play key roles in the control of neuronal excitability via the functional regulation (phosphorylation) of several receptor types/ion channels and the modulation of gene transcription. Certain types of mGlu receptor may also modify  $K^+$  and  $Ca^{2+}$ -ion currents, but such actions have not, as yet, been characterized at DH neurones (Conn and Pin, 1997). The implication of various mGlu receptor subtypes in the modulation of nociceptive transmission is currently being explored as a function of their differential levels of expression in the DH and of their contrasting influence upon intracellular transduction mechanisms. In this regard, it is likely that group I (mGlu<sub>1</sub> and mGlu<sub>5</sub>) receptors, which predominate in the superficial DH, play an important role in the mediation of nociceptive input from small calibre PAFs (Budai and Larson, 1998; Fisher and Coderre, 1996; Pin and Duvoisin, 1995; Toms *et al.*, 1996; Valerio *et al.*, 1997; Young *et al.*, 1997) (Section 10.3.2.3).

### 3.2.4. Actions of EAAs and SP at PAF Terminals in the DH

The modulation of nociception by EAAs in the DH reflects not only effects on intrinsic DH neurones, but also actions on the terminals of PAFs from which they are released (Ferreira and Lorenzetti, 1994). Indeed, NMDA and various mGlu receptors have been documented both *postsynaptically* to PAFs on DH neurones, as well as *presynaptically* on the central terminals of PAFs. The DRG of small calibre PAFs also express kainate and AMPA receptors, but their presence on *central* PAF terminals in the DH remains to be definitively demonstrated (Coggeshall and Carlton, 1997; Dickenson, 1997; Fletcher and Lodge, 1996) (Section 7.4.8). The activation of presynaptic populations of NMDA receptors on PAF terminals in the DH, via a positive feedback action, further increases the release of EAAs and SP, thereby amplifying synaptic transmission (Li *et al.*, 1997a; Liu *et al.*, 1994b; Marvizon *et al.*, 1997; Sato *et al.*, 1993a; Ye and Westlund, 1996). On the other hand, the activation of specific mGlu receptor subtypes localized on PAF terminals might either inhibit or enhance presynaptic release as a function of their coupling to intracellular transduction mechanisms, and the precise roles of individual mGlu receptor types on PAF terminals in the DH remain to be clarified. Currently, most evidence favours a predominantly inhibitory role of group II and III mGlu receptors via the inhibition of  $Ca^{2+}$  currents and/or an enhancement of  $K^+$ -currents (Fisher and Coderre, 1996; Herrero *et al.*, 1992; Li *et al.*, 1997a; Valerio *et al.*, 1997). In addition to NMDA and mGlu receptors, the presence of excitatory receptors for SP (presumably of the NK<sub>1</sub> type) on PAF terminals in the DH has been proposed (Coggeshall and

Carlton, 1997; Hu *et al.*, 1997). Like EAAs, then, SP in the DH may exert not only direct, postsynaptic actions on intrinsic DH neurones, but also positive feedback actions to enhance its own release from PAF terminals. Further, NMDA and AMPA receptors may also be present on the terminals of *large* calibre, A $\beta$  fibres in the DH (Coggeshall and Carlton, 1997; Wood and Docherty, 1997) raising the intriguing possibility that their activation may play a role in the induction of mechanical allodynia (Section 9.1.2). In addition to these direct feedback actions at PAF terminals, EAA and SP may indirectly enhance their own release by triggering the liberation of retrograde messengers (such as NO), from their target neurones in the DH (Section 3.2.8).

The above comments concern actions of EAAs and SP at sites *other* than intrinsic DH neurones. In addition, apart from PAF terminals, EAAs and SP in the DH may be derived from *other* sources: that is, intrinsic neurones, the terminals of descending pathways and/or glial cells (Coggeshall and Carlton, 1997; Todd and Spike, 1993; Willis and Coggeshall, 1991). Evidently, then, the role of EAAs/SP in the DH is not restricted to their release from small calibre PAF terminals and the subsequent, postsynaptic activation of intrinsic neurones in the DH. Nevertheless, those actions remain the principal focus of the present article in view of their key importance in eliciting central sensitization (Section 10.3).

### 3.2.5. Cooperative, Excitatory Actions of EAAs, Tachykinins and CGRP on DH Neurones

EAAs, tachykinins and CGRP all cooperatively and synergistically elicit excitatory postsynaptic potentials (EPSPs) in DH neurones with contrasting temporal patterns, and their respective roles depend upon the nature and duration of noxious stimulation (Section 10.3). The initial trigger is probably provided by activation of AMPA receptors, the principal mode of rapid, excitatory transmission throughout the CNS. AMPA receptors display extremely rapid kinetics and their stimulation mediates a rapid depolarization (inward current) over a few msec. The subsequent engagement of NMDA, group I mGlu, NK<sub>1</sub>, NK<sub>2</sub> and CGRP receptors is associated with slower and more sustained EPSPs of up to tens of seconds. Consequently, repetitive or persistent noxious stimulation can lead to temporal summation and amplification of responses in the DH. The precise sequence of events, as well as their significance for the induction of prolonged painful states, is explained in detail in Section 10.3. Presynaptic inhibition of the release of EAAs, tachykinins and/or CGRP, or blockade of their postsynaptic actions, offers, then, presynaptic and postsynaptic mechanisms, respectively, for the interruption of nociceptive transmission in the DH.

### 3.2.6. Other PAF-Derived Neuropeptides Potentially Modulating Nociception in the DH

In addition to tachykinins and CGRP, many other neuropeptides, displaying varying patterns of colocalization, are present in normal and/or injured,



fine and/or large calibre PAFs innervating the DH (Coggeshall and Carlton, 1997; Hökfelt *et al.*, 1994; Kashiba *et al.*, 1997; Lawson, 1992; Mense, 1993; Salt and Hill, 1983; Schaible and Grubb, 1993; Willis and Coggeshall, 1991). Several of these reappear later in this review as playing a role—either peripherally and/or centrally—in the modulation of nociception under pathological conditions (Sections 7.6 and 8.2.5).

In discussing the putative, functional properties of neuropeptides, it is important to note several, general characteristics common to EAAs, tachykinins and CGRP as follows.

1. They may be derived from several neuronal sources: PAFs, terminals of descending pathways and intrinsic DH neurones (Sections 4.6 and 5).
2. Individual neuropeptides may exert a complex pattern of pro and/or antinociceptive actions at multiple loci: intrinsic neurones in the DH, PAF terminals, preganglionic sympathetic neurones and non-neuronal (glial and immunocompetent cells). Similarly, in the periphery, they may act at PAF terminals, sympathetic fibre terminals, glial and immunocompetent cells and the vasculature, etc.
3. For most neuropeptides, they exert their actions via a multiplicity of receptor types.
4. In considering their influence upon the functional activity of target cells and nociception, it is *imperative* to take account of their coupling to intracellular transduction mechanisms, the nature of which may differ for specific receptor types.

Under normal conditions, levels of neuropeptide Y (NPY) in the DRG are very low. However, following PAF injury, NPY is up-regulated in small and, to a greater extent, large calibre PAFs (Hökfelt *et al.*, 1994) (Section 8.2.5). The spinal and peripheral role(s) of NPY in the modulation of nociception are highly complex (Munglani *et al.*, 1996). However, NPY appears to predominantly *decrease* nociception in the DH, yet primarily to *increase* nociception in the periphery. NPY exerts these actions via a multiplicity of 'Y' receptor types: all are negatively coupled to AC but they differentially enhance  $K^+$ -currents and reduce  $Ca^{2+}$ -currents and  $[Ca^{2+}]_i$  levels. These receptor subtypes are also differentially localized on intrinsic neurones in the DH, and on the central and peripheral terminals of PAFs and sympathetic nerves (Bromqvist and Herzog, 1997; Colmers and Bleackman, 1994; Munglani *et al.*, 1996; Sun *et al.*, 1998; Zhang *et al.*, 1994c, 1997b).

A further neuropeptide which exerts antinociceptive actions in the DH, somatostatin, is likewise negatively coupled via multiple receptor subtypes to AC and it is found principally in small calibre PAFs, independently of CGRP/SP (Carlton and Coggeshall, 1997; Kashiba *et al.*, 1996, 1997; Mollenholt *et al.*, 1990).

Corticotropin releasing factor (CRF) has been detected in capsaicin-sensitive, fine calibre PAFs in the DH, wherein it may play a role in the modulation of nociception via several different types of receptor positively coupled to AC (Coggeshall and

Carlton, 1997; Schäfer *et al.*, 1997; Skofitsch *et al.*, 1985).

For technical reasons, the demonstration of cholecystokinin (CCK) in PAFs has proven problematic and, under resting conditions, it is only weakly expressed. However, it is markedly induced by PAF injury (Hökfelt *et al.*, 1994) (Section 8.2.5). CCK interferes with antinociceptive mechanisms in the DH, possibly via an inhibition in the release of opioids and via the induction of PLC which leads to an increase in  $[Ca^{2+}]_i$  levels. In rodents, CCK<sub>B</sub> receptors, which are involved in these actions, have been detected both on intrinsic DH neurones and on the terminals of small and large calibre PAFs (Hökfelt *et al.*, 1994; Ossipov *et al.*, 1997; Stanfa *et al.*, 1994; Vanderah *et al.*, 1996a,b; Wang *et al.*, 1992; Wiertelak *et al.*, 1992a, 1994d). In primates and man, however, CCK<sub>A</sub> receptors predominate in the DH and may likewise contribute to the pronociceptive actions of CCK (Benedetti, 1997; section 9.5).

The role of galanin (GAL) is of particular interest inasmuch as it acts predominantly *pronociceptively* under normal conditions, yet *antinociceptively* following damage to PAFs (Section 8.2.5). It is found in both C and A $\beta$  fibres and exerts its effects via several receptor types. Of these, GAL<sub>1</sub> sites are coupled negatively to AC and they enhance and reduce  $Ca^{2+}$ - and  $K^+$ -currents, respectively. GAL<sub>1</sub> sites presumably mediate the antinociceptive actions of GAL on DH neurones—and, possibly, PAF terminals. In contrast, GAL<sub>2</sub> receptors are positively coupled to PLC. Small calibre DRG cells express both GAL<sub>1</sub> and GAL<sub>2</sub> receptors (Kask *et al.*, 1997; Parker *et al.*, 1995; Selve *et al.*, 1996; Shi *et al.*, 1997; Xu *et al.*, 1990; Xu *et al.*, 1996b, 1997d; Xu and Wiesenfeld-Hallin, 1997).

Vasoactive intestinal peptide (VIP) is more highly expressed in visceral than in cutaneous PAFs. Further, it is present in both small and large calibre cutaneous afferents. VIP acts pronociceptively in the DH, and this role may be accentuated subsequent to nerve injury (De Groat, 1986; Hökfelt *et al.*, 1994; Kask *et al.*, 1997; Vertongen *et al.*, 1997; Xu *et al.*, 1990) (Section 8.2.5). Pituitary adenylate cyclase activating peptide (PACAP), which is structurally related to VIP, possesses higher affinity than VIP at PACAP<sub>1</sub> receptors, and shares actions with VIP at PACAP<sub>2</sub>/VIP<sub>1</sub> and PACAP<sub>3</sub>/VIP<sub>2</sub> receptors. Various splice variants of PACAP<sub>1</sub> receptor differentially activate AC and PLC, while PACAP<sub>2</sub>/VIP<sub>1</sub> and PACAP<sub>3</sub>/VIP<sub>2</sub> receptors are positively coupled to AC (Rawlings and Hezareh, 1996). Like VIP, PACAP is detected in small calibre, capsaicin-sensitive fibres and it is an important trophic factor (Moller *et al.*, 1997a,b). PACAP can probably enhance nociception at the spinal level, though antinociceptive actions have also been reported (Xu and Wiesenfeld-Hallin, 1996; Yamamoto and Tatsuno, 1995; Zhang *et al.*, 1993c, 1996b, 1997g).

To summarize, many neuropeptides are present in small and/or large calibre PAFs innervating the DH. As discussed in Sections 7.6 and 8.2.5, respectively, their expression is subject to profound changes upon either stimulation and/or damage to PAFs. Various neuropeptides are differentially coupled via

multiple receptor types to contrasting transduction mechanisms and, correspondingly, fulfil divergent roles in the modulation of nociception. It is important to emphasize, thus, that actions of neuropeptides in PAFs do *not* exclusively enhance nociception. Further, the relationship between pronociceptive and antinociceptive species is modified by manipulations of PAFs which trigger prolonged pain. As discussed throughout this review, a 'balance' between pronociceptive and antinociceptive mechanisms may be a general feature of the processing and transfer of nociceptive information at all hierarchical levels, from the periphery via the DH to supraspinal centres. A disruption of this equilibrium may be reflected in the induction or aggravation of painful states (Section 15.1).

### 3.2.7. Putative Neurotransmitters in A $\beta$ Fibres

Activation by EAAs, such as GLU and aspartate, of AMPA receptors is likely the principal mechanism involved in the influence of A $\beta$  fibres upon intrinsic neurones in the DH (Coggeshall and Carlton, 1997; Cumberbatch *et al.*, 1994; Dickenson, 1997; Dougherty *et al.*, 1992b; Neugebauer *et al.*, 1993; Sherman and Loomis, 1996; Sherman *et al.*, 1997a,b; Xu *et al.*, 1993b). However, as mentioned above, following PAF stimulation and/or injury, the expression by A $\beta$  fibres of several neuropeptides is augmented, including NPY, GAL, CCK and, notably, SP (Höckfelt *et al.*, 1994; Willis and Coggeshall, 1991) (Section 8.2.5).

### 3.2.8. Pronociceptive Mediators in the DH Derived from PAF Terminals and Intrinsic DH Sources: Focus on ATP, NO and PGs

#### 3.2.8.1. Unconventional mediators of nociception in the DH

Recently, a role has emerged for ATP, NO and PG as potential transmitters of nociceptive information in the DH. Each of these mediators may be derived from small or large calibre PAF terminals, and the potential excitation of nocisponsive DH neurones by ATP and PG released from C fibres is a particularly intriguing possibility (Sections 3.2.8.2 and 3.2.8.4). In addition to PAF terminals, ATP, NO and PGs may also be derived from intrinsic neuronal and non-neuronal sources in the DH—in particular neurones targeted by PAFs themselves (Valtschanoff *et al.*, 1992, 1995; Stanfa *et al.*, 1996; Yaksh and Malmberg, 1994). Further, ATP, NO and PGs may all exert actions at intrinsic DH neurones, at PAF terminals and/or at non-neuronal cells.

#### 3.2.8.2. ATP

A putative role of ATP in the transmission of nociceptive input from PAF terminals onto DH neurones has attracted much recent attention. A diversity of ionotropic, metabotropic—and even cytolytic-receptor types exist for ATP (Burnstock, 1996; North and Barnard, 1997). Some years ago, ATP was reported to excite a sub-population of neurones in the DH, and to potentiate their responsiveness to NMDA (Jahr and Jessel, 1983). Such

actions likely involve excitatory, ionotropic and Ca<sup>2+</sup>-permeable receptors of the P<sub>2X</sub> family. Thus, P<sub>2X2</sub>, P<sub>2X3</sub>, P<sub>2X4</sub> and, possibly, other P<sub>2X</sub> receptor subtypes may be localized both on intrinsic neurones and on the central terminals of fine calibre, nocisponsive fibres in the DH (Collo *et al.*, 1996; Le *et al.*, 1998; Vulchanova *et al.*, 1996). A central, pronociceptive action of ATP would be analogous to its pronociceptive actions exerted via P<sub>2X2/X3</sub> receptors on the peripheral terminals of C fibres (King *et al.*, 1997b) (Section 7.4.4). Indeed, the activation of *presynaptic* P<sub>2X2</sub> receptors on the terminals of sensory neurones in the DH was recently shown to elicit the release of GLU (Gu and MacDermott, 1997). In addition, an action of ATP at G-protein coupled, metabotropic P<sub>2Y</sub> receptors activating PLC was previously indicated to enhance EAA-mediated transmission in the superficial DH (Li and Perl, 1995).

ATP is rapidly metabolized to adenosine which, like ATP, acts via a multiplicity of receptor subtypes. The role of adenosine in the modulation of nociception is complex and expressed in interaction with both opioids and monoamines. One consistent action is its ability to alleviate the mechanical allodynia associated with PAF- or CNS-injury (Section 13.2). This effect is likely mediated via A<sub>1</sub> receptors, which are negatively coupled to AC and which inhibit and enhance Ca<sup>2+</sup>- and K<sup>+</sup>-currents, respectively (Cui *et al.*, 1997b; Lee and Yaksh, 1996; Reeve and Dickenson, 1995; Salter and Henry, 1987; Sjölund *et al.*, 1996, 1998; Sollevi *et al.*, 1993; Sawynok and Sweeney, 1989; Sawynok and Reid, 1996; Yang *et al.*, 1994). The A<sub>1</sub> receptors involved in this action are probably localized on intrinsic DH neurones rather than on PAF terminals (Dickenson, 1997; Hu and Li, 1997; Sánchez-Prieto *et al.*, 1996; Sawynok and Sweeney, 1989). Indeed, A<sub>1</sub> receptor agonists inhibit C fibre/NMDA receptor-mediated sensitization of DH neurones (Dickenson, 1997; Reeve and Dickenson, 1995). The source of adenosine exerting these actions is unclear, but an intriguing possibility is that it may be derived from A $\beta$  fibres which themselves mediate mechanical allodynia (Salter and Henry, 1987) (Section 9.1.1). Based on studies in the hippocampus, A<sub>2A</sub> receptors, which are *positively* coupled to AC and PKA, may act *pronociceptively* in the DH via a postsynaptic enhancement of AMPA currents, though this remains to be directly demonstrated (Ben-Ari *et al.*, 1992; Kessey and Mogul, 1997; Salter *et al.*, 1993; Sawynok and Sweeney, 1989).

#### 3.2.8.3. NO

The intra and intercellular messenger, NO, is produced in a wide variety of cell types and exert actions both at its site of formation as well as, following extracellular diffusion and membrane penetration, at neighbouring sites. NO is generated upon the catabolism of L-arginine to L-citrulline by the enzyme, NO synthase. Several (3) isoforms of NO synthase exist, including 'neuronal' (NOS-I) and 'endothelial' forms, both of which are found in neurones and of which splice variants may exist (Dawson and Snyder, 1994; Garthwaite and Boulton, 1995; Zhang and Snyder, 1995). Neuronal

NO synthase is the major source of neuronal pools of NO. It shows *constitutive* (ongoing) activity, although its activity can also be enhanced by an increase in  $[Ca^{2+}]_i$ , triggered by, for example, stimulation of NMDA receptors. Indeed, NO may play a broad role throughout the CNS in alterations (facilitation) of synaptic efficacy mediated by NMDA receptors and other mechanisms (Brenman and Brecht, 1997; Dawson and Snyder, 1994; Hölscher, 1997; Lerea, 1997; Malen and Chapman, 1997; Stanfa *et al.*, 1996; Zhang and Snyder, 1995) (Section 10.4.2.2). Under certain conditions, such as tissue damage, non-neuronal glial and immunocompetent microglial cells may become important sources of NO and these cell types possess an *inducible* NO synthase likewise activated by  $[Ca^{2+}]_i$  and responsive to, for example, cytokines, neurotrophins and PGs (Section 4.8). NO is coupled to several intracellular transduction mechanisms, including the generation of cyclic guanine monophosphate (cGMP) which subsequently activates a specific PKG (Clementi and Meldolesi, 1997; Garthwaite and Boulton, 1995; Wang and Robinson, 1997) (Section 10.4.3.3).

In line with a pronociceptive role of NO in the DH, NO synthase is up-regulated in the DH- and DRG-under conditions of cutaneous or visceral inflammation and PAF injury, while drugs which either induce ('donors') or inhibit NO synthase, respectively, potentiate and inhibit the accompanying nociception (Herdegen *et al.*, 1993; Lam *et al.*, 1996; Meller and Gebhart, 1993; Meller *et al.*, 1992a,c; Rice, 1995b; Pandita *et al.*, 1997; Seguin *et al.*, 1995; Vergé *et al.*, 1992b; Xu and Wiesenfeld-Hallin, 1997; Wiesenfeld-Hallin *et al.*, 1993). Further, there is evidence that a C fibre-mediated induction of neuronal NO synthase is involved in the sensitization of DH neurones which underlies painful states due to inflammatory tissue damage and PAF injury (Meller and Gebhart, 1992; Seguin *et al.*, 1995; Stanfa *et al.*, 1996; Taylor *et al.*, 1995; Xu and Wiesenfeld-Hallin, 1997) (Section 10.4.2.2).

NO can exert actions intracellularly at its site of origin. It can also act as a vehicle of intercellular communication (Dawson and Snyder, 1994; Garthwaite and Boulton, 1995). Correspondingly, there are several potential mechanisms whereby NO may facilitate nociception.

1. NO may exert actions in intrinsic DH neurones transmitting nociceptive information to cerebral centres. These pools of NO are likely generated in the neurones themselves following C fibre stimulation/NMDA receptor activation and an increase in  $[Ca^{2+}]_i$ . In these DH neurones, NO plays a role in their sensitization by the generation of cGMP and the subsequent PKG-mediated phosphorylation of specific membrane-associated proteins: it also, in the longer-term, modulates gene expression (Clementi and Meldolesi, 1997; Garthwaite and Boulton, 1995; Wang and Robinson, 1997) (Section 10.4.2.5).
2. NO may increase nociception by retrogradely diffusing from sensitized DH neurones into presynaptic, fine calibre PAF terminals wherein it enhances the release GLU, SP and CGRP, poss-

ibly via a mechanism involving induction of cGMP, though this remains to be clarified (Coderre *et al.*, 1993; Coderre and Yashpal, 1994; Garry *et al.*, 1994c; Kitto *et al.*, 1992; Meller and Gebhart, 1993; Niedbala *et al.*, 1995; Sorkin, 1993). Intrinsic PAF and other pools of NO could also be involved in these actions.

3. Intrinsic and extrinsic pools of NO may modify the activity of non-neuronal glial and immune-competent cells: for example, enhancing their synthesis of PGs and cytokines (Section 4.8).

The relative importance of these mechanisms, and of PAF and other tissue sources of NO, in the modulation of nociception remains to be further clarified (Sections 4.8 and 10.4.2.2). Further, the precise role(s) of NO in the modulation of nociception are still under discussion inasmuch as NO likely exerts a multiplicity of actions upon many cell types, some of which may even lead to a *decrease* in the excitability of DH neurones transmitting nociceptive information (Clementi and Meldolesi, 1997; Dickenson, 1997; Haley *et al.*, 1992; Hoheisel *et al.*, 1995; Inoue *et al.*, 1997; Manzoni *et al.*, 1992; Miller *et al.*, 1997; Pehl and Schmid, 1997; Valtschanoff *et al.*, 1992, 1995; Xu *et al.*, 1997d; Xu and Wiesenfeld-Hallin, 1997; Wiesenfeld-Hallin *et al.*, 1993).

### 3.2.8.4. PGs

The enzyme, cyclooxygenase (COX), catalyses the synthesis of PGs from arachidonic acid, a ubiquitous component of cells which is generated from phospholipids by an action of phospholipase A<sub>2</sub> (PLA<sub>2</sub>). In analogy to NO, PGs are derived from both non-neuronal and neuronal pools and there exist several isoforms of COX. Generally-speaking, a constitutively-active COX 1 generates the physiological pools of PG required for cellular function while upon appropriate stimulation, an inducible COX 2 generates potentially huge and pathological quantities of PG. Although the COX 2 isoform identified in neurones shows some constitutive activity, its functional status can be markedly modulated by synaptic events. Notably, neuronal synthesis of PGs is accelerated via the activation of NMDA receptors and an increase in  $[Ca^{2+}]_i$  (Beiche *et al.*, 1996; Breder *et al.*, 1995; Willingale *et al.*, 1997; Yamagata *et al.*, 1993) (Section 10.4.2.3). This COX 2 isoform predominates in the spinal cord, wherein it is concentrated in several regions receiving nociceptive input: laminae I, II, and X (Section 4.1). COX 1 is also found in the DRG of PAFs (Beiche *et al.*, 1996; Willingale *et al.*, 1997).

The peripheral administration of capsaicin or exposure to inflammatory stimuli is accompanied by a rise in extracellular levels of PG in the spinal cord and by an increase in the gene expression of COX 2. However, the relative contribution of neuronal (PAF terminals and intrinsic neurones) and non-neuronal sources to increases in spinal levels of PG remains to be elucidated (Hay and Belleruche, 1997; Hingtgen and Vasko, 1994; Hingtgen *et al.*, 1995; Hua *et al.*, 1997; Ichitani *et al.*, 1997; Malmberg and Yaksh, 1995; Minami *et al.*, 1997b; Scheuren *et al.*, 1997; Willingale *et al.*, 1997; Yang *et al.*, 1996). In

line with an increase in PG activity, spinal administration of anti-inflammatory (COX-inhibiting) drugs suppresses C fibre reflexes, inhibits DH neuronal sensitization and attenuates prolonged, inflammatory pain (Beiche *et al.*, 1996; Bianchi and Panerai, 1996; Bustamante *et al.*, 1997; Herrero *et al.*, 1997; Malmberg and Yaksh, 1992; McCormack, 1994; Willingale and Grubb, 1996; Willingale *et al.*, 1997; Yamamoto and Nozaki-Taguchi, 1996, 1997). Under long-term, painful conditions, an antinociceptive action of *selective* COX 2 inhibitors has been observed, but COX 1 may *also* be involved in generating PGs when noxious stimulation is of a limited duration (Dirig *et al.*, 1997; Hammond and Gregory, 1996; Ichitani *et al.*, 1997; Yamamoto and Nozaki-Taguchi, 1996). Consistent with these findings, the spinal administration of PGs induces hyperalgesia to noxious stimuli and allodynia to innocuous, tactile stimuli (Minami *et al.*, 1997b; Taiwo and Levine, 1986).

The mechanisms underlying PG-induced nociception are unclear. One possibility is that PGs exert actions at excitatory receptors localized on intrinsic DH neurones targetted by PAF terminals (see next paragraph and Sections 7.4.3 and 7.5.2.3). A retrograde function might also be evoked whereby, following their release from PAFs or postsynaptic sites, PGs may enhance the release of GLU and SP from PAF terminals, likely via a mechanism involving an increase in levels of cAMP and an increase in  $\text{Ca}^{2+}$ - and/or  $\text{Na}^{+}$ -conductance (Ferreira and Lorenzetti, 1996; Hingtgen *et al.*, 1995; Minami *et al.*, 1997a,b; Nishihara *et al.*, 1995; White, 1996). In addition, arachidonic acid and leukotrienes, via an influence upon PKC activity in PAF terminals, may likewise retrogradely enhance GLU/SP release (Collins and Davies, 1998; Sánchez-Prieto *et al.*, 1996) (Section 10.4.2.3).

The role of multiple (G-protein coupled) prostanoïd receptors in mediating the pronociceptive actions of PGs also remains to be further clarified (Coleman *et al.*, 1994; Boie *et al.*, 1997). Notably,  $\text{PGD}_2$  and  $\text{PGI}_2$  are coupled to receptors increasing AC activity, while  $\text{PGE}_2$  is coupled to receptors increasing levels of phosphoinositides and  $[\text{Ca}^{2+}]_i$ —presumably via PLC (Coleman *et al.*, 1994; Minami *et al.*, 1997b; Mnich *et al.*, 1995; Taiwo and Levine, 1986). Of particular interest is  $\text{PGE}_2$ , which is probably the principal form of pronociceptive PG in the periphery (Sections 7.4.3 and 7.5.2).  $\text{PGE}_2$  acts via 4 receptor types coupled to the following transduction mechanisms:  $\text{EP}_1$  (elevation of  $[\text{Ca}^{2+}]_i$ );  $\text{EP}_2$  and  $\text{EP}_4$  (activation of AC) and  $\text{EP}_3$  (inhibition of AC and, possibly, generation of phosphoinositides and  $[\text{Ca}^{2+}]_i$ ) (Coleman *et al.*, 1994; Boie *et al.*, 1997). mRNA encoding  $\text{EP}_2$  receptors is concentrated in laminae I and II, while mRNA for  $\text{EP}_1$  and  $\text{EP}_3$  receptors has been found in sensory neurones (Sugimoto *et al.*, 1994; Kawamura *et al.*, 1997a). Although their relationship to multiple EP receptors is unclear, binding sites for  $\text{PGE}_2$  have been found both in the trigeminal nucleus and in superficial DH laminae (Matsumura *et al.*, 1992). This pattern of localization is consistent with putative actions of PGs at PAF terminals and/or intrinsic DH neurones in promoting nociception. While a role for *cerebral*

$\text{EP}_3$  receptors in enhancing mechanical nociception has been claimed (Oka *et al.*, 1997), the functional roles of individual EP receptor types at the level of the DH remains unclear. However, it has been suggested that  $\text{PGE}_2$  elicits allodynia via  $\text{EP}_1$  receptors and hyperalgesia via  $\text{EP}_2/\text{EP}_3$  receptors (Minami *et al.*, 1994).

As concerns the actions of various PGs, it has been suggested that  $\text{PGE}_2$  and  $\text{PGD}_2$  increase nociception via complementary GLU- and SP-mediated mechanisms, respectively. Thus,  $\text{PGE}_2$ - but not  $\text{PGD}_2$ -induced hyperalgesia is abolished in NMDA receptor knock-out mice, while  $\text{PGD}_2$ - but not  $\text{PGE}_2$ -induced hyperalgesia is blocked by the  $\text{NK}_1$  antagonist, CP 96 345 (Minami *et al.*, 1997a,b). These findings would be consistent with a role of PGs in facilitating the release of EAAs or SP from PAF terminals but require further mechanistic exploration (*vide supra*). Interestingly,  $\text{PGD}_2$  may play a more complex role in the modulation of nociception inasmuch as, apart from its intrinsic pronociceptive actions, it has been shown to *attenuate* tactile allodynia under certain conditions, possibly via an interaction with inhibitory glycinergic neurones in the DH (Minami *et al.*, 1997a) (Sections 4.6 and 10.6).

Over the longer term, for example following their induction by NMDA receptor activation, PGs likely act by modifying gene transcription in the DH. In this respect, in line with their more prominent role in the mediation of prolonged nociception (*vide supra*), it has been proposed that COX 2-derived pools of PG are principally involved (Lerea, 1997; Lerea *et al.*, 1997; Smith and De Witt, 1996).

### 3.2.8.5. Similarities in the actions of NO and PGs

To summarize, there are several intriguing similarities between NO and PGs as concerns their potential mechanisms of action in facilitating nociception in the DH. That is:

1. neuronal and non-neuronal sources;
2. multiple constitutive and inducible enzyme isoforms;
3. generation in DH neurones following stimulation of C fibres, leading to the activation of NMDA receptors and an increase in  $[\text{Ca}^{2+}]_i$  and
4. pronociceptive effects mediated both via intrinsic DH neurones and via PAF terminals.

Further, both NO and PGs modulate gene transcription in sensitized DH neurones. It is possible that the key action of NO is an intracellular role in the sensitization of DH neurones, whereas a receptor-mediated excitation of DH neurones—and PAF terminals—may be of particular importance for PGs. Thus, although the precise significance of spinal pools of NO and PGs, and their mechanisms of action, remain to be elucidated, they likely fulfil important (and interactive) roles in DH-integrated processes of sensitization underlying painful states. Further, as discussed in Sections 10.6.2 and 13.5, both NO and PGs fulfil important—but conflicting—roles in modulating degenerative processes triggered by CNS injury.

#### 4. SPINAL TARGETS OF PRIMARY AFFERENT NOCICEPTIVE INFORMATION: INTRINSIC ELEMENTS IN THE DH

##### 4.1. Laminae Organization of the DH

The grey matter of the spinal cord may be divided on a cytoarchitectonic basis into 10 laminae (Besson and Chaouch, 1987; Dubner and Bennett, 1983; Rexed, 1952; Willis and Coggeshall, 1991) (Fig. 1). Of these, laminae I (marginal layer), II (substantia gelatinosa), III and IV (nucleus proprius) and V and VI (deep layers) comprise the DH. Lamina VII corresponds to the intermediate grey matter, laminae VIII and IX comprise the medial and lateral ventral horn (VH), respectively, while lamina X is the region surrounding the canal. (It should be noted that lamina VI is clearly defined only in the lumbosacral and cervical enlargements.) The two most superficial laminae, I and II<sub>0</sub> (the outer part of lamina II), together with deeper laminae, V and VI, and lamina X, constitute those regions predominantly implicated in the reception, processing and rostral transmission of nociceptive information. Each DH lamina is organized in the horizontal plane to topographically encode the body surface. Individual cutaneous PAFs have, thus, clearly-defined, central targets and PAF input is also organized dorso-ventrally (Molander and Grant, 1986; Swett and Woolf, 1985).

Cutaneous nocisponsive C fibres project heavily to II<sub>0</sub> and, less intensely, to lamina I: they also provide a comparatively weak input to lamina V and, probably, lamina X. On the other hand, high threshold, cutaneous, nocisponsive A $\delta$  fibres terminate predominantly in lamina I, and to a sparse extent in II<sub>0</sub>: they also provide an input to laminae X. Unmyelinated, nocisponsive afferents from the viscera, joints and muscle project primarily to laminae I and V/VI. Unmyelinated, visceral afferents also innervate lamina X. There is a significant degree of convergence between input from various tissues such that individual DH neurones may be targetted by PAFs from different sources: for example, muscles and skin, or viscera and skin. As detailed in Section 9.1.4, this somatovisceral convergence onto individual DH neurones provides an anatomical basis for the phenomenon of 'referred' pain. In contrast to small calibre, nocisponsive fibres, larger, low threshold A $\beta$  fibres mediating non-nociceptive information arborize profusely in laminae III–IV, less markedly in laminae V/VI, possibly to a limited extent in laminae II<sub>i</sub> I, and do not innervate lamina II<sub>0</sub>.

At the cerebral level, the medullary caudalis nucleus of the trigeminal system ('trigeminal nucleus') fulfils a role similar to that of the spinal DH. It receives nociceptive information via the trigeminal nerve, of which the Vth cranial nerve transmits nociceptive input from the cerebral vasculature. The dilation (and inflammation) of subdural, Cerebral blood vessels (CBV)s activates the trigeminal nerve, thereby triggering the pain of migraine headache (Section 7.9).

##### 4.2. Response Characteristics of DH Neurones

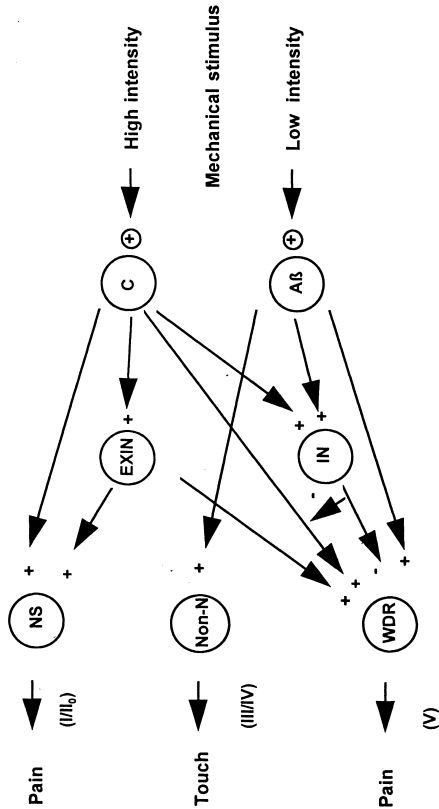
Within the DH, three basic types of neurone may be identified as concerns the nature of their response to nociceptive input (Cervero, 1995b; Dubner and Bennett, 1983; Mense, 1993; Schaible and Grubb, 1993; Willis and Coggeshall, 1991) (Figs 1 and 2). First, typically-silent, nociceptive-specific (NS) neurones which are activated exclusively by high intensity, noxious stimuli mediated by C and A $\delta$  fibres. They are most concentrated in laminae I (and II<sub>0</sub>), although they are also found in deeper laminae (V and VI). The ability of these neurones to encode stimulus intensity is limited. Secondly, multireceptorial or wide-dynamic range (WDR) neurones which manifest considerable convergence from cutaneous, muscle and visceral input (Gebhart, 1995; Mense, 1986, 1993; Ness and Gebhart, 1990). They are found predominantly in laminae V, as well as in laminae IV and VI, though they are also encountered in laminae I and II<sub>0</sub>, as well as in lamina X and the VH. 'WDR' refers to the fact that they produce a dynamic response over a broad stimulus range: that is, they manifest an incremental, stimulus-response relationship from innocuous to noxious stimulus intensities. Correspondingly, WDR neurones are the major type of DH neurone encoding stimulus intensity (Dubner *et al.*, 1989). WDR neurones are excited by thermal, mechanical and chemical stimuli mediated via both C and A $\delta$ - as well as A $\beta$ -fibres. WDR neurones in deeper laminae are most clearly implicated in C fibre-mediated processes of sensitization and amplification contributing to prolonged pain (Section 10.3). The third class of neurone is non-nociceptive (NON-N). They are found primarily in laminae II, III and IV, but a few may also occur in lamina I.

As concerns the marginal layer (I), recent studies have detected neurones responding specifically to cooling (cold), as well as polymodal units influenced by heat, pinch and cold (Dostrovsky and Craig, 1996; Zhang and Craig, 1997). These findings indicate that, in parallel to the functional diversity of various classes of PAF described in the previous paragraph (Section 3.1.1), the encoding properties of neurones in the DH may be more complex than accounted for by a simplistic NS, WDR and NON-N classification (Morgan, 1998).

##### 4.3. Receptor Fields of DH Neurones

Within the DH, all neurones possess a RF (Willis and Coggeshall, 1991). For each neurone, this corresponds to the region of skin from which stimulation increases its activity above resting levels. That is, the collective stimulation of nocisponsive PAFs within the RF region centrally summates to elicit action potentials (AP). Surrounding the RF region is a subliminal fringe from which stimulation may affect the neurone, for example, evoking EPSPs, but not sufficiently to provoke firing since a lesser, overall PAF input is recruited. For deep WDR neurones, even mild, mechanical stimuli at the epicentre of their RFs may yield APs whereas, at the periphery, only noxious stimuli trigger a response (Price *et al.*, 1978). In accordance with defined patterns of PAF

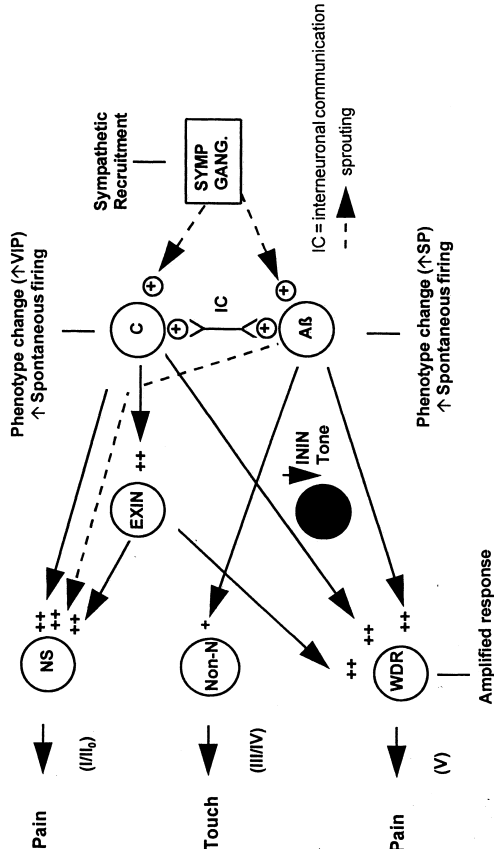
Physiological: Stimulation of PAF terminals



Physiological: Aβ (Touch), C (Pain)

← Unit response → ← Score →					
Fibre	NS	Non-N	WDR	Touch	Pain
C	++	0	+	0	+++
Aβ	0	+	0	+	0

Pathological (PAF injury): Spontaneous activity/stimulation of DRG and neuroma



Pathological: Aβ (Mechanical Allodynia), C (Hyperalgesia)

← Unit response → ← Score →					
Fibre	NS	Non-N	WDR	Touch	Pain
C	++++	0	++++	0	++++++
Aβ	++	+	++	(+)*	++++

\* Stimulus-response overshadowing likely submerges touch in a global, painful response (allodynia).

1. Descending inhibition and descending facilitation
2. Activation of injured PAFs by inflammatory substances
3. Aβ stimulation of ININs

Fig. 2. Transmission and integration of nociceptive C (Aδ), as compared to innocuous Aβ, fibre input to the DH, and its modification following peripheral nerve injury. C and Aδ fibres project predominantly to laminae II<sub>0</sub> and I, respectively. Abbreviations are as indicated in the general list. In the upper panel, the 'normal', resting situation is indicated and, in the lower panel, changes triggered by PAF injury at sensitized, nociceptive DH neurones, are illustrated. Following injury, both the DRG and the neuroma become the origin of spontaneous and stimulated discharges (Sections 8 and 11). The 'dark' ININs do not necessarily degenerate, but their functional inhibition of PNs is reduced by mechanisms described in the text (Section 10.6). There are three, additional changes which may also contribute to hyperalgesia and allodynia, but which are not illustrated for reasons of clarity: 1, a shift in the functional balance of descending controls from the inhibitory towards the excitatory; 2, an excitation of the neuroma and DRG of damaged nerves by cytokines, PGs and other inflammatory, pronociceptive substances; and 3, a loss of Aβ fibre stimulation of ININs.

input to specific DH laminae, neuronal RFs in the DH are organized into a somatotopic map whereby specific, but overlapping, populations of neurones represent specific areas of the skin (Schmidt *et al.*, 1997; Wang *et al.*, 1997c; Willis and Coggeshall, 1991). Tissue injury may be associated with an (at least transient) perturbation and expansion of the RFs of DH neurones which reflects not only an increase in peripheral input but also their sensitization by processes described in Section 10. Similarly, peripheral nerve injury can lead to the disruption, expansion and partial reorganization of the somatotopic RFs of neurones in the DH—as well as, the thalamus, cortex and other supraspinal centres (Darian-Smith and Gilbert, 1995; Koerber, 1996; Pettit and Schwark, 1996; Wilson and Kitchener, 1996; Zhang and Rowe, 1997) (Sections 10 and 12). Although the underlying mechanisms are unclear, such changes probably involve multiple processes including abnormal modes of PAF input, sensitization of DH (and supraspinal) neurones, an interference with local, inhibitory circuits in the DH and cerebral tissue and inappropriate patterns of DH innervation by regenerating, injured PAFs (Brewer and Ray, 1995; Lewin *et al.*, 1994a) (Sections 8 and 12). Somatotopic shifts in RFs may be pertinent to the phenomenon of referred pain (Section 9.1.4) and emphasize the importance of *central* processes in the response to peripheral tissue and nerve damage, a theme reiterated throughout this article (Wilson and Kitchener, 1996).

Although PAF input to the DH is predominantly ipsilateral, a small population of PAFs travel to the contralateral DH (Culberson *et al.*, 1979; Dumoulin *et al.*, 1996; Light and Perl, 1979; Sugimoto *et al.*, 1987; Sugiura *et al.*, 1986; Willis and Coggeshall, 1991). This contralateral input may also be pertinent to the phenomena of 'referred' pain and to certain *bilateral* neurochemical, morphological and functional changes provoked by *unilateral* manipulation of peripheral tissue and nerves (Section 9.1.4).

#### 4.4. Output Targets of DH Neurones

The above-discussed categories of WDS, NS and NON-N units provides one system for the classification of intrinsic DH neurones responsive to primary afferent, sensory information (Section 4.2). They may also be classed in terms of their output destination (Willis and Coggeshall, 1991). Supraspinal, that is, projection neurones (PNs); propriospinal intersegmental (and contralateral) neurones; *interlaminar*, intrasegmental interneurones (INs) and *intralaminar*, intrasegmental (local) INs (Biella *et al.*, 1997; Willis and Coggeshall, 1991). Propriospinal neurones likely play an integrative role within the spinal cord in communicating between various segments and between the ipsilateral and contralateral DH. In addition, they may be involved in initiating (and mediating) descending mechanisms of inhibition in the DH following activation by heterosegmental, noxious stimuli (Sandkühler, 1996). They may also participate in reverberatory, excited circuits implicated in DH processes of neuronal sensitization and referred pain (Sections 9.1.4.2 and 10.6.2). Nevertheless, the pre-

sent discussion focuses on the differential roles of PNs and INs.

In each case, these may comprise WDR, NS or NON-N neuronal types. Further, both PNs and INs are activated by nociceptive PAF input (Coggeshall and Carlton, 1997; Willis and Coggeshall, 1991). PNs transmitting nociceptive information supraspinally are predominantly found in laminae I and V/VI, although a few may be encountered in lamina II and X. By definition, only PNs directly transfer nociceptive information to supraspinal centres. In contrast, INs (particularly the population in lamina II) are involved in the inter- and intralaminar transfer, integration and modulation of PAF information. In this regard, INs may be sub-divided into excitatory (EXIN) and inhibitory (ININ) types. Although this subdivision is useful, it should not be forgotten that certain classes of IN interacting with intrinsic DH neurones and/or PAF terminals may be able to exert both inhibitory and/or excitatory actions, likely mediated by different receptor types.

#### 4.5. PNs and EXINs in the DH

Although PNs may be directly (monosynaptically) activated by C, A $\delta$  and A $\beta$  fibres, EXINs play a role in their indirect (polysynaptic) activation by PAF input (Fig. 2). EXINs may also mediate feedback, excitatory actions on PAF terminals. As concerns NS (and WDR) PNs in superficial laminae, many of these are *directly* targetted by A $\delta$  (I) and C fibres (II<sub>0</sub>). EXINs in lamina II<sub>0</sub>, which target NS PNs in lamina I, are also involved in their activation (Coggeshall and Carlton, 1997; Dubner and Bennett, 1983; Maxwell and Rethelyi, 1987; Price *et al.*, 1978; Ruda *et al.*, 1986; Willis and Coggeshall, 1991). Since A $\beta$  fibres do not markedly innervate laminae I and II<sub>0</sub>, it is reasonable to suppose that EXINs contribute to the influence of A $\beta$  fibres on those few WDR and NON-N neurones located therein. As regards deeper laminae, some WDR and NS neurones in lamina V receive a direct input from nociceptive C fibres attaining this region (De Koninck *et al.*, 1992). Further, some of these deeper PNs possess dendrites which project up to superficial laminae allowing for their monosynaptic activation. However, it is widely assumed that many PNs in deep laminae are *indirectly* (polysynaptically) activated by C fibres via intervening EXINs in lamina II<sub>0</sub> (Coggeshall and Carlton, 1997; Dubner and Bennett, 1983; Light and Kavookjian, 1988; Todd *et al.*, 1994b) or via processes of 'volume transmission' (Section 4.7). On the other hand, WDR and NON-N neurones of deeper laminae are directly innervated by A $\beta$  fibres. Thus, although C and A $\beta$  fibres directly target certain populations of PNs, a role of EXINs is also of importance in relaying their influence thereon.

While the transmitters involved in mediating the actions of EXINs have not been fully characterized, EAAs are likely involved. Further, many neuropeptides, such as neurotensin, VIP and SP, which have been detected in DH-localized INs, could be implicated (Coggeshall and Carlton, 1997; Dubner and Ruda, 1992; Paleckova *et al.*, 1992; Ruda *et al.*, 1986; Todd and Spike, 1993; Todd *et al.*, 1994b;

Willis and Coggeshall, 1991; Yajiri *et al.*, 1997; Yoshimura and Nishi, 1992).

Although they should not necessarily be classified as EXINs, DH-localized INs contain the pronociceptive peptide, neuropeptide FF, which counters the antinociceptive properties of opioids via actions expressed on PNs and, possibly, PAF terminals (Carlton and Coggeshall, 1997; Gouardères *et al.*, 1996, 1997). Although no changes have been detected in the levels of neuropeptide FF in the cerebrospinal fluid (CSF) of chronic pain patients (Sundblom *et al.*, 1997), DH concentrations of neuropeptide FF are increased under conditions of peripheral inflammation in rats (Gouardères *et al.*, 1996, 1997; Kontinen *et al.*, 1997). Similarly, a population of INs containing the pronociceptive peptide, CCK—which is likewise contained in descending pathways and, under certain conditions, PAFs (Sections 3.2.2, 8.2.5 and 10.8)—should be mentioned (Stanfa *et al.*, 1994; Willis and Coggeshall, 1991). In rats, an action of CCK at CCK<sub>B</sub> receptors on PAFs and/or PNs likewise counteracts opioidergic- and adrenergic-mechanisms of antinociception although, in primates and man, CCK<sub>A</sub> receptors may be involved in these actions of CCK (Benedetti, 1997). CCK may act by an interference with the ability of  $\mu$ -opioids and adrenergic agonists to decrease  $\text{Ca}^{2+}$ -currents and  $[\text{Ca}^{2+}]_i$ , thereby preventing their inhibitory influence upon neuronal excitability (Vanderah *et al.*, 1996a,b; Wang *et al.*, 1992). A decrease and increase in the activity of spinal pools of CCK may account for the enhancement and attenuation of  $\mu$ -opioidergic antinociception under conditions of inflammatory and neuropathic pain, respectively (Benedetti, 1997; Stanfa *et al.*, 1994; Vanderah *et al.*, 1996a; Xu *et al.*, 1993a,b, 1994; Xu and Wiesenfeld-Hallin, 1997) (Section 8.2.5). The pathophysiological significance of neuropeptides FF, CCK and other DH-localized, pronociceptive mediators would be of interest to explore further (Watkins *et al.*, 1997b). Further, the relative importance of PAF input and/or descending modulatory mechanisms (Section 5) in their engagement would be of interest to establish.

EXINs also represent a potential source of ATP, NO and PGs, the excitatory, pronociceptive actions of which are described in Section 3.2.8.

#### 4.6. ININs in the DH

##### 4.6.1. Actions and Neurochemical Classes of ININ

As discussed above, EXINs and PNs form a network (in series and activated by A $\delta$  and C fibres) underlying transfer of nociceptive information from PAFs to PNs and, subsequently, to supraspinal centres. ININs, by contrast, play an important modulatory role in limiting the flow of nociceptive information (Fig. 2). Although certain classes of ININ may attenuate the activity of EXINs, little direct information is available in this regard (Dubner and Ruda, 1992). Indeed, most ININs likely regulate nociceptive transmission by directly targeting WDR and NS PNs and/or the terminals of nocisponsive (and non-nocisponsive) PAFs (Hammond, 1997; Malcangio and Bowery, 1996b; Rudomin, 1990;

Schmidt, 1971; Todd and Spike, 1993; Todd *et al.*, 1996; Willis and Coggeshall, 1991). This organization offers, thus, *pre*- and *postsynaptic* mechanisms for the inhibition of nociceptive input from PAFs.

Many different, neurochemical classes of ININ have been identified and these display various patterns of neurotransmitter/neuropeptide co-localization (Coggeshall and Carlton, 1997; Dray and Urban, 1996; Hammond, 1997; Ruda *et al.*, 1986; Todd and Spike, 1993; Willis and Coggeshall, 1991). The following are of particular note inasmuch as they can exert an antinociceptive role.

1. Cholinergic ININs, which act via multiple muscarinic and—probably—nicotinic receptors localized on PAF terminals and intrinsic DH neurones (Coggeshall and Carlton, 1997; Damaj *et al.*, 1994; Höglund and Baghdoyan, 1997; Ribeiro-Da-Silva and Cuello, 1990; Sheardown *et al.*, 1997; Travagli, 1996).
2. Opioidergic ININs containing enkephalins and/or dynorphin (DYN), which exert their actions via  $\mu$ -,  $\delta$ - and/or  $\kappa$ -opioid receptors (Coggeshall and Carlton, 1997; Fields and Basbaum, 1994; Millan, 1986, 1990; Ossipov *et al.*, 1997; Todd and Spike, 1993).
3. Gamma-amino-butyric acid (GABA)ergic ININs, which act via GABA<sub>A</sub> and GABA<sub>B</sub> receptors. GABA<sub>A</sub> receptors are composed of four different sub-units organized as a pentamer to form the wall of a chloride-permeable ion channel, the activation of which usually hyperpolarizes cells. Many (> 10) heteromeric isoforms of GABA<sub>A</sub> receptor occur in the CNS. GABA<sub>B</sub> receptors are G protein-coupled. Their stimulation inhibits AC and decreases and increases  $\text{Ca}^{2+}$ - and  $\text{K}^{+}$ -currents, respectively, thereby hyperpolarizing neurones and decreasing transmitter release. Multiple GABA<sub>B</sub> subtypes may also exist (Ben-Ari *et al.*, 1997; Dirig and Yaksh, 1995; Diversé-Pierluissi *et al.*, 1997; Hammond, 1997; Kaneko and Hammond, 1997; Kaupmann *et al.*, 1997; Nadeson *et al.*, 1996; Teoh *et al.*, 1996; Valeyev *et al.*, 1996). GABAergic ININs display a varied pattern of co-localization with several other neurotransmitters involved in the modulation of nociception. Thus, one subpopulation is co-localized with acetylcholine, another with enkephalin and an additional subpopulation is co-localized with a further, major class of inhibitory neurotransmitter, glycine, which exerts its actions via strychnine-sensitize glycinergic (glycine<sub>A</sub>) receptors. Glycinergic receptors are composed of two units arranged to form the pentameric wall of a chloride-permeable ion channel, the activation of which hyperpolarizes neurones. They are predominantly postsynaptic to PAFs and several isoforms/splice variants may exist (Hammond, 1997; Kemp *et al.*, 1996; Sorkin and Puig, 1996; Todd and Spike, 1993; Todd *et al.*, 1996). The co-localization of GABA with NO synthase in a sub-population of neurons in lamina II is of note in light of the implication of NO in the modulation (primarily *facilitation*) of spinal nociception (Valtschanoff *et al.*, 1992) (Sections 3.2.8.3 and 10.4.2.2). This observation



illustrates the difficulty of ascribing an exclusively 'pro'- or 'anti'-nociceptive role to specific classes of DH neurone. Further, various classes of (non-glycinergic) GABAergic ININ may contain a diversity of neuropeptides: these include GAL/ NPY and GAL/enkephalin subpopulations (Munglani *et al.*, 1996; Simmons *et al.*, 1995; Todd and Spike, 1993). Like GABA, GAL and NPY fulfil principally antinociceptive roles in the DH (Munglani *et al.*, 1996; Xu and Wiesenfeld-Hallin, 1997) (Section 3.2.6).

ININs are themselves targeted by nocisponsive C and A $\delta$  fibres, as well as by A $\beta$  fibres (Bernardi *et al.*, 1995; Coggeshall and Carlton, 1997; Hayes and Carlton, 1992; Todd and Spike, 1993; Todd *et al.*, 1994a; Yoshimura and Nishi, 1992, 1995; Willis and Coggeshall, 1991). This suggests that C and A $\delta$  fibres exert a form of 'counter-regulatory', inhibitory feedback control upon their parallel excitation of WDR and NS PNs. Consequently, the pain elicited upon direct PN stimulation by C and A $\delta$  fibres may be limited by simultaneous activation of ININs, at least when noxious stimulation is of *short* duration and sub-maximal intensity (Fig. 2).

#### 4.6.2. A $\beta$ Fibre Activation of ININs: the Absence of Pain Upon Selective A $\beta$ Fibre Stimulation

The existence of ININs also helps provide an explanation as to why A $\beta$  fibre stimulation is *not* normally perceived as noxious.

1. Like C fibres, A $\beta$  fibres also activate a sub-population of ININs targeting WDR PNs, thereby indirectly interfering with their direct excitation of the latter. However, in *contrast* to C fibres, the activation of A $\beta$  fibres does *not* excite NS neurones in parallel, but rather *NON-N* neurones. Thus, their global influence upon DH output is qualitatively different to that of C fibres (Fig. 2).
2. The influence of selective A $\beta$  fibre stimulation upon PNs *differs* to that of C fibre activation. Fast synaptic actions triggered by A $\beta$  fibres are probably mediated by AMPA receptors which primarily gate a Na<sup>+</sup>-conductance, and rapidly desensitize. Selective activation of A $\beta$  fibres will not, thus, normally lead to a protracted excitation of WDR neurones via Ca<sup>2+</sup>-permeable NMDA receptors, and NK/CGRP/group I mGlu receptors positively coupled to AC/PLC/[Ca<sup>2+</sup>]<sub>i</sub> are quiescent (Fletcher and Lodge, 1996) (Sections 3.2.2 and 10.3). Thus, even though AMPA receptor activation engages voltage-dependent calcium channels (VDCCs), increases in [Ca<sup>2+</sup>]<sub>i</sub> remain modest and sensitization mechanisms are not initiated.
3. NMDA and AMPA receptors are, to a certain extent, expressed on different classes of neurone in the DH. Further, even where colocalized, there is increasing evidence for compartmentalization of changes in the intracellular concentrations of [Ca<sup>2+</sup>]<sub>i</sub> and other intracellular signals (Bito *et al.*, 1997; Deisseroth *et al.*, 1998; Kharazia and Weinberg, 1997; Lerea, 1997; Morris, 1997; Ottersen and Landsend, 1997; Simpson *et al.*, 1995). Thus, any limited increase in [Ca<sup>2+</sup>]<sub>i</sub> levels provoked via the activation of AMPA receptors

(and VDCCs) may be topographically separated from neuronal regions targetted by C fibre terminals and bearing NMDA receptors (Section 10.3).

To summarize, the intensity and duration of the excitation of WDR PNs neurones by A $\beta$  fibres is less pronounced than that provoked by C fibres, A $\beta$  fibres activate *NON-N* rather than NS PNs in parallel and the discrete engagement of AMPA receptors by A $\beta$  fibres does not engage intracellular processes leading to PN sensitization. Consequently, A $\beta$  and C fibre-mediated sensation is perceived as non-noxious and noxious, respectively, and the *selective* activation of A $\beta$  fibres does not sensitize PNs in the DH (Table 3) (Section 10.5).

#### 4.6.3. Consequences of a Loss of ININ Tone in the DH

When the crucial, inhibitory role of ININs in the DH fails—under conditions of nerve injury or pharmacological blockade, for example—the consequences for both A $\delta$ /C and A $\beta$  fibre-mediated transmission are serious: hyperalgesia and allodynia, respectively, due to 'escape' of sensitized WDR and NS PNs from ININ control (Fig. 2) (Dickenson, 1997; Hammond, 1997; Traub, 1997) (Section 10.6). Further, when WDR neurones in the DH are pre-excited by a persistent C fibre input, and/or a decrease in ININ tone, the superimposition of A $\beta$  fibre stimulation may be able to elicit their sensitization and aggravate hyperalgesia and allodynia (Section 10.3).

### 4.7. Novel Modes of Neuronal Communication

The above-described, differential localization in various DH laminae of the majority of C fibre terminals (II<sub>0</sub> and I) as compared to the majority of deeper laminae WDRs has led to the suggestion that, apart from the intervention of EXINs, volume transmission may play a role in the activation of PNs in deeper laminae by fine calibre PAFs conveying nociceptive input to the DH (Coggeshall and Carlton, 1997; Fuxe and Agnati, 1991; Zoli and Agnati, 1996). A role of volume transmission would also be consistent with the overall mismatch between the DH localization of SP in PAF terminals (primarily in lamina II) and NK<sub>1</sub> receptors (primarily in laminae I and, less densely, in deeper laminae IV/V/VI) (Abbadie *et al.*, 1996; Bleazard *et al.*, 1994; Coggeshall and Carlton, 1997; De Koninck *et al.*, 1992; Lawson *et al.*, 1997; Littlewood *et al.*, 1995; Liu *et al.*, 1994a; Marshall *et al.*, 1996; Sugimoto *et al.*, 1997; Valtchanoff *et al.*, 1995). Indeed, NKA and SP may spread and persist following their localized release in the DH (Duggan *et al.*, 1990). Volume transmission may, thus, be of significance in the neuropeptide-mediated transfer of nociceptive information from PAF terminals to intrinsic neurones in the DH (Coggeshall and Carlton, 1997) and to other regions of the spinal cord, such as preganglionic neurones in the intermediolateral cell column (Pollock *et al.*, 1997). Nevertheless, recent studies have indicated a certain degree of correspondence between DH patterns of

SP input on the one hand, and the dendritic arbors and nociceptive responsiveness of NMDA receptor-bearing NS and WDR cells in laminae I and IV/V, on the other. This suggests that, at least for certain neurones, SP may act close to its site of release (King *et al.*, 1997a; Mantyh *et al.*, 1997; Naim *et al.*, 1997; Weiya *et al.*, 1996).

Volume transmission should, thus, be conceived of as complementary to conventional modes of transmission for SP and other neuropeptides released from PAFs (Coggeshall and Carlton, 1997). It is *not* likely to play a major role in fast synaptic transmission mediated by EAAs at ionotropic receptors, although *extrasynaptic* actions of GLU ('spillover') at NMDA and AMPA receptors in other structures have recently attracted attention (Barbour and Häusser, 1997; Ben-Ari *et al.*, 1997; Coggeshall and Carlton, 1997; Kullmann and Asztely, 1998). Indeed, a potential role of non-synaptic, volume transmission should not be regarded as restricted to PAF input inasmuch as:

1. GABAergic ININs have been shown to non-synaptically modify the activity of certain ascending pathways (Sakatani *et al.*, 1993);
2. volume transmission may be of significance in mediating the effects of descending monoaminergic fibres (Section 5) upon DH neurones (Millan, 1997; Ridet *et al.*, 1993); and
3. opioids may also exert actions in the DH via volume transmission (Coggeshall and Carlton, 1997) (Section 10.6.2.2).

As concerns other non-conventional, putative modes of neuronal communication, a recent morphometric analysis of rat spinal cord suggested the existence of a substantial number of 'mixed' (chemical-electrical) synapses on somata and dendrites: they even appeared to predominate as concerns excitatory synapses (Rash *et al.*, 1996). This observation suggests *bi-directional* transfer of information and, if functionally-active, such 'mixed' synapses would raise fundamental questions as regards the interrelationships amongst various DH elements involving in the modulation of nociception: in particular, as regards the synchronized (bursting) activity of certain populations of sensitized DH neurones underlying painful states (Eblen-Zajjur and Sandkühler, 1997) (Sections 9.1.4.2 and 10.6). Such putative, 'bidirectional' forms of neuronal transmission might, further, be considered as analogous to 'retrograde' modes of synaptic transmission displayed by postsynaptic, DH neuronal pools of EAAs, NO and PGs at presynaptic terminals controlling their release (Sections 3.2.4 and 3.2.8).

'GAP' junctions (membrane channels allowing for direct, interneuronal passage of molecules and ions) may also play a role in the rhythmic neuronal firing engendered by a loss of ININ tone in the DH (Section 10.6). In addition, supraspinally, they may be involved in the transmission of 'cortical spreading depression' which is implicated in the genesis of migraine headaches, in particular the accompanying 'aura'. This process involves both neurones and glial cells in which waves of successive depolarization and hyperpolarization—triggered by 'stress' and ischaemic or other forms of tissue damage—descend

the cortex and, subsequently, deeper structures (Nedergaard *et al.*, 1995; Olesen and Janssen-Olesen, 1997; Peinado *et al.*, 1993; Verkhatsky and Kettenmann, 1996) (Section 7.9).

Unconventional modes of communication between damaged PAFs are discussed in Section 8.2.3.

#### 4.8. Glial and Immunocompetent Cells: Focus on Cytokines

##### 4.8.1. Glial Cells

Resident glial cells (astrocytes and oligodendrocytes) have traditionally been considered to perform an essentially homeostatic role in the CNS in offering physical support for neurones, improving synaptic efficacy, preserving tissue integrity upon CNS injury and guaranteeing an appropriate ionic and physical environment for neuronal activity (Murphy, 1993; Pfrieger and Barres, 1997; Ridet *et al.*, 1997; Vernadakis, 1996).

However, glial cells are now known to bilaterally communicate with neurones via both chemical messengers and electrotonic junctions, and they may play a more direct role in modulating neuronal transmission than previously imagined. Changes in glial and neuronal levels of  $[Ca^{2+}]_i$  appear to play a key role in this regard (Kaplan *et al.*, 1997; Pasti *et al.*, 1997; Pfrieger and Barres, 1997; Verkhatsky and Kettenmann, 1996; Nedergaard, 1994). Indeed, glial cells:

1. possess cation-permeable ion channels;
2. display multiple types of neurotransmitter receptor, including several which modulate nociceptive transmission—adrenergic, serotonergic, purinergic, GABAergic, AMPA, mGlu and glycinergic;
3. play a major role in transmitter uptake—for example, of GABA and GLU; and
4. liberate several substances which may modify nociception (Chessel *et al.*, 1997a,b; Coggeshall and Carlton, 1997; Conn and Pin, 1997; Conti *et al.*, 1997; Jalonen *et al.*, 1997; Kimelberg, 1995; Martin, 1990; Mayer *et al.*, 1997; Miller *et al.*, 1997; Smith, 1994; Sontheimer *et al.*, 1996; Steinhäuser and Gallo, 1996; Vernadakis, 1996; Vulchanova *et al.*, 1997; Winder and Conn, 1996) (see below).

Notably, GLU controls gene expression and differentiation in glial cells, while AMPA and mGlu receptors on astrocytes provoke a  $Ca^{2+}$ -dependent release of GLU and NO (Bezzi *et al.*, 1998; Steinhäuser and Gallo, 1996). Glial cells also respond to SP and additional signals, such as NO itself, by an increase in the activity of COX and the release of PGs, which provokes a further feedback increase in NO production (Bezzi *et al.*, 1998; McCormack, 1994). Both NO and PGs exert pronociceptive actions in the DH, and glial cells are an abundant source of a further pronociceptive mediator, ATP (Section 3.2.8). Consistent with the liberation of NO, PG, ATP and other potential, pronociceptive agents by glial cells, their recruitment in the DH has been implicated in mechanisms

underlying inflammatory nociception (Meller *et al.*, 1994; Watkins *et al.*, 1997a).

#### 4.8.2. Microglial Cells

The CNS contains resident, immunocompetent microglial cells, which enter tissue via blood vessels. In addition to microglial cells, following tissue damage or inflammation, immigrant macrophages, T cells and mast cells, also provide a potential source of glutamate NO, PGs, ATP and other potential mediators (Chao *et al.*, 1996; Ebadi *et al.*, 1997; Minghetti *et al.*, 1997; Minghetti and Levi, 1998; Piani *et al.*, 1991). Further, microglial cells also possess several receptor types. Although these are less well characterized than those on glial cells, the presence of multiple receptors for ATP has been reported, including both metabotropic  $P_{2Y}$  receptors as well as ionotropic  $P_{2X}$  sites (Chessel *et al.*, 1997a,b; Collo *et al.*, 1997; Heese *et al.*, 1997; Mayer *et al.*, 1997; Nörenberg *et al.*, 1997; Vulchanova *et al.*, 1997). Activation of  $P_{2X7}$  receptors promotes the formation of large, cytolytic pores which may provoke the release of cell contents (Chessel *et al.*, 1997b).

#### 4.8.3. Actions of Cytokines: Relevance to Nociception

Glial cells, microglial cells and other immunocompetent cells are all abundant sources of cytokines. Via interactions with both neurones and non-neuronal cells, cytokines can potentially modify synaptic transmission and nociception (Connor and Leonard, 1998; Ebadi *et al.*, 1997; Eder, 1997; Elmquist *et al.*, 1997; Gadiant and Otten, 1997; Merrill and Benveniste, 1996; Pan *et al.*, 1997; Watkins *et al.*, 1995, 1997a).

For example, interleukin (IL)-6 induces allodynia and hyperalgesia via actions in the DH (De Leo *et al.*, 1996) while IL-1 $\beta$  enhances the release of SP in the spinal cord (Malcangio *et al.*, 1996) and induces COX 2 expression (Newton *et al.*, 1997). Further, tissue necrosis factor  $\alpha$  (TNF $\alpha$ ) may facilitate post-synaptic, EAA-dependent ion currents (Grassi *et al.*, 1994). A potential role of cytokines in modulating nociceptive transmission and synaptic plasticity in the DH is supported by studies of other CNS structures. Thus, there is evidence that ILs contribute to cortical mechanisms of sensitization. Indeed, IL-6 has been shown to modify sensory responses in the cortex and to elicit nociception upon intracerebroventricular administration to rats via a mechanism involving PGs (Oka *et al.*, 1995; Shin *et al.*, 1997). On the other hand, central application of IL-1 $\beta$  elicits antinociception and certain other actions of cytokines may also potentially reduce nociception (Yabuuchi *et al.*, 1997). Thus, IL-1 $\beta$  enhances GABAergic transmission and suppresses, via a post-synaptic mechanism, the induction of NMDA receptor-mediated processes of amplification in the hippocampus: this phenomenon, termed 'long-term potentiation' (LTP), provides a synaptic substrate for memory formation and presents many parallels to NMDA-mediated, sensitization of DH neurones, a process underlying prolonged painful states (Bliss and Collingridge, 1993; Coogan and O'Connor,

1997; D'Arcangelo *et al.*, 1997; Heyser *et al.*, 1997; Malek-Ahmadi, 1996; Miller *et al.*, 1991; Neumann *et al.*, 1996; Tancredi *et al.*, 1990) (Sections 10.2.1 and 10.3). Levels of IL-1 $\beta$  and TNF $\alpha$  are increased in the DH following peripheral nerve damage (De Leo *et al.*, 1997). Further, it was recently shown that a further cytokine, leukaemia inhibitory factor (LIF), which plays an important role in the periphery following PAF injury (Sections 8.2.4.1 and 8.2.6.2), is upregulated in superficial DH laminae by inflammation and damage to PAFs (Thompson *et al.*, 1996, 1997).

These observations suggest that cytokines may affect nociception via the modification of NMDA receptor-mediated, and GABA receptor-modulated, processes of sensitization integrated in the DH.

#### 4.8.4. Tissue-Protective and Tissue-Destructive Actions of Cytokines

Cytokines such as LIF, TNF $\alpha$  and IL-1 $\beta$ , as well as glutamate NO, PGs, reactive oxygen species and other substances released from glia and microglial cells, modulate processes of neuronal survival, recuperation and degeneration. Their complex patterns of cytotoxic and mitogenic/regenerative actions likely involve contrasting, intracellular transduction mechanisms (Chao *et al.*, 1996; Kawamura *et al.*, 1997a,b; Minghetti and Levi, 1998; Nishio and Watanabe, 1998; Pan *et al.*, 1997; Piani *et al.*, 1991). Such mechanisms may be involved in the loss of intrinsic ININs (and other neuronal types) which occurs upon lesions to PAFs or to the CNS itself (Sections 10.6.2 and 13.4). These actions of cytokines are effected in interaction with neurotrophins and other trophic factors, the secretion and binding of which is similarly modified in glial and immunocompetent cells following injury to the CNS or PAFs (Kotzbauer *et al.*, 1996; Liedtke and Edelmann, 1996; Rubio, 1997; Sontheimer *et al.*, 1996). Indeed, an induction of growth factors (neurotrophins) in non-neuronal and neuronal cells may assist in the recovery from CNS injury (Section 13.5), and like cytokines, via the modification of synaptic transmission, neurotrophins may more directly and rapidly participate in the processing of nociceptive informations (Kotzbauer *et al.*, 1996; Liedtke and Edelmann, 1996; Rubio, 1997; Sontheimer *et al.*, 1996) (Section 14).

#### 4.8.5. Activation of Glial and Immunocompetent Cells: a Summary

To summarize, glial and immunocompetent cells in the DH, via the secretion of diverse substances, including GLU, cytokines, neurotrophins, NO, PGs and ATP, and by virtue of their interactions with both neuronal and other non-neuronal elements, likely play an important role in the functional, adaptive and organizational changes underlying pain caused by damage to the CNS itself or to events in the periphery (Vernadakis, 1996). Emphasizing the potential role of such mechanisms in the induction of neuropathic pain, peripheral nerve damage may provoke both glial and microglial hypertrophy in the DH (Kane *et al.*, 1997; Molander *et al.*, 1997). The complex and multifarious roles of glial and

immunocompetent cells in the DH (and supraspinal structures) in modulating nociception are still at an early stage of characterization, but are likely to attract increasing attention.

## 5. MODULATION OF NOCICEPTIVE PROCESSING IN THE DH BY DESCENDING INHIBITORY AND FACILITATORY PATHWAYS

### 5.1. Descending Inhibition

Descending pathways originating in the brainstem and other cerebral structures play an important role in the modulation and integration of nociceptive messages in the DH. Serotonergic, noradrenergic and, to a lesser extent, dopaminergic networks comprise major components of these descending mechanisms (Fields and Basbaum, 1994; Holstege *et al.*, 1996; Millan, 1995, 1997; Sandkühler, 1996; Willis, 1988; Yeziarski *et al.*, 1983; Zhang *et al.*, 1997f). The following general points should be emphasized.

1. In line with their assumed antinociceptive role, descending pathways modulate (generally reduce) the release of neurotransmitters from the terminals of nocisponsive PAFs (Fields and Basbaum, 1994; Millan, 1997; Travagli and Williams, 1996). Further, the activation of descending pathways inhibits nocisponsive PNs both directly, and indirectly, via the inhibition of EXINs and the excitation of ININs. These actions of descending pathways at intrinsic DH neurones—‘*post-synaptic*’ with respect to PAF terminals—are probably of the greater importance in their modulation of nociception (Fields and Basbaum, 1994; Lin *et al.*, 1994, 1996c,d; Lopez-Garcia and King, 1996; Grudt *et al.*, 1995; Millan, 1997; Peng *et al.*, 1996; Sandkühler, 1996; Willis and Coggeshall, 1991; Yang *et al.*, 1998). Certain studies have indicated that descending pathways preferentially inhibit the excitation of WDR neurones by noxious as compared to innocuous stimuli (Fields and Basbaum, 1994; Millan, 1997; Willis, 1994). There are several possible (and non-exclusive) mechanisms which might allow for such a selective interference with noxious A $\delta$  and C fibre vs innocuous A $\beta$  fibre mediated activation of WDR neurones:

1. as indicated above, descending pathways may presynaptically inhibit the release of nociceptive transmitters from A $\delta$  and C, but not A $\beta$ , fibres targeting WDR neurones;
2. descending pathways may also indirectly inhibit the activity of A $\delta$  and C vs A $\beta$  fibre terminals via the engagement of an intervening population of specific ININs (for example, GABAergic);
3. descending pathways may inhibit the activity of EXINs selectively targeted by A $\delta$  and C, but not by A $\beta$ , fibres; and
4. descending pathways may, at the level of PNs themselves, exert effects upon ionic and soluble second messenger transduction which *selectively* interfere with actions mediated by NMDA and other receptor types coupled to C

fibres. For example, via alterations in intracellular levels of  $[Ca^{2+}]_i$ , NO or the activity of various PKs (Section 10.4). Further, inasmuch as modifications in  $[Ca^{2+}]_i$  and other intracellular signals in DH neurones may be spatially restricted (Kharazia and Weinberg, 1997; Lerea, 1997; Morris, 1997; Ottersen and Landsend, 1997; Simpson *et al.*, 1995), a selective influence of descending fibres upon the excitation of WDR neurones by C (and A $\delta$ ) vs A $\beta$  fibres would be possible should terminals of C fibres and descending pathways be *contiguous*, yet those of A $\beta$  fibres topographically *separated* (Sections 4.6.2 and 10.5).

2. Several electrophysiological studies have suggested that, under certain conditions, the inhibitory influence of descending systems on WDR neurones in deeper laminae can be *non-selectively* expressed against both noxious (A $\delta$  and C fibre) input *and* innocuous (A $\beta$ ) input, in line with a direct, monosynaptic inhibition of PN excitability (Fields and Basbaum, 1994; Lin *et al.*, 1996c,d; Willis, 1994; Willis and Coggeshall, 1991). Such observations have received comparatively scant attention but appear of importance in light of the phenomenon of mechanical, A $\beta$  fibre-mediated allodynia (Section 9.1.2). Indeed, a ‘*lack of selectivity*’ might translate to an antinociceptive action of descending pathways against A $\beta$ -fibre mediated allodynia under pathological conditions. Such an inhibition of A $\beta$  fibre-mediated activity could be expressed both presynaptically at their terminals, and postsynaptically at PNs which they target. In this regard, it is of interest that the DRG of both fine calibre (A $\delta$ /C) and *large* calibre (A $\beta$ ) PAFs express mRNA encoding  $\alpha_{2A}$ -adrenoreceptors (ARs): that is, the predominant  $\alpha_2$ -AR subtype mediating the antinociceptive actions of descending adrenergic pathways in the DH (Gold *et al.*, 1997; Hunter *et al.*, 1997a; Millan, 1997, 1998; Millan *et al.*, 1994).
3. Much behavioural evidence for descending inhibition (and facilitation) is based upon reflexive, algosimetric tests involving a motor response. The underlying reflex, motor arc is *not* necessarily modulated by DH mechanisms in an identical fashion to nociceptive information ascending to cerebral centres. For example, serotonin (5-HT) may suppress reflexes triggered by noxious stimuli *without* modifying passage of this nociception information to the supraspinal level (Borszcz *et al.*, 1996; Millan, 1997; Zemlan *et al.*, 1983).
4. Although monoamines are generally considered to be the major neurotransmitters released from descending pathways, a key role of 5-HT in mediating descending inhibition has been challenged (Gao *et al.*, 1997; Millan, 1995, 1997) and centrifugal networks contain a diversity of other neurotransmitters potentially involved in the modulation of nociception. Several of these may be colocalized with serotonergic and noradrenergic pathways. In this light, acetylcholine, enkephalin and GABA, all of which are found in intrinsic ININs in the DH, deserve special mention (Section 4.6) Interestingly, evidence for

cholinergic and, possibly, GABAergic mechanisms of descending inhibition has been presented (Antal *et al.*, 1996; Arvidsson *et al.*, 1995; Jones *et al.*, 1991b; Iijima *et al.*, 1992; Maxwell *et al.*, 1996; Millan, 1997; Peng *et al.*, 1996) (Section 4.6). These observations suggest that a component of the antinociception mediated by descending pathways may be exerted via mechanisms common to ININ-mediated antinociception in the DH (Antal *et al.*, 1996; Blomqvist *et al.*, 1994; Bouaziz *et al.*, 1996; Lin *et al.*, 1994, 1996c; Lin *et al.*, 1996d; Millan, 1997; Sorkin *et al.*, 1993). Further, many neuropeptides found in PAF terminals, such as CCK and SP, are also contained in descending pathways—although primarily in the VH (Fang and Proudfoot, 1996; Millan, 1997; Nicholas *et al.*, 1992; Urban *et al.*, 1996a,b; Wu and Wessendorf, 1992; Zhuo and Gebhart, 1990; Xu and Wiesenfeld-Hallin, 1997) (Sections 3.2.2 and 3.2.6).

The existence of multiple DH pools of neurotransmitters and neuropeptides derived from different neuronal sources complicates studies of their modulation and—likely diverse-functional roles. Moreover, the above observations underpin the assertion that descending mechanisms for the modulation of nociception in the DH are by no means restricted to a 'textbook' role, whereby 5-HT and noradrenaline (NAD) reduce the release of SP or other pronociceptive transmitters from small calibre, PAF terminals.

## 5.2. Descending Facilitation

Descending pathways do *not* exclusively exert inhibitory actions in the DH. Indeed, individual transmitters may exert multiple actions in the DH as a function of the type of neurone targetted (ININ vs PN, for example) and the receptor activated (inhibitory vs excitatory serotonergic receptors, for example) (see below). Moreover, descending inhibitory and *facilitatory* pathways to the DH may even be derived from the same structure. For example, descending inhibitory and facilitatory pathways run from the medullary nucleus reticularis gigantocellularis pars alpha to WDR laminae IV/V and NS laminae I neurones, respectively (Monhemius *et al.*, 1997). Interestingly, spinal channels conveying descending facilitatory as compared to inhibitory influences to the DH from the rostroventromedial medulla may be topographically separated. (Zhuo and Gebhart, 1997). (The differential roles of various spinal channels in transmitting ascending sensory information to higher centres is outlined in Section 6.1.3) In addition, other cerebral regions, including the cortex, may be the origin of excitatory (and inhibitory) influences to the DH (Yeziarski *et al.*, 1983; Zhang *et al.*, 1996a). There is evidence that descending facilitatory mechanisms exert *excitatory* actions both on the terminals of nociceptive PAFs, as well as on intrinsic DH neurones (Almeida *et al.*, 1996; Bardin *et al.*, 1997; Grudt *et al.*, 1995; Jones, 1992; Jordan *et al.*, 1979; Millan, 1995, 1997; Urban *et al.*, 1996a,b; Urban and Gebhart, 1997; Zhuo and Gebhart, 1997). Some of these intrinsic

neurones may be ININs, but others are likely EXINs and PNs themselves. In the latter case, their activation will result in an *enhancement* of nociceptive transmission.

The roles of various DH-localized transmitters in mediating descending facilitation is still under exploration, although an involvement of DH pools of EAAs, NO and CCK is probable (Nicholas *et al.*, 1992; Sorkin *et al.*, 1993; Urban *et al.*, 1996a,b; Wiertelak *et al.*, 1994b) (Section 10.8). As concerns monoamines, there is evidence that they exert inhibitory or excitatory actions on individual DH neurones via distinct receptor subtypes differentially coupled to intracellular transduction mechanisms. For example, 5-HT<sub>1A</sub> receptors hyperpolarize cells by opening K<sup>+</sup>-channels, whereas 5-HT<sub>2</sub> and 5-HT<sub>3</sub> receptors depolarize neurones by closing K<sup>+</sup>-channels and/or opening cation-permeable ion channels/VDCCs. Further, 5-HT<sub>1A</sub> receptors are coupled negatively to AC, whereas 5-HT<sub>2A</sub> and 5-HT<sub>3</sub> receptors activate PLC (Boess and Martin, 1994; Millan, 1995) (Section 10.8). Correspondingly, where colocalized on individual neurones, 5-HT<sub>1A</sub> as compared to 5-HT<sub>2</sub>/5-HT<sub>3</sub> receptors will *oppositely* modulate nociception in the DH. Further, the activation of 5-HT<sub>1A</sub> and 5-HT<sub>2</sub>/5-HT<sub>3</sub> receptors on ININs and PNs, respectively, may result in a *facilitation* of nociception (Millan, 1995, 1997). Dopaminergic D<sub>1</sub> and D<sub>2</sub> receptors, which stimulate and inhibit AC activity, respectively, may also enhance and inhibit nociception, respectively, by actions on PNs (Millan, 1997). Finally, PN-localized excitatory  $\alpha_1$ -ARs (positively coupled to PLC) and inhibitory  $\alpha_2$ -ARs (negatively coupled to AC) may also, respectively, increase and decrease nociception (Millan, 1997). Such differential roles of multiple monoaminergic receptor types would clarify many contradictory and confusing data in the literature concerning the role of 5-HT, NAD and dopamine (DA) in the DH (Millan, 1997) (Section 10.8).

A potentiation and attenuation of descending facilitation and inhibition, respectively, may contribute to the enhancement in the sensitivity of DH neurones triggered by PAF inflammation or injury (Section 10.8). Correspondingly, the selective *inactivation* of descending *facilitatory* pathways might offer a strategy for analgesia complementary to the traditional approach of *mimicking* the activity of descending inhibitors pathways (Section 15.3).

## 6. TRANSFER OF NOCICEPTIVE INFORMATION TO SUPRASPINAL CENTRES: DISCRIMINATIVE-SENSORY AND AFFECTIVE-COGNITIVE DIMENSIONS OF PAIN

### 6.1. Ascending Nociceptive Pathways: Organization

#### 6.1.1. Ascending Pathways: Neurotransmitters and their Roles

Following integration in the DH, nociceptive information is conducted via PNs to higher centres in the brain (Almeida and Lima, 1997; Berkley and Hubscher, 1995; Bernard *et al.*, 1995; Besson and Chaouch, 1987; Besson *et al.*, 1995; Burstein *et al.*,

1990; Giesler *et al.*, 1994; Guilbaud *et al.*, 1994; Willis, 1985, 1989; Willis and Coggeshall, 1991) (Table 4). Many neurotransmitters and modulators involved in the rostral transmission of nociceptive information likely remain to be discovered. However, electrophysiological studies suggest that GLU and other EAAs, via actions at both ionotropic and mGlu receptors, are involved in the transfer of nociceptive information from the spinothalamic tract (STT) to the thalamus, and from the spinomesencephalic tract to the periaqueductal grey (PAG) (Azkue *et al.*, 1997; Eaton and Salt, 1995; Ericsson *et al.*, 1995; Jensen and Yaksh, 1992; Salt and Eaton, 1995, 1996). Further, AMPA receptors have been specifically implicated in the input of postsynaptic dorsal column (PSDC) pathways to the gracile and cuneate nuclei (Popratiloff *et al.*, 1997) (Section 6.2.3).

The presence of several excitatory neuropeptides, including SP and CCK, in supraspinal projections suggests that they may also play a role. Further, the discovery of DYN in ascending pathways is intriguing since it acts principally as an inhibitory transmitter via activation of  $\kappa$ -opioid receptors (Li *et al.*, 1996; Li *et al.*, 1997b; Millan, 1986, 1990, 1993; Ossipov *et al.*, 1997; Willis and Coggeshall, 1991). It is conceivable that DYN inhibits ININs in supraspinal centres such as the thalamus, thereby disinhibiting nocisponsive neurones and contributing to the onward flow of nociceptive information. Further, as discussed in Section 10.6.2.2, there is evidence that an allosteric interaction of DYN at (the glycinergic site of) NMDA receptors enhances their activity, offering a further mechanism whereby DYN might facilitate the passage of nociceptive information in ascending pathways. However, the possibility that DYN (or other inhibitory transmitters in ascending pathways) may *negatively* modulate the passage of nociceptive information to higher centres might be raised. In this light, it is of interest that evidence for a spino-supraspinal 'antinociceptive' pathway has been presented: this was suggested to tonically stimulate a cerebral, opioidergic mechanism facilitating descending inhibition (Gear and Levine, 1995).

Thus, in analogy to descending inhibition and facilitation, there may exist a component of *ascending antinociception* as well as *nociception*. This provides a parallel to the existence of both excitatory (pronociceptive) as well as inhibitory (antinociceptive) transmitters in PAFs innervating the DH (Section 3.2.6). Nevertheless, the overwhelming function of ascending pathways is the transmission of nociceptive information from the skin, viscera and other organs to the brain. Therein, specific relay neurones further process nociceptive information and undertake its transfer to cortical structures which, in interaction with limbic circuits, are responsible for the conscious appreciation of pain.

#### 6.1.2. Ascending Pathways: Supraspinal Targets of Nociceptive Information

The neuroanatomy and organisation of ascending pain projection pathways is highly complex (Almeida and Lima, 1997; Berkley and Hubscher,

1995; Bernard *et al.*, 1995; Besson and Chaouch, 1987; Besson *et al.*, 1995; Bullitt, 1990; Burstein *et al.*, 1990; Giesler *et al.*, 1994; Guilbaud *et al.*, 1994; Lanteri-Minet *et al.*, 1994; Willis, 1985, 1989; Willis and Coggeshall, 1991). Table 4 summarizes several of their key characteristics. Neuroanatomically-speaking, two types of ascending pathways may be recognized. These may conveniently be termed 'monosynaptic' and 'polysynaptic', respectively.

'Monosynaptic' pathways project *directly* to higher, cerebral structures and include the STT, the spinomesencephalic tract, the spinoparabrachial tracts, the spinohypothalamic tract and the spinoreticular tract. One component of the spinoreticular tract—of limited relevance herein—projects to the lateral reticular formation, a precerebellar nucleus involved in motor control. The other component projects to the medial, pontomedullary reticular formation and, therefrom, to thalamocortical circuits. The spinomesencephalic pathway is considered to possess a 'spinoannular tract' running to the PAG and a 'spinotectal' tract projecting mainly to the deep superior colliculus (Keay *et al.*, 1997; Willis and Coggeshall, 1991). A major target of the spinomesencephalic tract is the parabrachial nucleus (PBN) of the pons, a region which plays an important role in integrating the cardiovascular, autonomic and motivational response to pain (Allen and Pronych, 1997; Bernard *et al.*, 1995) (Section 6.3.5). Two specific channels running to the PBN are termed the spinoparabrachiohypothalamic and spinoparabrachioamygdaloid pathways, respectively, in accordance with the subsequent projections of two subpopulations of PBN neurones (Bernard and Besson, 1990; Bernard *et al.*, 1990, 1993, 1994, 1995; Bester *et al.*, 1997; Burstein and Potrebic, 1993; Jasmin *et al.*, 1997; Menendez *et al.*, 1996). The PBN can, thus, be accessed by *several* ascending pathways and the direct and/or indirect innervation of specific cerebral nuclei by *multiple* ascending pathways is a general rule exemplified in Table 4. Further, single neurones in the PBN may provide axons to both the thalamus and spinal cord emphasizing its integrative role in sensory transmission (Li and Mizuno, 1997; Yoshida *et al.*, 1997). The amygdala, globus pallidus/putamen (striatum of rats and lenticular nucleus of man), nucleus accumbens and septum, as well as the frontal, orbital (cingulate) and infralimbic cortex may also be directly accessed by spinal nociceptive neurones (Burstein and Potrebic, 1993; Giesler *et al.*, 1994; Jasmin *et al.*, 1997; Newman *et al.*, 1996; Willis and Coggeshall, 1991) (Section 6.3.5). Certain limbic targets of ascending nociceptive information are closely interlinked with the hypothalamus and have been referred to as a 'spinotelencephalic' projection: this appears to represent a rostral and bilateral extension of the spinohypothalamic tract, the course of which is outlined below (Section 6.1.3). Further, other collaterals from the spinohypothalamic pathway project to the thalamus (including its ventroposterior and posterior aspects) and also innervate the medulla and pons of the brainstem, sites of origin of descending, modulatory pathways (Fields and Basbaum, 1994; Giesler *et al.*, 1994; Kostarczyk *et al.*, 1997; Millan, 1997) (Section 5).

Table 4. Overview of ascending pathways transmitting nociceptive information to higher centres

Tract	Laminae of origin	Cell types	Tissue input	Ascending pathways	Principal sub-cortical targets	Somatic Organization	Axon types	Phylogenetic distribution	Possible roles
Spinothalamic tract	I II (few) IV V/VI VII/VIII LSN	NS WDR Non-N (few)	Skin Viscera Joints/muscle	Mainly VLF DLF (I, LSN) Mainly contralateral	Thalamus: VLF → VPL/VPM DLF → VPMo/VPI/MDvc Also PAG and collaterals →Reticular structures	Yes (I–IV)	Unmyelinated Small and large myelinated	All mammals Prominent in primates	Discriminative-sensory (VLF) Motivational-affective (DLF) Descending inhibition
Spinoreticular tract	I V/VI VII/VIII X (few)	NS (most) WDR Non-N (few)	Skin Viscera Muscle	Mainly VLF Mainly contralateral But ipsilateral (I–V) via dorsal columns to DRN	RF of brainstem → LRN (NPGC/NGC), medial thalamus and DRN (few)	No	Small and large myelinated	All vertebrates	Motivational-affective? Descending inhibition
Spinomesence-phalic tract	I–II IV/V VII X LSN	NS (I) WDR Non-N	Skin Viscera Joints/muscle	Mainly VLF DLF (I, LSN) Mainly contralateral	Midbrain and PAG Deep SCL, NCF and PBN Thalamus (few)	Weak	Unmyelinated Small and large myelinated	All vertebrates	Motivational-affective. Autonomic, motor
Spinoparabrachio-amygdaloid tract	I II (few)	NS	Skin Viscera Joints/muscle	DLF-LF Mainly contralateral	PBN → amygdala and stria terminalis	Yes	Unmyelinated Small, myelinated	Mammals	Motivational-affective. Autonomic
Spinoparabrachio-hypothalamic tract	I II (few)	NS	Skin Viscera Joints/muscle	DLF-LF Mainly contralateral	PBN → hypothalamus (VMH).	No	Unmyelinated Small, myelinated	Mammals	Motivational-affective. Endocrine
Spinohypothalamic (spinoencephalic) tract	I V X LSN	NS WDR Non-N (few)	Skin Viscera	VLF Mainly contralateral	Hypothalamus and thalamus. Also pons, amygdala, striatum (bilateral)	?	Unmyelinated Small, myelinated	Mammals	Sleep, autonomic and endocrine function Thermoregulation
Spinocervical tract	I (few) III/IV (most) V	WDR Non-N (most)	Skin Joints/muscle	DLF Ipsilateral—then contralateral (from LCN)	Relay LCN (C1–C3 level) →Contralateral thalamus (VPL/VMPo) and midbrain (PAG and SCL) Some LCN cells → spinal cord	Cats and monkeys Not rats	Small and large myelinated	All vertebrates Prominent in carnivores and primates	Discriminative-sensory Motivational affective Autonomic?
Postsynaptic dorsal column (ML) pathway	III–V (most) VI VII	NS WDR Non-N	Skin Viscera Joints/muscle	DF (and DLF) Ipsilateral—then contralateral (from DCN)	Relay DCN of caudate medulla: via ML → contralateral thalamus (VPL/VMPo) Also SCL and spinal cord (few)	Yes (VPL)	Small and medium myelinated	Not fish Prominent in mammals	Discriminative-sensory (VPL) Motivational-affective (VMPo)

WDR, wide-dynamic range; NS, nociceptive-specific; Non-N, non-nociceptive; CL, centrolateral; DCN, dorsal column nuclei; DF, dorsal funiculus; DLF, dorsolateral funiculus; DRN, dorsal raphe nuclei; LCN, lateral cervical nucleus; LRN, lateral reticular nucleus; LSN, lateral spinal nucleus; ML, median lemniscus; NCF, nucleus cuneiformis; MDvc, medial dorsal thalamus, ventral aspect; NPGC/NGC, nucleus (paro) gigantocellularis; PAG, periaqueductal grey; PBN, parabrachial nucleus; PO, posterior group of thalamic nuclei; RF, reticular formation; SCL, superior colliculus; VLF, ventrolateral funiculus; VMPo, ventromedial posterior thalamus; VPL/VPM, ventroposterolateral/ventroposteromedial thalamus; VPI, ventroposteroinferior thalamus and VMH, ventromedial hypothalamus. →Symbolizes subsequent, second order projections.

'Polysynaptic' pathways possess, in contrast to their monosynaptic counterparts, a relay station of second order neurones *en route* to higher centres. The two, principal polysynaptic routes are the spinocervical pathway, which projects to the lateral cervical nucleus at the C1–C3 level, and the PSDC pathway (or 'lemniscal system'), which projects to the cuneate (from thoracic and cervical segments) and gracile (from lumbosacral segments) dorsal column nuclei (DCN) of the caudal medulla. The DCN receives, in addition, a direct ascending innervation from PAFs carrying proprioceptive and normally innocuous rather than nociceptive information. It is possible that this channel plays a role in the mediation of mechanical allodynia (Al-Chaer *et al.*, 1996a; Berkley and Hubscher, 1995; Miki *et al.*, 1998). (Some spinoreticular tract neurones may also ascend in the dorsal columns.) From the lateral cervical nucleus, information runs via the cervicothalamic tract to several thalamic nuclei, including ventroposterior and posterior groups of nuclei, and via a cervicomesencephalic pathway to the midbrain, including the PAG and superior colliculus. As concerns the DCN, output neurones project via the medial lemniscus (ML) to the ventroposterior and posterior groups of nuclei of the thalamus and to the superior colliculus, while a few fibres descend the spinal cord.

Thus, there is a complex—and likely interactive—pattern of direct and indirect, multiple innervation of the thalamus, midbrain, limbic system, cortex, reticular formation and many other cerebral structures via *multiple* ascending pathways. These supraspinal regions are extensively interlinked and they also interact with mechanisms of descending modulation running to the DH (Sections 6.3.5 and 6.4).

#### 6.1.3. *Ascending Pathways: Contralateral and Ipsilateral Channels in the Spinal Cord*

The PSDC pathway occupies the dorsomedial region of spinal cord white matter and this ascending channel is referred to as the dorsal (posterior) funiculus (Hirshberg *et al.*, 1996). Some PSDC neurones access the DCN via the dorsolateral funiculus (DLF) which corresponds to the dorsolateral quadrant of the white matter. The DLF is also the major route for ascending spinocervical and, probably, spinoparabrachial pathways. Specific populations of PNs contributing to the STT and the spinomesencephalic tract may also use the DLF: in particular, STT neurones in lamina I and the lateral spinal nucleus (located within the VH). This dorsally-segregated, lamina I-derived STT pathway is sometimes referred to as the 'dorsal' STT in contrast to the 'ventral' STT which runs, together with the spinomesencephalic and spinoreticular tracts, in the ventrolateral funiculus (VLF): that is, the anterolateral quadrant of the white matter (Apkarian, 1995b) (see Section 6.2.2 for differences in cerebral targets of the dorsal/ventral STT). Within the VLF, there is a lateral organization of ascending pathways such that PNs originating in cervical and thoracic segments occupy the most medial, and PNs originating in lumbar and sacral segments, the most lateral, pos-

itions—a pattern opposite to that seen in the PSDC. In parallel to this segregation of ascending pathways, it is of interest that descending inhibitory and facilitatory pathways from the ventral rostro-medial medulla are localized in the DLF and VLF, respectively (Zhuo and Gebhart, 1997).

As concerns the three 'classical', *monosynaptic* pathways, the STT, the spinoreticular tract and the spinomesencephalic tract, their projections are predominantly *contralateral*. That is, their PNs of origin traverse the midline within the same segment or, possibly, at the level of an adjacent segment, before ascending to their cerebral targets. The spinoparabrachial pathways in the DLF are also largely contralateral. In distinction, the *polysynaptic*, spinocervical and PSDC pathways are *ipsilateral* at the spinal level. However, *subsequent* to synaptic contact with their second order neurones in the lateral cervical nucleus and the DCN, respectively, the output from these relay nuclei decussates to the contralateral brain. The spinohypothalamic pathway possibly constitutes an exception. The majority—though not all—fibres attain the hypothalamus via the contralateral VLF. However, following their hypothalamic sites of termination in diverse nuclei, collaterals pursue their course to the supraoptic decussation, at which point many make a 'U-turn' to the contralateral brain and continue to run caudally to innervate the hypothalamus itself, the thalamus, pons and limbic structures, such as the amygdala, septum and striatum (Giesler *et al.*, 1994; Giesler, 1995a,b; Li *et al.*, 1997b; Newman *et al.*, 1996). Thus, some axons appears to provide a *bilateral* innervation of the hypothalamus and thalamus while their innervation of limbic structures is ultimately ipsilateral, since they decussate both in the spinal cord before entering the VLF and again at the supraoptic level (Giesler *et al.*, 1994). Detailed quantitative descriptions of uni- and bi-, ipsi- and contralateral projections of this pathway have recently appeared (Burststein *et al.*, 1996; Kostarczyk *et al.*, 1997).

Thus, although the supraspinal receipt of nociceptive input is predominantly contralateral, there *does* exist a significant component of ipsilateral nociceptive input to cerebral structures. This is of note with respect to studies of the activation of specific cerebral regions by pain in man (Section 6.3.2).

#### 6.1.4. *Ascending Pathways: Sensory-Discriminative and Affective-Cognitive Dimensions of Pain*

For an understanding of the role of ascending pathways and supraspinal mechanisms in the modulation and experience of pain, it is imperative to distinguish between its two fundamental components, processed by distinctive, yet interconnected and interactive, circuits.

1. The sensory-discriminative: that is, the perception and detection of noxious stimuli *per se* as concerns their intensity, location, duration, temporal pattern and quality.
2. The affective-cognitive: that is, the relationship between pain and mood, the attention to and memory of pain, the capacity to cope with and tolerate pain and its rationalization (Besson *et*



*al.*, 1995; Craig, 1994, 1996; Derbyshire *et al.*, 1997; Jones and Derbyshire, 1996; Millan, 1990).

In this respect, it is possible to differentiate between the roles of particular ascending pathways—and even specific components of individual tracts. Accordingly, ascending pathways possess differing networks of connectivity to various supraspinal centres, while their PNs of origin in the DH and their target neurones in higher structures display contrasting patterns of response to noxious stimuli. In this light, then, it is necessary to take account of the ability of neurones to localize and intensity-code noxious stimuli. For example, as described in detail below (Section 6.2.2), deep laminae WDR neurones with small RFs encoding the intensity and location of cutaneous, noxious stimuli provide a major contribution to the ventral STT. This pathway densely innervates thalamic nuclei involved in the sensory-discriminative aspects of pain and possessing neurones with *similar* response properties to their DH counterparts. In distinction, NS-neurones of lamina I project—via the dorsal STT—predominantly to other thalamic nuclei concerned with the emotional-cognitive aspects of pain and similarly possessing nociceptive neurones with *less* refined stimulus-coding properties (Besson *et al.*, 1995; Craig *et al.*, 1994; Dostrovsky and Guilbaud, 1990; Lima and Coimbra, 1988; Ralston and Ralston, 1992). In analogy to the ventral STT, the spinocervical tract and a component of the PSDC pathway indirectly project, via the lateral cervical nucleus and DCN, respectively, to thalamic regions involved in the intensity-coding of noxious stimuli, suggesting that they may also play a role in the discriminative-sensory dimension of pain. On the other hand, those components of the spinocervical and PSDC pathways which project to (posterior) thalamic nuclei targeted by the dorsal STT, the spinomesencephalic tract (in particular via the PAG), the spinoreticular pathway (via thalamocortical circuits), the spinoparabrachialamygdaloid pathway and the spinohypothalamic pathway all play an important role in the affective dimension of pain (Apkarian, 1995b; Besson *et al.*, 1995; Jones and Derbyshire, 1996; Willis and Coggeshall, 1991) (Table 4).

Although it would be naive to recognise an absolute dichotomy between sensory and affective roles of individual ascending nociceptive systems, which are collectively responsible for the *overall* experience of pain (Jones and Derbyshire, 1995, 1996) (Section 6.3.7), this distinction has evident implications for the induction and treatment of clinical pain. An example is provided by the apparently multiple roles of the STT, which is still widely considered the principal route via which nociceptive information accesses the brain. Thus, a 'breakthrough' of clinical pain may be observed in patients who have undergone an apparently total anterolateral cordotomy of the VLF to interrupt the STT (Gybel and Sweet, 1989; White and Sweet, 1969). This supports the notion that the *ventral* STT—as well as the spinomesencephalic, the spinoreticular and the spinohypothalamic tracts, which also use the VLF—are *not* the only sources of nociceptive information underlying clinical pain. Indeed, it has been proposed, on

the basis of these and other observations (including imaging studies in man), that the classical ventral VLF/STT pathway may *not* be a major avenue for the induction of intractable, visceral pain (Apkarian, 1995b). This may be an overgeneralization but serves to emphasize the point that other pathways are involved in the induction of *clinical* pain. Notably, the *dorsal* component of the STT which is *spared* by VLF cordotomy (Craig *et al.*, 1994). In this regard, the potential significance of the spinoparabrachial tracts, the spinocervical tract and, in particular as concerns abdominal and pelvic visceral pain, the PSDC, should be accentuated (Al-Chaer *et al.*, 1996a, 1997a,b; Berkley and Hubscher, 1995; Bernard *et al.*, 1993, 1994, 1995; Hirshberg *et al.*, 1996; Nauta *et al.*, 1997; Willis and Coggeshall, 1991) (Table 4). Each of these ascending pathways utilizes channels *other* than the VLF and each plays an important role in the affective component of clinical pain.

Finally, a more general role has been attributed to a spinothalamocortical projection originating from both NS and other types of 'polymodal' neurone in lamina I whereby this pathway is assumed to permit 'a generalized assessment of the physiological status of the entire organism' (Craig, 1996; Zhang and Craig, 1997) (Section 4.2).

To summarize, in particular as concerns visceral (and deep somatic) clinical pain, it is arguable that *no* single pathway for the ascending passage of nociceptive information should, in principle, be considered as dominant. Dependent on the precise locus of pain, the duration and type of noxious stimulus and many other factors, multiple channels of nociceptive (and other modes of sensory) information likely converge and interact at the supraspinal level to yield the global sensation of pain (Apkarian *et al.*, 1995; Berkley, 1997; Berkley and Hubscher, 1995; Besson *et al.*, 1995; Gebhart, 1995; Hirshberg *et al.*, 1996; Watkins *et al.*, 1995; Wiertelak *et al.*, 1994c) (Section 6.3.7). This contention is further underpinned by imaging studies of patterns of cerebral activation elicited by pain (Section 6.3.2).

#### 6.1.5. Visceral Nociceptive Input to the Thalamus

When discussing the emotional and cognitive components of acute and prolonged *clinical* pain, the viscera and other deep tissues are of special pertinence. Thalamic encoding of cutaneous as compared to visceral input differs since, in accordance with the large, poorly-defined RFs of PAFs innervating the viscera and the limited ability to localize visceral pain, input from visceral tissues to the thalamus is, in general, *not* topographically organized (Cervero, 1994, 1995b; Gebhart, 1995; McMahon *et al.*, 1994). As mentioned above, the STT is *not* the only ascending pathway which conveys nociceptive information from the viscera to higher centres (Table 4). For example, the marked responsiveness of spinohypothalamic tract neurones in the DH to noxious, visceral stimulation has been underlined by several authors (Bullitt, 1990; Burstein *et al.*, 1991, 1996; Giesler, 1995a,b; Giesler *et al.*, 1994). Via projections to limbic regions, this pathway may also play an important role in the induction of pain from

the thoracic (chest) region (Katter *et al.*, 1996a,b; Newman *et al.*, 1996). The high degree of thalamic convergence of cutaneous, deep somatic and visceral information from multiple ascending pathways is in line with the presence of a substantial population of neurones responding to noxious stimulation of the viscera and the skin at both the DH and thalamic level, in particular, its ventroposterior aspect (Apkarian, 1995b; Brüggemann *et al.*, 1994; McMahon *et al.*, 1994). The interrelationship between nociceptive information arriving from various tissue regions onto a common population of thalamic neurones is an issue of obvious relevance to the phenomenon of 'referred' pain (Apkarian *et al.*, 1995) (Section 9.1.4). Although little quantitative information concerning the relative influence of somatic vs visceral input upon supraspinal neurones is available, it is of note that the induction of visceral inflammation modifies the balance of efficacy in exciting convergent neurones from the skin towards the viscera (Al-Chaer *et al.*, 1996b). Indeed, it more markedly sensitizes cells of the PSDC pathway to noxious visceral, mechanical as compared to cutaneous input (Al-Chaer *et al.*, 1997a,b).

As indicated above, recent studies suggest that the PSDC/ML system may fulfil a hitherto unsuspectedly important role in visceral pain transmission, notably from the pelvic region and abdomen. In accordance with this view, surgical myelotomy to interrupt this pathway has been used for the alleviation of pelvic pain (Berkley, 1997; Hirshberg *et al.*, 1996; Houghton *et al.*, 1997; Nauta *et al.*, 1997). Although clinical observations are, as yet, *limited*, such findings should be considered in the light of the above-mentioned reports that surgical interruption of the VLF *fails* to invariably and irreversibly eliminate clinical, visceral pain (Berkley, 1997).

Thus, the thalamus clearly receives multiple sources of visceral input: notably, via the VLF from the ventral STT, and via the dorsal funiculus/DLF and ML from the PSDC (Al-Chaer *et al.*, 1997a,b; Berkley and Hubscher, 1995; Gybels and Sweet, 1989; Hirshberg *et al.*, 1996; Katter *et al.*, 1996a,b; Vierck *et al.*, 1986; Newman *et al.*, 1996) (Table 4). It would be of interest to directly examine the comparative influence, and possibly synergistic interactions, of diverse pathways mediating visceral pain upon the activity of specific, nocisponsive units in the thalamus. A pathological disequilibrium in the flow of nociceptive and other forms of sensory information to the thalamus, PBN, solitary tract nucleus (via the parasympathetic, vagal nerve) and other supraspinal structures involved in the integration of sensory, emotional and autonomic processes may result in the overall, clinical phenomenon of visceral pain (Aylwin *et al.*, 1997; Berkley, 1997; Hubscher and Berkley, 1995; Wiertelak *et al.*, 1994c; Watkins *et al.*, 1995).

## 6.2. Cerebral Targets of Ascending Nociceptive Pathways: Functional Roles

### 6.2.1. The Key Role of the Thalamus

Table 4 indicates several of the principal cerebral sites of termination of ascending pathways for the

transmission of nociceptive information. It has long been considered that the most important pathway for the experience of 'pain' is the VLF-channelled component of the STT which innervates the thalamus and, subsequently, the postcentral gyrus of the cortex. However, as discussed herein and elsewhere (Apkarian *et al.*, 1992, 1995; Apkarian *et al.*, 1995; Berkley and Hubscher, 1995; Berkley, 1997; Besson *et al.*, 1995), this appears to be an oversimplification, in particular as concerns visceral pain and the affective-emotional dimension of prolonged, clinical pain. In line with this ostensibly predominant role of the STT, the thalamus has long been regarded as the key relay structure for the supraspinal receipt, integration and onward transfer of nociceptive information (Willis and Coggeshall, 1991; Guilbaud *et al.*, 1994). As indicated in Table 4, for motivational, cognitive, motor and autonomic aspects of pain, other direct and indirect targets of ascending nociceptive information are also of major importance. Nevertheless, the thalamus is not only targetted by the ventral SST, but also, directly and indirectly, by other tracts carrying nociceptive information (Table 4). Thus, the thalamus must still be considered as *the* crucial relay for the reception and processing of nociceptive (and other forms of sensory) information en route to the cortex (Bushnell, 1995). Indeed, the thalamus encodes information concerning the type, temporal pattern, intensity and—for cutaneous input—topographic localization of pain. Further, it interlinks with cortical and limbic structures responsible for both the sensory-discriminative and emotional dimension of pain (Section 6.3.5). The thalamus also plays an *active*, adaptive role in processing nociceptive information (Section 12.2.3). Recent experimental and clinical studies suggest that contrasting functional roles of individual thalamic nuclei should be carefully distinguished.

### 6.2.2. Contrasting Roles of Thalamic Nuclei with Respect to the Sensory-Discriminative and Affective-Cognitive Components of Pain

A discussion of the roles of various thalamic nuclei in the integration and relaying of nociceptive information is complicated by confusing terminological and species-dependent inconsistencies. Nevertheless, electrophysiological, clinical and anatomical observations, as well as metabolic studies of energy utilization, have identified several major clusters of thalamic nuclei (described herein primarily according to primate nomenclature) involved in the receipt, processing and onward transfer of nociceptive information, all of which receive an intense nociceptive input from DH neurones, in particular those in laminae I and V/VI (Apkarian, 1995a,b; Besson *et al.*, 1995; Bullitt, 1989, 1990; Bushnell, 1995; Chapman and Besson, 1997; Clément *et al.*, 1996; Coghill *et al.*, 1994; Craig, 1995; Dong and Chudler, 1995; Guilbaud *et al.*, 1994; Jones, 1985; Jones *et al.*, 1991a; Jones and Derbyshire, 1995; Price *et al.*, 1995).

1. Much of the literature refers to the 'ventrobasal complex' of the rat (e.g. Eaton and Salt, 1995; Guilbaud *et al.*, 1994), and the term 'principal

sensory nucleus' has been employed in the primate to define a key, thalamic region for the arrival and processing of nociceptive input. For many authors, the current preference is to distinguish the ventroposteriolateral (VPL) and ventroposteromedial (VPM) components of this region in primates, as well as a contiguous (though functionally distinct) area of the lateral thalamus, termed the ventroposteroinferior nucleus (VPI) (Apkarian, 1995b; Besson *et al.*, 1995; Bushnell, 1995). Whereas the ventral STT terminates primarily in the VPL/VPM, the dorsal STT appears to preferentially innervate the VPI.

2. The posterior complex of thalamic nuclei incorporates the pulvinar oralis, the posterior nucleus and the posterior division of the ventromedial nucleus (VMpo)—or posteriolateral thalamus. This region is a major site for the integration of nociceptive and thermosensory input, and its functional dysregulation has been implicated in thalamic pain (Craig *et al.*, 1994, 1996; Dostrovsky and Craig, 1996) (Section 13.4). Like the VPI, it is primarily accessed by the *dorsal* rather than ventral STT (Apkarian, 1995b; Craig *et al.*, 1996). Cortical inactivation can inhibit the response of certain thalamic neurones to noxious stimulation and it has been suggested that the posterior thalamus forms part of a reverberating, cortico-thalamo-cortical loop whereby the cortex reinforces the excitation of thalamic neurones by nociceptive input and *vice versa* (Eaton and Salt, 1995; Nothias *et al.*, 1988) (Sections 12.3 and 13.3). Further underpinning a role of the posterior thalamic region in nociceptive processing, most nocisponsive STT neurones of the sacral spinal cord terminate herein, whereas those preferentially responsive to innocuous, mechanical stimuli project predominantly to other thalamic nuclei (Katter *et al.*, 1996a).
3. The medial thalamus of the rat includes the nucleus submedialis and the nucleus parafascicularis. The primate homologue of the rat nucleus submedialis may be the ventrocaudal portion of the medial thalamus which is termed its medial dorsal (MDvc) aspect. This region, like the VMpo, receives a pronounced input from lamina I neurones of the dorsal STT (Bushnell, 1995; Dostrovsky *et al.*, 1995; Guilbaud *et al.*, 1994). The anatomically-related nucleus centralis lateralis of the intralaminar nucleus also receives a pronounced input from the STT and is interconnected with the striatum and other regions controlling attention and motor function, including the cerebellum. These links are consistent with the notion that this division of the thalamus is involved in the escape reaction to acute pain (Apkarian, 1995b; Casey *et al.*, 1996a,b; Molinari *et al.*, 1986). Interestingly, imaging studies of the cerebellum have revealed a pronounced response to noxious stimuli in man (Allen *et al.*, 1997b).
4. Lenz (1995) identified a region in the human and primate thalamus which, by virtue of its interconnections with corticolimbic structures, may play a key role in the emotional-cognitive aspects of pain. This area was—somewhat cryptically—

characterized as 'posterior-inferior to the Vc'. The 'Vc' (ventralis caudalis) corresponds, apparently, to the core region of the 'principal sensory nucleus' (VPL/VPM). This suggests that the term 'posterior-inferior to the VC' may be functionally equivalent to the VPI and posterior thalamic nuclei. Notwithstanding its nebulous localization, Lenz *et al.*, 1997 have made the interesting proposition that this region plays a key role in memorization of the affective dimension of pain.

Many neurones in the above-mentioned thalamic nuclei, which include both NS as well as WDR types, can encode and discriminate the intensity of noxious stimuli (Bushnell, 1995; Guilbaud *et al.*, 1994). However, parallel electrophysiological and psychophysical studies in primates suggest that the VPM and VPL may be the most finely-tuned in this regard and, in behavioural tests, their reversible inactivation by lidocaine markedly diminishes the ability to detect minor changes in noxious temperatures applied to the skin (Bushnell, 1995). Moreover, RFs of neurones in this region are consistently small and contralateral, as compared to the larger, less well-defined—and often bilateral-RFs for neurones in posterior thalamic nuclei. The VPM/VPL region is particularly suited, thus, to the encoding of both the intensity and location of noxious stimuli, consistent with an important sensory-discriminatory role. In distinction, neurones in the VPI, posterior group of nuclei (VMpo etc) and other thalamic regions, such as the nucleus submedialis/MDvc, may be more sensitive to attentional, cognitive and emotional states and, correspondingly, involved in the affective aspects of pain (Bushnell, 1995; Dostrovsky and Guilbaud, 1990; Lenz, 1995). This contention is underpinned by anatomical studies of the differential patterns of connectivity of these thalamic regions to specific, cortical structures (Section 6.3.3).

To summarize, then, specific thalamic nuclei play distinctive and complementary functions in integrating the sensory-discriminative (e.g. VPL/VPM) as compared to affective-cognitive (e.g. VMpo/VPI) components of pain. These divergent roles of individual regions reflect, in particular:

1. the contrasting electrical properties of their neurones (stimulus intensity-encoding and RF size);
2. differential sources of direct and indirect nociceptive input from the SST and other ascending pathways; and
3. contrasting patterns of connectivity to cortical and other supraspinal structures (Section 6.3.3).

#### 6.2.3. Neurotransmitters Involved in the Processing of Nociceptive Transmission in the Thalamus: Focus on EAAs and GABA

As mentioned above (Section 6.1.1), the precise identity of neurotransmitters involved in conveying nociceptive information via ascending pathways to the thalamus and other supraspinal structures remains unclear. Nevertheless, EAAs are implicated and they have been shown to exert a pronounced, excitatory influence upon the activity of nocisponsive neurones in the thalamus and other regions receiving nociceptive information (Aylwin *et al.*,

1997; Azkue *et al.*, 1997; Di Biasi *et al.*, 1994; Eaton and Salt, 1995; Ericsson *et al.*, 1995; Jensen and Yaksh, 1992; Salt and Eaton, 1996). In this regard, in analogy to the DH (Sections 3.2.8.3 and 10.4.2.2), NO may be involved in the activation by NMDA receptors of nocisponsive neurones in the thalamus (Do *et al.*, 1994; Kolhekar *et al.*, 1997). Studies of the VPL/VPM and posterior thalamic nuclei have suggested a predominant, and possibly cooperative, role of NMDA and mGlu receptors in mediating the influence of noxious stimuli upon thalamic neurones (Dougherty *et al.*, 1996; Eaton and Salt, 1995, 1996; Kolhekar *et al.*, 1997). Interestingly, in analogy to thalamic projections to the cortex (Section 6.3.3), reciprocal, cortical pathways to thalamic nuclei utilize EAAs acting at NMDA (and mGlu) receptors. This is consistent with the notion that a feedback action of the cortex may increase the 'gain' (amplify the response) of some nocisponsive, thalamic neurones (Eaton and Salt, 1995; Isaac *et al.*, 1997; Nothias *et al.*, 1988). A role of NMDA receptors in mediating the excitation of thalamic neurones by ascending, nociceptive input is of particular interest since, in analogy to the DH (Section 10.3), NMDA receptor-mediated processes of synaptic sensitization may contribute to the increased activity of thalamic neurones seen upon prolonged, noxious stimulation (Guilbaud *et al.*, 1994; Kolhekar *et al.*, 1997) (Section 12.3.3). Interestingly, in contrast to noxious input, *non*-noxious, sensory activation of thalamic neurones may primarily involve activation of NMDA and AMPA other than mGlu receptors (Eaton and Salt, 1995, 1996).

Providing a further analogy to neuronal mechanisms in the DH of the spinal cord (Sections 4.6 and 10.6), the thalamus is equipped with inhibitory, modulatory mechanisms in which GABAergic ININs play a prominent role. These local-circuit, GABAergic ININs constitute a substantial proportion (10–25%) of the total population of neurones in the thalamus (Ralston *et al.*, 1995; Ulrich and Huguenard, 1997) and they play a major role in setting the output properties of thalamic relay neurones. The possibility that a perturbation in the activity of GABAergic ININs contributes to thalamic pain and other painful conditions is outlined in Sections 12.3 and 13.3. (Alloway *et al.*, 1989; Kim *et al.*, 1997a; Oliveras and Montagne-Clavel, 1994; Paré *et al.*, 1991; Roberts *et al.*, 1992; Ralston *et al.*, 1995; Ulrich and Huguenard, 1997).

In analogy to actions characterized in the DH (Section 4.5), neuropeptide FF has been shown to act pronociceptively in the thalamus (Dupouy and Zajac, 1997). Indeed, a variety of other neuropeptides are also likely to be involved in the modulation and transfer of nociceptive information at the supraspinal level (Altier and Stewart, 1997a,b; Heinricher *et al.*, 1997; Morgan *et al.*, 1997; Saleh, 1997; Yasui *et al.*, 1989).

### 6.3. Thalamic Input to the Cortex: Differential Integration of Sensory-Discriminative as Compared to Affective-Cognitive Aspects of Pain

#### 6.3.1. Neurotransmitters Involved in Processing Nociceptive Information in the Cortex

There is little precise information available concerning the neurochemistry of neurones transmitting nociceptive information to the cortex and, similarly, little is known regarding the transmitters involved in the exchange of nociceptive information amongst various cortical regions. Nevertheless, the following general points should be noted.

Studies of sensory input to the somatosensory cortex, in particular the visual cortex, suggest that EAAs acting at NMDA, AMPA and group I mGlu receptors likely play a key role in the cortical transfer of nociceptive information by thalamic output neurones, which comprise the majority of neurones in the thalamus (Armstrong-James *et al.*, 1993; Castro-Alamancos and Connors, 1997; Conti and Hicks, 1996; Conti *et al.*, 1997; Gil and Amitai, 1996a,b; Isaac *et al.*, 1997; Itazawa *et al.*, 1997; Ralston *et al.*, 1995; Salt *et al.*, 1995; Vickery *et al.*, 1997; Zhou and Hablitz, 1997) (Section 14.4). The detection of COX 2 synthase in excitatory, cortical cells is of particular interest since NMDA receptors have been shown to enhance its activity in the cortex: a putative role of PGs in the cortical modulation of nociceptive transmission would, thus, be of interest to examine (Kaufmann *et al.*, 1996; Miettinen *et al.*, 1997; Vanegas *et al.*, 1997). The presence of a substantial population of GABAergic ININs in the sensory cortex, engaged by thalamo-cortical afferents and acting via GABA<sub>A</sub> and GABA<sub>B</sub> receptors, should be underlined (Castro-Alamancos and Connors, 1997; Conti and Hicks, 1996). Cytokines and neurotrophins may also, via interactions with EAAs/NMDA receptors and GABAergic transmission, be involved in the modulation of nociceptive processing in the cortex (Sections 4.8 and 14.4). The potential significance of neuropeptides in cortical transmission of nociceptive information remains to be elucidated.

Sections 12.3.3 and 13.5 discuss the potential role of cortical NMDA receptors and GABAergic transmission in adaptive processes underlying pain due to peripheral noxious input and CNS damage.

#### 6.3.2. Cortical Structures Activated by Noxious Stimulation: Patterns of Responsiveness

It has generally been considered that nociceptive information emanating from the thalamus is directed to the first, somatosensory area (S I) of the postcentral, cortical gyrus. However, more recent studies employing:

1. parallel electrophysiological and anatomical observations;
  2. metabolic and cerebral blood flow imaging techniques for the identification of tissues activated by noxious stimuli in man; and
  3. an examination of the effects of damage to various cortical structures upon nociceptive processing,
- have collectively refined our understanding of the

relationship between specific thalamic nuclei and circumscribed regions of the cortex and other sub-cortical structures.

Such studies reinforce the concept of a *differential* role of particular thalamocortical networks in the sensory-discriminative (e.g. S I) as compared to the affective-cognitive (e.g. anterior cingulate) aspects of pain (Apkarian *et al.*, 1992; Casey *et al.*, 1994; Casey and Minoshima, 1995; Coghill *et al.*, 1994; Derbyshire *et al.*, 1997; Di Piero *et al.*, 1997; Dong *et al.*, 1996; Jones *et al.*, 1991a; Jones and Derbyshire, 1995, 1996; Kenshalo and Willis, 1991; Rainville *et al.*, 1997).

The following cortical regions (defined primarily according to primate anatomy) possess nocisponsive NS and/or WDR neurones and, in imaging studies, they are consistently activated by noxious stimulation to cutaneous and other tissue regions:

1. the S I of the postcentral gyrus;
2. the somatosensory area II (S II) which occupies the (parietal) operculum in the sylvian sulcus of the lateral parietal cortex;
3. several regions of the inferior and anterior parietal cortex;
4. the insular cortex;
5. the anterior cingulate cortex; and
6. the medial prefrontal cortex (Casey and Minoshima, 1995; Casey *et al.*, 1996b; Davis *et al.*, 1997b; Derbyshire *et al.*, 1997; Jones and Derbyshire, 1995; May *et al.*, 1998; Neal *et al.*, 1990; Svensson *et al.*, 1997).

These cortical structures display a complex pattern of connections amongst themselves and they may also be interlinked *via* the thalamus or various limbic structures (Sherman and Guillery, 1996). For example, the S II is interconnected with both the S I and the insular cortex (Cavala and Goldman-Rakic, 1989; Neal *et al.*, 1990). EAAs acting at NMDA (and non-NMDA) sites are probably involved in these intracortical networks (Conti *et al.*, 1997; Gil and Amitai, 1996b; Nothias *et al.*, 1988; Salt *et al.*, 1995; Sherman and Guillery, 1996). It is possible thus, that in addition to *direct* thalamocortical projections, certain cortical structures may be *indirectly* activated via such pathways (Pons *et al.*, 1991). In this light, *temporal* features of the activation of specific, cortical regions are of importance. For example, the S I and cingulate cortex appear to be rapidly activated and may participate in the sequential activation of the prefrontal cortex, the S II and the insula cortex (Casey and Minoshima, 1995; Casey *et al.*, 1996b; Davis *et al.*, 1997b; Jones and Derbyshire, 1995; Neal *et al.*, 1990; Svensson *et al.*, 1997; Zhang *et al.*, 1996a).

In imaging studies, cortical activation is generally detected *contralaterally* to noxious stimulation—and almost exclusively so in the case of the S I region, in line with a pain-localizing, discriminative-sensory function of this region. However, some studies have reported an additional ipsilateral activation, for example, in prefrontal cortex, anterior cingulate cortex—as well as the cerebellum and thalamus (Casey and Minoshima, 1995; Casey *et al.*, 1996b; Derbyshire *et al.*, 1997; Di Piero *et al.*, 1997; Jones

and Derbyshire, 1995, 1996; May *et al.*, 1998; Svensson *et al.*, 1997; Telford *et al.*, 1996). The reasons for this are unclear, although some cortical cells show bilateral RFs and a contribution of ipsilateral pain projection pathways provides one obvious explanation (Dong *et al.*, 1994; Lenz, 1995) (Section 6.1.3., Table 4). Alternatively, the interhemispheric cortical transfer of nociceptive information might be possible via either commissural connections or the thalamus (Bramham *et al.*, 1996; Calford and Tweedale, 1990; Jones and Powell, 1969; Sherman and Guillery, 1996; Shin *et al.*, 1997; Zhang *et al.*, 1996a). Further, pain intensity is an important factor in activation patterns (Di Piero *et al.*, 1997) and it appears that intense and prolonged, repetitive stimulation is preferentially accompanied by a *bilateral* activation of the cortex. This observation implicates mechanisms of sensitization (and alterations in RFs) in response spread: indeed, a transfer of synaptic plasticity (LTP) has been documented from ipsilateral to contralateral cortex (Bramham *et al.*, 1996). In addition, emotional-cognitive factors may underlie a secondary, bilateral pattern of activation in regions, such as the cingulate and prefrontal cortex—plus interlinked thalamic nuclei, implicated in the *affective* aspects of pain (Jones and Derbyshire, 1996; Masterman and Cummings, 1997; Rainville *et al.*, 1997; Soares and Mann, 1997; Vogt *et al.*, 1996). Various types of pathological condition may be accompanied by ipsilateral and/or bilateral patterns for activation. For example, neuropathic pain has been associated with a bilateral activation of cortical structures (Casey *et al.*, 1996a; Hsieh *et al.*, 1995; Jones *et al.*, 1995; Vogt *et al.*, 1996). On the other hand, patients with unilateral cluster headaches showed a lateralized perturbation of nociceptive processing (Di Piero *et al.*, 1997).

In analogy to the thalamus, then, specific cortical regions may fulfil *contrasting* roles in the sensory-discriminative and emotional-cognitive components of pain, a contention further supported by several lines of evidence:

1. differential innervation by various thalamic nuclei;
2. the contrasting ability of neurones in various cortical regions to localize and intensity-code noxious stimuli; and
3. contrasting pattern of connectivity to subcortical limbic structures (Besson *et al.*, 1995).

These observations are considered in the following paragraphs.

### 6.3.3. Patterns of Thalamic Input to the Cortex: Relationship to Discriminative-Sensory and Cognitive-Affective Dimensions of Pain

Anatomical relationships between individual thalamic and cortical structures involved in the processing of nociception generally correlate with their mutual roles in the perception as compared to the conscious appreciation of pain (Apkarian, 1995b; Bushnell, 1995; Craig *et al.*, 1982, 1996; Coffield *et al.*, 1992; Dostrovsky *et al.*, 1995; Hsu and Shyu, 1997; Lenz, 1995; Vogt *et al.*, 1993; Rausell *et al.*, 1992a; Schmähmann and Pandya, 1990; Zhang *et al.*

*et al.*, 1997f). As concerns thalamic sources of nociceptive input to the cortex, the following points should be emphasized:

1. the VPL/VPM provides an intense input to SS I;
2. the nucleus submedius of the medial thalamus innervates the ventrolateral orbital cortex in rats—which subsequently projects to the PAG and SS I. This may be homologous to a projection from the MDvc (and nucleus parafasciculus) to the cingulate cortex in primates;
3. the VPI and intralaminar nuclei project to S II.

Further, in man, a structure ‘posterior-inferior to the Vc’ region of the thalamus, which likely incorporates the posterior thalamic nuclei, projects to the S II and the insula cortex (Lenz *et al.*, 1997) (Section 6.2.2). Apkarian (1995b) has commented on the quantitatively different input to S I vs S II regions of the cortex. For the S I, the principal source is, as indicated above, the VPL (64%) with the VPI (16%) and the posterior nuclei (VMpo) (3%) fulfilling comparatively minor roles. In contrast, the equivalent values are 18, 36 and 20%, respectively, for the S II.

The above observations imply that the distinction between the ventral STT-VPL/VPM-S I and dorsal STT-VPI/VMpo-S II divisions of the STT may, at least partially, be maintained up to the level of the cortex. The former and latter networks are, to reiterate, concerned primarily with the discriminative as compared to affective dimensions of pain. This separation, then, together with an important role of other ascending pathways in the emotional response to pain (Table 4), explains the viewpoint of certain authors that the prototypical STT/VLF pathway to the VPL/VPM of the thalamus, and therefrom to the S I, may *not* be the most important tract involved in mediating clinical pain (Apkarian, 1995b) (Section 6.1.4). As further indicated below, the above-described, differential innervation of various, cortical regions by specific thalamic nuclei has clear functional implications.

#### 6.3.4. *Contrasting Roles of Specific Cortical Regions: Encoding Properties of Nocisponsive Neurons*

Both NS and WDR neurones responsive to noxious stimuli are found in those cortical regions which respond to noxious stimulation (Section 6.3.2) and, in analogy to the thalamus and DH, a substantial degree of convergence for cutaneous and visceral noxious stimuli has been established: some neurones are even affected by other modes of sensory stimuli (Apkarian, 1995b; Dong and Chudler, 1995; Dong *et al.*, 1989, 1996; Lenz, 1995). In the thalamus, PBN, amygdala and other cerebral targets of ascending nociceptive information, the ability of nocisponsive neurones to intensity-encode nociceptive stimuli is variable (Section 6.2.2) and similar differences are found amongst nocisponsive neurones in various cortical regions (Bernard *et al.*, 1990; Bushnell, 1995; Dong *et al.*, 1989; Menendez *et al.*, 1996).

Consistent with an involvement in the sensory-discriminative aspects of pain, the S I cortex contains many WDR and NS neurones with small (contralateral) RFs encoding both the location and intensity

of noxious stimuli (Dong and Chudler, 1995; Dong *et al.*, 1989; Kenshalo and Willis, 1991). These observations correspond well with the preferential innervation of S I by the ventral STT and the VPL/VPM, the principal thalamic nuclei involved in sensory-discriminative function. Indeed, in analogy to anaesthesia of the VPL/VPM nuclei of the thalamus (Bushnell, 1995), lesions to the S I in man reduce the ability to discriminate noxious stimulus intensity but do *not* markedly alleviate clinical pain (Devinsky *et al.*, 1995; Kenshalo and Willis, 1991). Further, in analogy to the VPL region of the thalamus, many S I neurones respond to both visceral and cutaneous noxious stimuli indicating the occurrence of convergence at the cortical level, an observation of relevance to referred pain (Section 9.1.4). Interestingly, the response of WDR cells in the S I increases upon repeated, noxious, thermal stimulation of the skin, a finding indicating that sensitization mechanisms are apparent at cortical levels (Kenshalo and Isensee, 1983). This issue is discussed further in Section 12.

Other cortical regions involved in nociceptive processing do *not* necessarily display such a high fidelity of intensity-coding. For example, neurones in the inferior parietal cortex reveal large, bilateral, cutaneous RFs and less precisely encode stimulus location and intensity than those in S I (Chatrian *et al.*, 1975; Dong and Chudler, 1995; Dong *et al.*, 1994). Further, neurones in the ventrolateral orbital cortex of the rat also display large RFs incompatible with a precise localizing function (Dostrovsky *et al.*, 1995; Zhang *et al.*, 1997f). Indeed, homologous neurones in the anterior cingulate cortex of the primate may show half or whole body RFs in line with their often bilateral patterns of activation by pain (Jones and Derbyshire, 1996; Vogt *et al.*, 1993, 1996) (Section 6.3.2). This comparative inability to intensity-code and locate noxious stimuli is consistent with observations that these cortical regions receive nociceptive information from thalamic nuclei likewise less efficient in registering the sensory-discriminative aspects of pain (Section 6.2.2). Thus, to reiterate, the S II, inferior parietal, anterior cingulate, prefrontal and insular cortices likely play key roles in the affective rather than discriminative components of pain (Craig, 1995; Dong and Chudler, 1995; Coghill *et al.*, 1994; Kenshalo and Willis, 1991; Masterman and Cummings, 1997; Soares and Mann, 1997; Rainville *et al.*, 1997). Further, within the cingulate cortex itself, further subdivisions have been attributed specific functions concerning the affective, attentional and other components of the emotional-cognitive dimension of pain (Davis *et al.*, 1997b; Jones and Derbyshire, 1996).

To summarize, in parallel with the specific thalamic nuclei via which they are innervated, discrete cortical regions appear to be differentially involved in the sensory-discriminative (S I cortex) vs affective-cognitive (S II, cingulate, inferior parietal, prefrontal and insular cortex) aspects of pain.

### 6.3.5. Relationship of Cortical Structures to Limbic Regions Involved in Nociceptive Processing

The differential involvement of particular cortical (and thalamic) regions in the sensory as compared to emotional components of pain may also reflect their contrasting patterns of connectivity to diverse, limbic regions. Indeed, cortical structures possessing nociceptive neurones display an extensive pattern of reciprocal connections not only with the thalamus but also with limbic (and motor) regions such as the amygdala, striatum (lenticular nucleus of man), hypothalamus, accumbens, PBN, PAG and hippocampus (Casey and Minoshima, 1995; Casey *et al.*, 1997; Coghill *et al.*, 1994; Derbyshire *et al.*, 1997; Lenz, 1995; Jones and Derbyshire, 1995; Vogt *et al.*, 1993; Zhang *et al.*, 1997f). These structures are both involved in nociceptive processing (Table 4) and also fulfil key roles in the control of cognition and mood (Bloom and Kupfer, 1995; Craig, 1994). By virtue of their particularly extensive limbic connections, the insular cortex and the anterior cingulate cortex justify special attention (Devinsky *et al.*, 1995; Dong and Chudler, 1995; Kenshalo and Willis, 1991; Lenz, 1995; Tommerdahl *et al.*, 1996). Notably, a component of the analgesic properties of  $\mu$ -opioids may be mediated by an action in insular cortex (Burkey *et al.*, 1996). In addition, the primate cingulate cortex, together with the adjacent and interconnected prefrontal cortex region, plays a key role in the control of cognition, attention and mood (Masterman and Cummings, 1997; Millan and Gobert, 1997; Soares and Mann, 1997). Correspondingly, manipulations of the cingulate region modify nociception in rodents and in man and, of particular note, its lesioning can alleviate chronic, clinical pain (Devinsky and Luciano, 1993; Gybels and Sweet, 1989; Jones and Derbyshire, 1995; Pastoriza *et al.*, 1996; Vaccarino and Melzack, 1989; Zhang *et al.*, 1997f).

The above-mentioned limbic regions receive, both directly (e.g. the PAG and PBN) and indirectly, via the thalamus and cortex, etc, nociceptive input from the spinal cord (Table 4). Further, their lesioning and/or pharmacological modulation can modify nociception, effects which likely involve an influence upon the activity of opiodergic, monoaminergic and/or other networks therein (Altier and Stewart, 1996, 1997a,b; Dong and Chudler, 1995; McKenna and Melzack, 1994; Vaccarino and Melzack, 1992). Although the lenticular nucleus (striatum) is not generally associated with nociception and pain, is of particular interest since:

1. it is contralaterally activated by noxious stimulation in man (Casey and Minoshima, 1995);
2. it receives direct input from spinal nociceptive—including visceral—PNs (Cliffer *et al.*, 1991; Giesler *et al.*, 1994; Giesler, 1995a; Giesler, 1995b; Newman *et al.*, 1996) and
3. a perturbation of its function may be associated with pain in Parkinson's disease (Boivie and Östeberg, 1995; Dong and Chudler, 1995).

The PAG is also of especial interest. This region is:

1. excited by noxious stimulation from visceral and other organs;

2. receives a pronounced input from the anterior cingulate in primates (and ventro-orbital cortex in the rat);
3. plays a pivotal role in integrating behavioural and autonomic responses to pain; and
4. is of key importance in the modulation of mood, especially the response to aversive stimulation (Clément *et al.*, 1996; Dostrovsky *et al.*, 1995; Graeff *et al.*, 1993; Jones and Derbyshire, 1996; Zhang *et al.*, 1997f).

Further, the PAG comprises a major site for the polysynaptic activation of descending, inhibitory pathways to the DH (Basbaum and Fields, 1984; Fields and Basbaum, 1994; Le Bars, 1988; Millan, 1986, 1990, 1993, 1997).

Thus, although the precise, functional inter-relationships between the limbic system, the thalamus and the cortex require further clarification, processes integrated in cortical and limbic structures are likely of crucial significance as concerns the cognitive and affective aspects of pain and its modulation. In this regard, monoaminergic and opiodergic systems are of particular relevance and demand a brief digression.

### 6.3.6. Pain and Mood: Focus on Monoamines and Opioids

As indicated above, several limbic and cortical regions targetted by ascending nociceptive information play key roles in the regulation of mood, and specifically in the induction of anxious (amygdala, hippocampus and PAG) and depressive (nucleus accumbens, septum, cingulate cortex and frontal cortex) states (Bloom and Kupfer, 1995; Graeff *et al.*, 1993; Masterman and Cummings, 1997; Millan and Gobert, 1997; Noel and Gratton, 1995; Soares and Mann, 1997). In this light, the reciprocal relationship between mood and pain deserves accentuation. For example, anxiety often accompanies, and may intensify, the sensation of pain in response to an acute, noxious stimuli. On the other hand, in experimental models of 'conditioned fear', the anticipation of noxious stimulation may be sufficient to engage opiodergic mechanisms of antinociception: these fulfil an adaptive role in preparing and protecting the organism under conflict situations (Millan, 1986; Watkins *et al.*, 1994, 1997b; Wiertelak *et al.*, 1992b) (Section 2). Chronic pain states are frequently comorbid with, and exacerbated by, depression. However, the question of whether the efficacy of antidepressant agents in treating chronic pain reflects their intrinsic antidepressant properties, or the activation of antinociceptive mechanisms, is still under discussion (Abrams, 1996; Craig, 1994; DelleMijn and Fields, 1994; Eschaler *et al.*, 1994; Millan, 1997; Romano and Turner, 1985; Ruoff, 1996). The distortion and erroneous processing of noxious and other forms of sensory information in psychiatric and geriatric patients is also well-known, while the rewarding properties of drugs may be modified under painful conditions (Suzuki *et al.*, 1996).

Both the thalamus, as well as diverse regions of the cortex and limbic system involved in the integration of nociceptive information, possess an

intense monoaminergic input and a crucial role of monoaminergic mechanisms in the modulation of mood and cognition is well-established (Bloom and Kupfer, 1995; Millan and Gobert, 1997; Oke *et al.*, 1997). For example, the anxiolytic properties of  $\alpha_2$ -AR agonists—which reduce adrenergic transmission via actions at  $\alpha_{2A}$ -autoreceptors—are of importance to their clinical utility in the induction of anaesthesia (Hayashi and Maze, 1993; Millan, 1997). An impressive illustration of the importance of mood in the experience and relief of pain is provided by  $\mu$ -opioid agonists, such as morphine. It has been suggested that the euphorogenic, mood-improving properties of morphine are fundamental to the unique quality of pain relief which it affords (Franklin, 1989; Millan, 1990). Indeed, a component of the analgesic actions of  $\mu$ -opioids may be directly expressed in limbic and cortical structures (Burkey *et al.*, 1996; Franklin, 1989). Contrariwise,  $\kappa$ -opioid agonists, which exert a negative impact upon mood (dysphoria), may not, despite their spinal antinociceptive actions, be able to engender equivalent pain relief (Millan, 1990) (Section 15.2). Such differential, affective actions of  $\mu$ - vs  $\kappa$ -opioid agonists involve a contrasting facilitation and diminution, respectively, of the activity of mesolimbic dopaminergic pathways: this projection plays a pivotal, prohedonic role in processes of positive reinforcement (Altier and Stewart, 1997a; Di Chiara and Imperato, 1988; Millan, 1990; Noel and Gratton, 1995; Xi *et al.*, 1998). Moreover, mesolimbic dopaminergic pathways originating in the ventro tegmental area are themselves activated by noxious stimulation and have been speculated to comprise an endogenous 'pain-suppression' system (Ma *et al.*, 1993). Interestingly, in addition to  $\mu$ -opioids, this projection is activated by an action of SP at NK<sub>1</sub> receptors—despite their opposite, pronociceptive role in the periphery and DH (Altier and Stewart, 1997b) (Sections 7.4.9 and 10.3). Other structures, such as the PBN, may also be involved in nociceptive processing, the control of mood and opioidergic mechanisms of reward (Bernard *et al.*, 1994, 1995; Moufid-Bellancourt *et al.*, 1996).

A positive and negative impact upon mood may, thus, respectively, attenuate and intensify the global sensation of pain. A further exploration of the interrelationships between nociceptive processing in corticolimbic regions and the roles of monoaminergic, opioidergic and other systems in the control of mood and cognition should yield important insights into mechanisms underlying the induction and management of clinical pain.

### 6.3.7. *Sensory-Discriminative and Emotional-Cognitive Dimensions of Pain: a Summary of Complementary Roles*

To summarize, then, it is reasonable to distinguish several circuits fulfilling contrasting and complementary roles in the detection and appreciation of pain (Berkley, 1997; Craig, 1994; Vogt and Gabriel, 1993) (Table 4). Certain of these, including the VPL/VPM-S I link, which receives a major input from the ventral STT via the VLF, play a decisive role in gauging the intensity, and determining the lo-

cation, of noxious stimuli (Kenshalo and Willis, 1991). This sensory-discriminatory component of nociception/pain is likely of adaptive value in triggering evasive action to a threatening noxious stimulus in the comparative absence of modulation by emotional and cognitive factors (Section 2.1). On the other hand, regions involved in the emotional-cognitive aspects of pain, such as the cingulate, prefrontal and insular cortices, receive a major input from the dorsal STT (and PSDC) via the VPI/VMpo and medial thalamus: they possess an extensive network of connections with other cortical and limbic regions involved in the control of pain, mood, cognition and attention. Certain of these structures, such as the amygdala, the PAG, the PBN and the lenticular nucleus, also receive nociceptive input from ascending pathways other than the ventral STT (Table 4). These circuits implicated in the affective dimension of pain will both influence, *and* be influenced *by*, emotional and cognitive factors. Rather than the detection of noxious stimuli *per se*, such circuits are of particular relevance to the ability to rationalize, cope with and tolerate pain, in particular long-term, clinical pain of diverse origins (Table 3). These structures are thus intimately associated with mood changes reflecting and modifying pain. The ability of  $\mu$ -opioids to relieve pain (as echoed in the familiar anecdote, 'I can still feel it but it doesn't bother me any more') may be principally related to a modulation of their activity (Franklin, 1989; Millan, 1990).

Nevertheless, it would be simplistic to impose an absolute dissociation between the sensory-discriminative and emotional-cognitive dimensions of pain. These aspects should be regarded as complementary and as operating reciprocally and interactively rather than independently. Further, a 'pain centre' or 'pain centres' may not, as such, exist. Rather, a matrix of cerebral structures and multiple, parallel thalamocorticolimbic networks synergistically contributes to the global experience of pain (Apkarian, 1995b; Berkley, 1997; Coghill *et al.*, 1994; Crick and Koch, 1998; Derbyshire *et al.*, 1997; Dong *et al.*, 1994; Parker *et al.*, 1998; Xu *et al.*, 1997b). Illustrative of this point, removal of the S I does not abolish clinical pain, an observation analogous to the recurrence of clinical pain despite surgical elimination of the VLF (Devinsky *et al.*, 1995; Kenshalo and Willis, 1991) (Section 6.1.5). Precisely which supraspinal elements require manipulation for the selective alleviation of clinical pain, and how to achieve this, will require further evaluation. It is *unlikely* that the inactivation of any *single* component would suffice. Indeed, in line with the above assertion, recent imaging studies in man (Xu *et al.*, 1997b) have indicated that pain involves complex neural networks (a 'neuromatrix') with a limited somatotopic organisation, implying that neurosurgical interventions in specific regions are unlikely to achieve complete and broad-based pain relief (Sections 6.1.5, 6.3.7 and 15.1).



#### 6.4. Modulation of Descending Pathways by Ascending, Nociceptive Information

The roles of descending pathways to the DH are not the major subject of this review (Sections 5 and 10.8). Nevertheless, it should be noted that nociceptive input to the brain exerts a pronounced influence upon the activity of centrifugal pathways projecting to the DH of the spinal cord. This influence is expressed both directly and indirectly via complex circuits and mechanisms outlined above. For example, via a supraspinal loop, localized noxious, cutaneous stimulation can activate heterotropic mechanisms of descending inhibition which elicit a generalized antinociception in tissues innervated by other spinal segments. Such observations, which have been assimilated into the notion of 'diffuse noxious inhibitory controls' and various other conceptual models, are of relevance to 'referred' changes in nociception seen in tissue regions distinct from the site of noxious stimulation (Basbaum and Fields, 1984; Fields and Basbaum, 1994; Le Bars, 1988; Millan, 1997) (Sections 9.1.4.2 and 10.8). In the present context, it is of pertinence that the inactivation of descending inhibition, or the engagement of descending facilitation, may *enhance* the onward flow of nociceptive information to the brain (Section 10.8). Further, the existence of supraspinal loops triggered by noxious input underpins the potential importance of above-described, cerebrally-integrated events in modulating nociception at the level of the DH. Inasmuch as DH mechanisms can modulate activity in PAFs (Section 9.1.4.2), further, the activation of descending pathways by supraspinal nociceptive information completes a complex and extensive circuit whereby, at least theoretically, activity in nocisponsive PAFs might, via the DH, ascending pathways, supraspinal processes of integration, descending pathways and secondary DH mechanisms ultimately lead to an alteration in their own activity and/or that of other PAFs.

Thus, via modulation of mechanisms of descending inhibition and facilitation, nociceptive messages arriving in the brain may negatively or positively modify the subsequent access of nociceptive information to ascending pathways and cerebral structures (Section 10.8).

### 7. NOCICEPTIVE, INFLAMMATORY PAIN: PERIPHERAL PROCESSES

#### 7.1. Nociceptive Pain Associated with Inflammation and Tissue Damage

Cutaneous tissue damage provoked by chemical irritants (such as capsaicin), heat injury, local electrical stimulation or, in some cases, dermatological disease, is associated with two principal zones of pain (Aloe *et al.*, 1997; Bessou and Perl, 1969; Davis *et al.*, 1993b; Hardy *et al.*, 1950; Lewis, 1942; Raja *et al.*, 1984; Simone *et al.*, 1989a,b, 1991; Treede *et al.*, 1992b). The first, termed the zone of 'primary' hyperalgesia, comprises the region of tissue damage itself and is characterized by spontaneous pain and an increased sensitivity to heat, mechanical (and chemical) stimuli. Surrounding this area is the unda-

maged zone of 'secondary' hyperalgesia which displays an increase in sensitivity to mechanical but *not* heat stimuli, and which may also manifest supersensitivity to cold stimuli. An increase in sensitivity implies a decrease in the stimulus threshold required to provoke a response, and an exaggerated response to a suprathreshold stimulus. Such changes are accompanied—though not invariably—by spontaneous pain (Bessou and Perl, 1969; Kilo *et al.*, 1994). Primary hyperalgesia may involve a contribution of processes integrated in the CNS, but can predominantly be explained by events occurring at the level of peripheral nociceptors themselves. On the other hand, secondary hyperalgesia (and the phenomenon of mechanical allodynia in general) can predominantly be attributed to *central* mechanisms and is discussed in Section 9.

#### 7.2. Primary Hyperalgesia: Thermal and Mechanical Hypersensitivity

As mentioned above, the primary hyperalgesia which accompanies tissue damage is characterized by a displacement of thermal and mechanical stimulus-response curves to the left (decreased threshold), an increased maximal effect of suprathreshold stimuli and tonic, stimulus-independent pain. This increased responsiveness to *heat* stimuli appears to involve an enhanced sensitivity of *individual*, peripheral nociceptors and can also be seen in human skin (Dray and Urban, 1996; Reeh *et al.*, 1986, 1987; Torebjörk *et al.*, 1984; Treede and Magerl, 1995; Treede *et al.*, 1992b). The class of nociceptor implicated appears to depend upon stimulus intensity and/or the type of skin, whether non-hairy (glabrous) or hairy. In the latter case, selective blockade of A fibres does not modify the time-course of sensitization suggesting that polymodal C fibres are primarily responsible (LaMotte *et al.*, 1982; Treede *et al.*, 1992b). In contrast, in non-hairy skin, the responsiveness of polymodal C fibres may even be diminished, whereas high threshold, 'Type I', mechanosensitive A $\delta$  fibres may develop an increased sensitivity to heat. This suggests that the latter are predominantly involved. In line with this argument, their blockade can block hyperalgesia to heat in non-hairy skin (Meyer and Campbell, 1981; Meyer *et al.*, 1994; Treede *et al.*, 1992b). The respective roles of C and A $\delta$  fibres require, thus, further characterization (Section 3.1.1). At the molecular level, there may exist multiple classes of nociceptor responsive to heat, including a recently-cloned vanilloid receptor (Caterina *et al.*, 1997) (Section 7.4.5). In addition, studies of DRG neurones have revealed a potential multiplicity of heat-activated currents which only partially adapt upon repetitive heat stimulation, and which are potentiated by PGs and other algogenic agents (Belemonte and Cervero, 1996; Cesare and McNaughton, 1996; Lynn *et al.*, 1996; Reichling and Levine, 1997).

Notwithstanding behavioural evidence for mechanical supersensitivity in primary hyperalgesia, neurophysiological evidence that a peripheral sensitization of *individual* mechanoreceptors underlies *mechanical* hyperalgesia and allodynia is unconvincing.

cing, and only rare instances of chemical sensitization of some branches of mechanosensitive (A $\delta$ ) fibres have been documented (Cline *et al.*, 1989; Fitzgerald and Lynn, 1977; Raja *et al.*, 1984; Reeh *et al.*, 1987; Treede *et al.*, 1992b). The question arises, thus, as to the underlying mechanisms. In some tissues, an increase in the sensitivity of polymodal C fibres might contribute to mechanical hyperalgesia. Further, it is possible that the RFs of individual, mechanosensitive fibres may be expanded (spatial summation): that is, the number of mechanosensitive nociceptors stimulated per fibre (and, correspondingly, per DH neurone) is enhanced (Reeh *et al.*, 1987; Thalhammer and LaMotte, 1982). In this regard, assuming that they become sensitive to pressure, the engagement of otherwise 'silent' nociceptors under tissue injury and inflammation might amplify the collective, afferent barrage to the DH in response to mechanical stimulation (Cohen and Perl, 1988; Davis *et al.*, 1991; Koltzenburg *et al.*, 1995; Kress *et al.*, 1992; Schaible and Schmidt, 1988) (Section 3.1.3). That is, for the induction of mechanical hyperalgesia, the recruitment of silent nociceptors is equivalent to the adding of *new* units rather than to an increase in the sensitivity of existing units *per se*.

Nevertheless, it is difficult to extrapolate an involvement of the above-specified mechanisms, including silent nociceptors, to the mechanical allodynia which occurs *outside* the area of cutaneous tissue damage (secondary hyperalgesia), and which accompanies nerve injury. As discussed below (Sections 10 and 12), processes of *central* sensitization in the DH (and higher centres) offer a complementary theory for the induction of mechanical allodynia, a major component of which is mediated via A $\beta$ -fibres (Section 9.1.2).

### 7.3. Multiple, Interactive, Peripheral Mechanisms of Hyperalgesia

The primary hyperalgesia which ensues upon tissue injury can, then, at least partially, be accounted for by changes in the transduction sensitivity, responsiveness and activity of peripheral nociceptors and by the recruitment of 'silent' nociceptors. Processes underlying the activation and sensitization of nocisponsive PAF terminals are highly complex. They involve synergistic and supra-additive actions of a diversity of substances derived from nocisponsive PAFs themselves, damaged tissue, immunocompetent cells, the vasculature and sympathetic terminals (Dray and Perkins, 1993; Dray *et al.*, 1994; Handwerker, 1991; Handwerker and Kobal, 1993; Keele and Armstrong, 1964; Levine and Taiwo, 1994; Reeh and Kress, 1995; Wilcox, 1993a; Wood and Docherty, 1997) (Figs 3 and 4, Table 5). Bradykinin (BK), 5-HT and PGs have long been implicated and, more recently, attention has been directed towards several novel, pro-nociceptive mediators, such as protons, cytokines and the neurotrophin, NGF. It is possible to distinguish several mechanisms whereby the function of nocisponsive PAFs is affected, and all may *ultimately* be mediated by alterations in the properties of ion channels controlling their electrical activity. Herein,

these mechanisms are termed 'excitation', 'sensitization', 'phenotype alteration' and 'indirect modulation'. The first two of these mechanisms concern actions expressed directly on sensory neurones and the last concerns actions mediated, by definition, via *other elements* of the inflammatory response. Phenotype alteration may be mediated either directly and/or indirectly (Cohen and Perl, 1988; Dray and Urban, 1996; Reeh and Kress, 1995; Levine and Taiwo, 1994; Taiwo and Levine, 1988, 1992).

The distinction between mechanisms of excitation as compared to mechanisms of sensitization is exploited herein as a descriptive framework. Generally-speaking, excitation of PAFs involves their rapid and direct depolarization following by spike activity and the induction of APs. In contrast, sensitization refers to a prolonged increase in the likelihood of firing in response to additional stimulation. Nevertheless, processes of excitation and sensitization are not necessarily separated either temporally or spatially, and may even be simultaneously triggered via common transduction mechanisms. On the other hand, specific pronociceptive agents may initiate both excitation or sensitization via interactions with multiple receptor types coupled to contrasting, intracellular transduction mechanisms.

The following account is based largely upon observations made in cutaneous tissue, but the basic events are of broader relevance to other organs (Cervero, 1995a; Gebhart, 1995; Mense, 1993; Schaible and Grubb, 1993).

### 7.4. Substances Modulating the Activity of Nocisponsive PAF Terminals: Tissue Sources, Receptors Implicated and Excitatory Actions

#### 7.4.1. Orthodromic and Antidromic Activation of PAFs

The pronociceptive actions of algogenic substances on nocisponsive PAFs ultimately reflect their depolarization and the orthodromic transmission of impulses to the DH. Concurrently—corresponding to their efferent function—antidromic impulses may be triggered in collateral fibres ('axon reflex'). This provokes the peripheral release of EAAs, SP and other mediators which enhance nociception both by feedback actions on PAF terminals themselves, and by actions on other tissues involved in pronociceptive and pro-inflammatory processes (Section 7.9).

The actions of algogenic substances on nocisponsive PAFs, together with their tissue sources and the receptors involved in their actions, may be summarized as follows (Figs 3 and 4, Table 5).

#### 7.4.2. BK

Tissue damage, inflammation and an acidic environment result in the activation of plasma and tissue, proteolytic kallikreins (Marceau, 1995). These enzymes generate the kinins, BK (the major product in plasma) and kallidin (the major product in tissue), from circulating polypeptide (kininogen) precursors (Marceau, 1995). BK and kallidin are rapidly metabolized to des-arg<sup>9</sup>-BK and des-arg<sup>10</sup>-

kallidin (Lys-des-arg<sup>9</sup>-BK), respectively. These, and other, metabolites, may also be involved in modulating nociception (Marceau, 1995). Intradermal infusion of BK, application of BK to skin blister bases or intravenous (i.v.) injection of BK evokes an immediate and intense pain in parallel with an excitation of polymodal C and mechanosensitive, high threshold A $\delta$  fibres in cutaneous and other tissues (Khan *et al.*, 1992; Lang *et al.*, 1990; Manning *et al.*, 1991; Whalley *et al.*, 1987). Two G-protein coupled receptor types exist: B<sub>1</sub> receptors, for which the des-arg derivatives have higher affinity than BK and kallidin themselves, and BK<sub>2</sub> receptors, at which BK and kallidin are preferentially active (Hall, 1997; Marceau, 1995). Although B<sub>1</sub> receptors are not normally present in tissue (except in blood vessels), they play a pronociceptive role under conditions of prolonged inflammation following their induction by, for example, NGF and the cytokines, TNF $\alpha$  and IL-1 $\beta$  (Dray and Perkins, 1993; Dray and Urban, 1996; Petersen *et al.*, 1998b; Raymond *et al.*, 1996; Rueff *et al.*, 1996; Seguin *et al.*, 1995) (Section 7.7). Interestingly, in a model of persistent joint inflammation, B<sub>1</sub> and B<sub>2</sub> receptors were recently suggested to exert predominantly excitatory and sensitizing actions, respectively (Tonussi and Ferreira, 1997). Nevertheless, pharmacological approaches, as well as studies of transgenic mice, have indicated that B<sub>2</sub> rather than B<sub>1</sub> receptors normally mediate the phasic, algic actions of BK on sensory neurones. Correspondingly, selective B<sub>2</sub> antagonists exert more marked antinociceptive properties than B<sub>1</sub> antagonists against pain of limited duration (Buritova *et al.*, 1997; Haley *et al.*, 1990; Heapy *et al.*, 1993; Rupniak *et al.*, 1997; Seabrook

*et al.*, 1997; Seguin *et al.*, 1995; Whalley *et al.*, 1987).

Studies of sensory neurones and cell lines suggest that the excitation (depolarization) of PAF terminals by B<sub>2</sub> receptors reflects a rapid increase in cation membrane conductance, primarily to Na<sup>+</sup> (Burgess *et al.*, 1989; Dray and Perkins, 1993; Dray and Urban, 1996). This action is likely initiated via stimulation of PLC leading to the generation of [Ca<sup>2+</sup>]<sub>i</sub> and DAG which, via the synergistic activation of PKC, result in the phosphorylation (increased activity) of a Na<sup>+</sup>-permeable ion channel (Burgess *et al.*, 1989; Cesare and McNaughton, 1996; Dray and Perkins, 1993; Dray *et al.*, 1994; Higashida *et al.*, 1986; McGuirk and Dolphin, 1992). The rise in [Ca<sup>2+</sup>]<sub>i</sub> levels can potentially initiate a broad array of intracellular mechanisms modifying PAF activity, including neuropeptide release, PG synthesis, stimulation of NO synthase and enhancement of AC activity (Burgess *et al.*, 1989; Dray and Urban, 1996; Gammon *et al.*, 1989) (Section 7.5.2).

Although neuronal depolarization activates VDCCs, there are reports that, at least in heterologous expression systems, stimulation of B<sub>2</sub> receptors *reduces* the activity of N- and L-type VDCCs (Ewald *et al.*, 1988; Connor and Henderson, 1997). A role of a mitogen-activated PK has been implicated in this action (Wilk-Blaszczak *et al.*, 1998). Further, the increase in [Ca<sup>2+</sup>]<sub>i</sub> elicited via cloned B<sub>2</sub> receptors has been shown to activate hyperpolarizing chloride channels (McEachern *et al.*, 1991). It is unclear whether such effects are of physiological importance in PAF terminals. However, they would counterbalance the stimulatory actions of BK and a

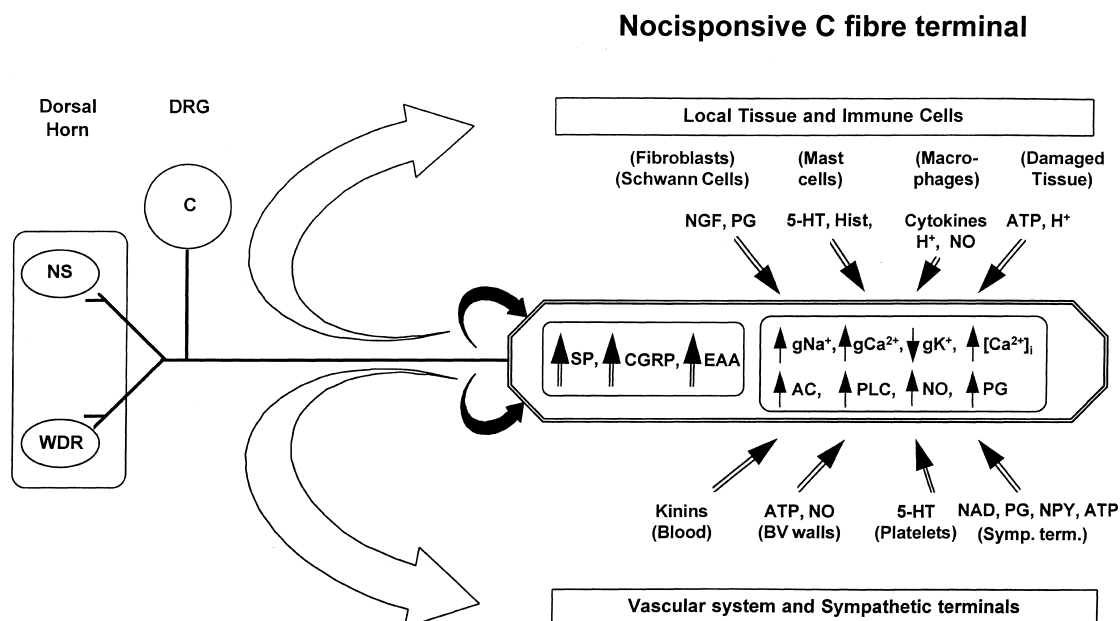


Fig. 3. Influence of pronociceptive, inflammatory mediators upon the activity of nocisponsive, polymodal C fibres. Abbreviations are as indicated in the general list. In addition, BV, blood vessel. There is a reciprocal, facilitatory relationship between nocisponsive PAF terminals and the various components of the inflammatory response. Positive feedback actions of EAAs and SP at PAF terminals should be noted. The schema is non-exhaustive. Details of the relationships between various mediators and intracellular transduction mechanisms are given in Section 7. See also Fig. 4.

### Nocisponsive C fibre terminal

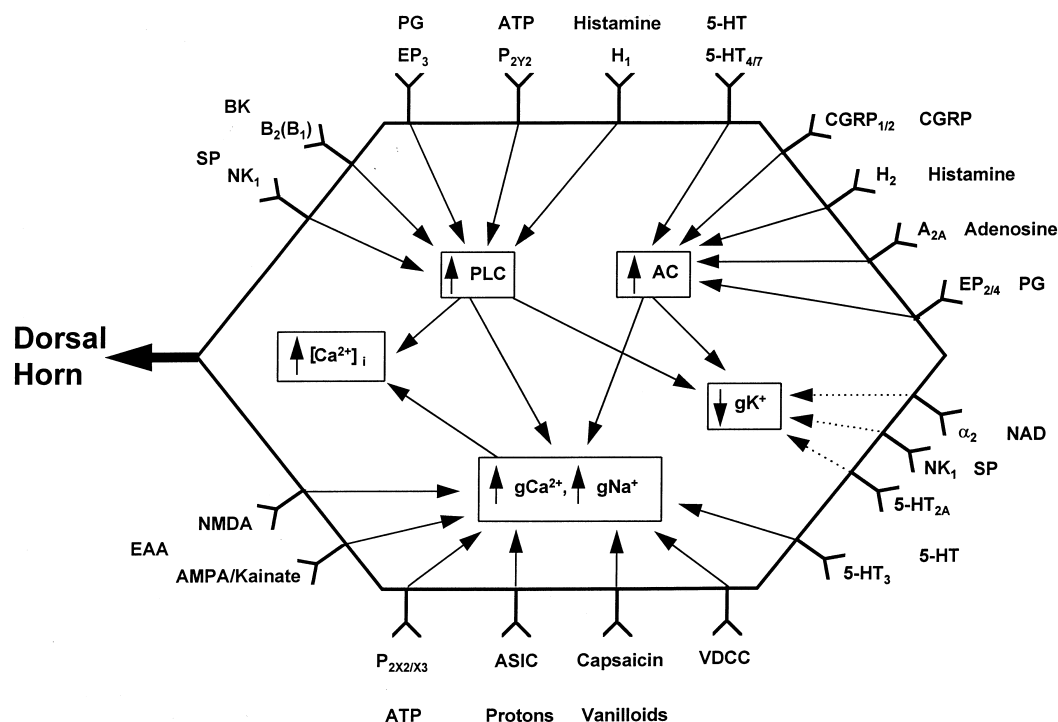


Fig. 4. Roles of diverse receptors and intracellular signals in mediating the actions of pronociceptive mediators at nocisponsive, polymodal C fibre terminals. Abbreviations are as indicated in the general list. In addition, ASIC, acid-sensing-ion-channel. The mechanisms indicated relate to common modes of action, and not necessarily to common loci of action. For example,  $\text{Ca}^{2+}$ -permeable ion channels coupled to vanilloid receptors are distinct from  $\text{Ca}^{2+}$ -permeable ion channels coupled to NMDA receptors. Dotted lines are given where interactions may be indirect and/or remain uncertain. Actions of ATP at metabotropic  $\text{P}_{2\text{Y}2}$  receptors, potentially involved in mediating mechanical allodynia, are exerted at  $\text{A}\beta$  rather than C fibres, but are included for comparative purposes. Roles of multiple EP receptors for PGs are indicated, but their respective contributions remains to be elucidated. A modulation of gene transcription probably plays a role in the longer-term actions of several mechanisms indicated, as well as those of NGF/TRK A receptors (not illustrated) (Section 7).

Table 5. Summary of principal mechanisms underlying the induction of prolonged, painful states due to noxious stimulation of nocisponsive PAFs (see Section 10)

#### A. Peripheral mechanisms

1. Direct excitation of nocisponsive PAFs. Mediated via, for example,  $5\text{-HT}_3$ ,  $\text{P}_{2\text{X}3}$  and vanilloid receptors coupled to excitatory, cation-permeable ion channels
2. Sensitization of nocisponsive PAFs by the engagement of intracellular transduction systems: includes the activation of AC and PLC, as well as increases in  $[\text{Ca}^{2+}]_i$ . Thereby, the likelihood, intensity and duration of further discharges is increased. Mediated via, for example, PG and BK receptors
3. Modulatory events involving a complex pattern of reciprocal interactions amongst PAF terminals, glial cells, immunocompetent cells, sympathetic terminals and other elements of the inflammatory response. Mediated via, for example, cytokines, NO and NGF
4. Altered phenotype of PAFs. For example, an increase in the synthesis of SP and of specific, excitatory  $\text{Na}^+$ -channel subtypes
5. 'Antidromic' activation of nocisponsive PAFs. This further enhances their activity by a positive feedback mechanism, and elicits vascular effects and other processes underlying NI. Mediated by, for example, SP (especially NI), CGRP (especially vasorelaxation) and EAAs (especially feedback actions). This mechanism is of relevance to events in cerebral blood vessels underlying migraine headaches

#### B. Central mechanisms

1. Sensitization and increased excitability of DH neurones (PNs and EXINs) transmitting nociceptive information to higher centres. The engagement of NMDA receptors by activation of small calibre, C fibre input plays a particularly important role in triggering intracellular mechanisms (increases in  $[\text{Ca}^{2+}]_i$ , PK activity, NO synthesis, IEG expression, etc. underlying these changes
2. Diminution and accentuation of descending mechanisms of nociceptive inhibition and facilitation, respectively
3. Adaptive changes in the thalamus, cortex and other higher centres responsible for the discriminative-sensory and affective-cognitive dimension of pain

further consequence of the increase in  $[Ca^{2+}]_i$  levels elicited by  $B_2$  receptors may be the initiation of  $Ca^{2+}$ -dependent processes for their desensitization by dephosphorylation (Kress and Reeh, 1996). Together with the putative activation by  $[Ca^{2+}]_i$ /PKC of an ATPase-dependent pump for  $Ca^{2+}$ -extrusion (Young *et al.*, 1998), such processes would further counteract the stimulatory actions of BK at PAF terminals. Nevertheless, it has been questioned whether, under physiological conditions, desensitization to the actions of BK is pronounced in PAF terminals (Kress and Reeh, 1996). Thus, even though BK is rapidly metabolized, the generation of active metabolites (*vide supra*), its ongoing synthesis and the progressive development of  $B_1$  receptor-mediated mechanisms of nociception (Section 7.7) suggest that BK plays a major role in direct and indirect mechanisms underlying PAF activation and primary hyperalgesia (Rueff *et al.*, 1996).

It should be mentioned that both kinins and BK receptors exist in the CNS. In the DH, BK receptors (probably of the  $B_2$  type) are found on PAF terminals, intrinsic neurones and terminals of descending pathways. A possible role of these central pools of BK in the modulation of nociception is currently under exploration (Coggeshall and Carlton, 1997; Walker *et al.*, 1995).

#### 7.4.3. Prostaglandins and Leukotrienes

As summarized in Section 3.2.8.4, arachidonic acid is metabolized by several constitutive and inducible isoforms of COX to generate PGs, on the one hand, and via lipoxygenase enzymes, to generate leukotrienes, thromboxanes and hydroxyeicosotetraenoic acid derivatives, on the other.

Although PGs may be derived from virtually all tissue types, under conditions of tissue inflammation and nerve injury, immunocompetent cells and sympathetic terminals may be particularly important sources (Levine and Taiwo, 1994; Levine *et al.*, 1986b; Miao *et al.*, 1996; Taiwo and Levine, 1988). A contribution of the constitutive COX 1 enzyme to pro-nociceptive pools of PGs should *not* be discounted. However, activation of the (predominantly) inducible COX 2 synthase is likely the principal pathological source of PGs interacting with nociceptive PAFs upon inflammatory tissue damage (Buritova *et al.*, 1996; Dirig *et al.*, 1997; Dray and Urban, 1996). Factors potentially responsible for the induction of COX 2 include NO (Section 7.7) and immune cell-derived cytokines, such as IL-1 and TNF $\alpha$ , although certain other cytokines, such as IL-4 and IL-10, may actually *inhibit* COX 2 activity and reduce nociception/inflammation (Appleton, 1997; Bakhle and Botting, 1996; Pairet and Engelhardt, 1996; Perkins and Dray, 1996; Wagner *et al.*, 1998).

Of the many species of PG known, the major contributors to hyperalgesia, PGE<sub>2</sub> and PGI<sub>2</sub> (prostacyclin)—which may retrogradely modify COX 2 activity—act via (multiple) EP receptors and IP receptors, respectively (Appleton, 1997; Bakhle and Botting, 1996; Boie *et al.*, 1997; Coleman *et al.*, 1994; Khasar *et al.*, 1995; Matsumura *et al.*, 1995; Schaible and Grubb, 1993) (Section 3.2.8.4).

Although application of PGs to skin is not usually painful, high levels of PGE<sub>2</sub> and PGI<sub>2</sub> may contribute to excitatory mechanisms through the suppression of a  $K^+$ -conductance and the increase in a  $Na^+$ - (and  $Ca^{2+}$ )-conductance. These actions may lead to an increase in neuropeptide release from C fibre terminals (Birrell *et al.*, 1991; Collins and Davies, 1998; Nicol *et al.*, 1992, 1997; Puttick, 1992; Sánchez-Prieto *et al.*, 1996; Schaible and Schmidt, 1988; Schepelmann *et al.*, 1992; Wang *et al.*, 1996a) (Sections 7.5.2.3 and 7.5.2.4). Further, as discussed below (Section 8.2.1), following nerve damage, PGs can excite C fibres in neuromas. The receptor subtypes mediating such effects remain unclear, but actions at EP/IP receptors positively coupled to activation of  $[Ca^{2+}]_i$  and AC and/or PLC are, presumably, involved (Coleman *et al.*, 1994). Interestingly, PGI<sub>2</sub>-deficient, transgenic mice were recently shown to display a reduction in peripheral inflammation and nociception, consistent with a role of PGI<sub>2</sub> in mediating nociception (Murata *et al.*, 1997).

Comparatively little is known about the putative, pronociceptive actions of leukotriene (and thromboxane) products of the lipoxygenase (non-COX) pathway of arachidonic acid metabolism. However, leukotriene B<sub>4</sub> (derived from the 5-lipoxygenase arm), which accumulates in inflamed tissue, appears to trigger the release of 8R,15S, diHETE (derived from the 15-lipoxygenase arm), from polymorphonuclear leukocytes. This leukotriene subsequently interacts with nociceptive cutaneous C fibre terminals to elicit hyperalgesia via an, as yet, unclear mechanism (Amann *et al.*, 1996; Bisgaard and Kristensen, 1985; Levine and Taiwo, 1994; Levine *et al.*, 1984, 1986a; Martin, 1990; Martin *et al.*, 1988; White *et al.*, 1990) (Section 7.7).

#### 7.4.4. ATP

ATP can elicit marked pain upon infusion into the skin, apparently due to the direct excitation of a subset of small calibre PAFs (Bland-Ward and Humphrey, 1997; Burnstock, 1996; Burnstock and Wood, 1996; Rang *et al.*, 1991). These actions of ATP involve the stimulation of rapidly-desensitizing, cation-permeable, *ionotropic* receptors of the  $P_{2X}$  family. Their engagement results in an immediate depolarization (reflecting an inward cation flux) and an increase in  $[Ca^{2+}]_i$  (Bouvier *et al.*, 1991; Robertson *et al.*, 1996; Sawynok and Reid, 1997; Thorne and Housely, 1996). mRNA encoding at least six of the seven members of the  $P_{2X}$  family is found in the DRG and trigeminal ganglia, to a variable degree colocalized with SP and CGRP. However, only the  $P_{2X3}$  receptor subtype is expressed *exclusively* in small calibre, sensory neurones (Burnstock, 1996; North and Barnard, 1997; Vulchanova *et al.*, 1997). Indeed,  $P_{2X3}$  receptors are localized on a capsaicin-sensitive population of fibres projecting specifically to lamina II which contain *little* or no CGRP, SP or receptors for NGF, and which are defined by presence of the lectin, IB-4 (Vulchanova *et al.*, 1996) (Section 3.2.1). Although excitatory actions of ATP at  $P_{2X2}$  receptors and other classes of  $P_{2X}$  receptor should not be discounted, (King *et al.*, 1997b; Simon *et al.*, 1997),

$P_{2X3}$  receptors may be of particular importance in the rapid, excitatory actions of ATP on nocisponsive PAF terminals (Chen *et al.*, 1996; Cook *et al.*, 1997; Guzman *et al.*, 1997; Lewis *et al.*, 1995; Collo *et al.*, 1996; North, 1996).

$P_{2X3}$  receptors rapidly desensitize, possibly due to a  $Ca^{2+}$ - (and/or calmodulin)-dependent dephosphorylation mediated by the phosphatase calcineurin (King *et al.*, 1997b; North, 1996; Vulchanova *et al.*, 1996).  $P_{2X2}$  receptors do *not*, in contrast, rapidly desensitize and the co-expression of  $P_{2X2}$  and  $P_{2X3}$  receptor subtypes in oocytes produces heteromultimeric channels with *slower* deactivation kinetics than  $P_{2X3}$  receptors alone. Inasmuch as  $P_{2X2}$  and  $P_{2X3}$  receptors are *co-localized* in some DRG cells, and such heteromultimeric channels might be assembled *in vivo*, this observation may be of relevance to longer-term, sensitizing actions of ATP (Bland-Ward and Humphrey, 1997; Lewis *et al.*, 1995; North and Barnard, 1997; Vulchanova *et al.*, 1997; Werner *et al.*, 1996). Indeed, there is preliminary evidence for similar, slowly—desensitizing actions of ATP at endogenous receptors on rat DRG neurones (Sansum *et al.*, 1997; Vulchanova *et al.*, 1997).

An additional aspect of potential relevance to pain and allodynia is the presence of ATP-excitabile, *metabotropic*  $P_{2Y}$  receptors (coupled to PLC and an increase in  $[Ca^{2+}]_i$ ) on *large*—but not small-calibre PAFs (Collo *et al.*, 1996; Khakh *et al.*, 1997; Mayer *et al.*, 1997; Svichar *et al.*, 1997a). Indeed, mRNA encoding a G-protein-coupled, metabotropic  $P_{2Y}$  receptor was recently extracted from sensory neurones and shown to render oocytes mechanosensitive to light touch (Nakamura and Strittmatter, 1996; Svichar *et al.*, 1997b). A putative, pathophysiological role of  $P_{2Y}$  sites in mediating mechanical allodynia would, thus, be of interest to evaluate.

Although ATP is universally present in cells, and may be derived from multiple tissue sources, several, specific pools may generate those high levels of ATP which pathologically activate nocisponsive terminals (Burnstock, 1996). For example:

1. tumour cells contain high levels of ATP and may be implicated in the activation of PAFs in cancerous tissue;
2. vascular, endothelial cells and/or platelets may be a source of pronociceptive ATP in migraine, angina and ischaemic muscle pain (Crea *et al.*, 1990); and
3. sympathetic nerve endings, which release ATP as a co-transmitter to NAD, might be involved in a variety of conditions including cutaneous, joint and muscle inflammation, as well as PAF damage (Guieu *et al.*, 1996).

Indeed, sympathetically-maintained pain is sensitive to manipulations, such as guanethidine treatment and surgical sympathectomy, which block release from sympathetic terminals, although other sympathetic mediators, such as NAD and PGs, are also involved in the modulation of nociception by sympathetic fibres (Section 8.2.4).

ATP is rapidly metabolized to adenosine which modulates nociception via several receptor types, and which may interact with the pronociceptive

effects of ATP at  $P_{2X2}/P_{2X3}$  receptors (Aley and Levine, 1997; Dray and Urban, 1996; Doak and Sawynok, 1995). Activation of  $A_{2A}$  receptors, which are positively coupled to AC, appears to be pronociceptive. In contrast, activation of peripheral  $A_1$  receptors, which inhibit cAMP formation, and which increase and decrease  $K^+$ - and  $Ca^{2+}$ -currents, respectively, appears to be antinociceptive, in analogy to the role of spinal  $A_1$  sites (Aley and Levine, 1997; Dray and Urban, 1996; Doak and Sawynok, 1995; Taiwo and Levine, 1991) (Sections 3.2 and 7.5.2). In line with a pronociceptive role of (peripheral)  $A_{2A}$  receptors, knock-out mice lacking these sites display hypoalgesia (Ledent *et al.*, 1997).

The importance of Schwann cells as a source of inflammatory mediators and factors controlling the phenotype and regeneration of damaged PAFs is underscored in Sections 7.7, 8.2.6 and 11.3.4.1 (Bolin *et al.*, 1995). It is, thus, intriguing to note that Schwann cells bear metabotropic  $P_{2Y2}$  receptors as well as ionotropic  $P_{2X}$  receptors. These findings may be compared to reports of  $P_{2X2}$  and  $P_{2X7}$  receptors on CNS-localized microglial cells (Chessel *et al.*, 1997a,b; Collo *et al.*, 1997; Mayer *et al.*, 1997; Nörenberg *et al.*, 1997; Robitaille, 1995; Vulchanova *et al.*, 1997) (Section 4.8). A potential, functional role of Schwann cell-localized  $P_{2Y}$  and  $P_{2X}$  sites in the modulation of nociception would be of interest to evaluate.

#### 7.4.5. Protons and Vanilloids

##### 7.4.5.1. Excitation of PAF terminals by acidosis (a reduction in pH)

Although an increase in the extracellular concentration of  $K^+$  ions has long been considered an excitatory component of inflammatory exudates, the actions of  $K^+$  may be non-specific. More recently, attention has been directed towards the potential importance of a further ion,  $H^+$  (protons), as an algogenic agent for nocisponsive PAF terminals (Bevan and Geppetti, 1994; Waldmann *et al.*, 1997a,b; Wood and Docherty, 1997). Under certain conditions, nociceptors may be exposed to an environment sufficiently acidic to trigger their excitation. For example:

1. inflammatory exudates (in which immigrating leucocytes provide an important source of protons);
2. ischaemic muscle, in which low pHs may be attained under intensive exercise;
3. cardiac tissue following an infarction;
4. synovial fluid of arthritic joints;
5. haematomas provoked by fractures; and
6. tissue surrounding tumours.

Further, disruption of the mucosal lining of the gut could expose intestinal tissue to pHs as low as 3.0, while damage to the urothelium might expose renal tissue to acidic urine (Bevan and Geppetti, 1994; Steen *et al.*, 1995). Application of acidic solutions ( $pH \leq 5.0$ ) to the skin is painful and the activation of PAFs by protons may, in accordance with the above observations, contribute to inflammatory pain, muscle cramps, gastric ulcers and cystitis, etc. (Steen *et al.*, 1992; Steen and Reeh, 1993).

Studies of isolated sensory neurones suggest that protons depolarize PAFs by at least two mechanisms (Bevan and Yeats, 1991).

1. In a majority of neurones—though these are *not* all necessarily nocisponsive—comparatively mild, physiological changes in pH (down to 7.0) may trigger a transient, rapidly inactivating  $\text{Na}^+$ -permeable ion channel.
2. In a smaller population of neurones involved in pain transmission, more pronounced changes in pH directly lead to the opening of poorly-selective ion channels permeable to  $\text{Na}^+$ ,  $\text{K}^+$  and  $\text{Ca}^{2+}$  (Bevan and Geppetti, 1994; Docherty *et al.*, 1991; Liu *et al.*, 1997c; Wegner, 1996; Wood and Docherty, 1997; Zeilhofer *et al.*, 1996, 1997). This is associated with an inward current and a *sustained* depolarization over minutes (slow inactivation).

#### 7.4.5.2. Relationship of proton-gated ion channels to vanilloid-Gated ion channels

Although some neurones apparently respond with excitation to either protons or capsaicin (and other so-called vanilloids), there is very considerable overlap, if not identity in these populations (Bevan and Geppetti, 1994; Steen *et al.*, 1992; Wood and Docherty, 1997). Further, like protons, capsaicin provokes intense pain by opening cation-permeable ion channels and there exists several similarities in the actions of protons and capsaicin on nocisponsive neurones (Bevan and Geppetti, 1994). Thus, it has been suggested that protons and vanilloids may, via a common binding domain, co-activate a mutual ion channel localized on cutaneous, visceral and other types of nocisponsive PAF (Bevan and Geppetti, 1994; Szallasi, 1997; Winter *et al.*, 1995). Protons might, then, be conceived of as ‘mimics’ or ‘ligands’ of vanilloid receptors, for which endogenous agonists remain unknown (Wood and Docherty, 1997). The possibility of a common site of action is supported by observations that a low pH inhibits binding of [ $^3\text{H}$ ]resiniferatoxin (a capsaicin analogue) to vanilloid receptors (Szallasi and Blumberg, 1996). Further, the capsaicin antagonist, capsazepine, prevents protons from opening a population of cation-sensitive ion channels (Liu and Simon, 1994). However, the following counter-arguments may be advanced:

1. capsazepine does *not* block all responses to protons (Bevan and Geppetti, 1994; Bevan *et al.*, 1993; Liu and Simon, 1994; Steen *et al.*, 1992);
2. capsaicin-gated channels are preferentially  $\text{Ca}^{2+}$ -permeable in contrast to their proton-gated counterparts (Zeilhofer *et al.*, 1997);
3. in cultured DRG neurones, vanilloid-gated channels are *not* activated by protons (Oh *et al.*, 1996); and
4.  $\text{Ca}^{2+}$ -influx lead to the rapid *desensitization* of vanilloid—but not proton-gated receptors, probably via a calcineurin-dependent dephosphorylation triggered by an increase in  $[\text{Ca}^{2+}]_i$  (Docherty *et al.*, 1996; King *et al.*, 1997b; Koplas *et al.*,

1997; Wood and Docherty, 1997; Zeilhofer *et al.*, 1997).

In addition, it has been demonstrated that capsazepine behaves as an antagonist at VDCCs suggesting caution in the interpretation of its actions (Docherty *et al.*, 1997). A possible role of an intervening chemical transmitter in the excitatory actions of protons cannot, further, be entirely excluded (Dray, 1996; Lou and Lundberg, 1992).

#### 7.4.5.3. Properties of cloned, vanilloid-gated, as compared to cloned, proton-gated, ion channels

The above observations tend to question the concept of a *single* and *common* site mediating the actions of protons and vanilloids. In fact, an important insight into the relationship between proton and vanilloid receptors was recently afforded by the cloning of an acutely-desensitizing, vanilloid receptor from sensory neurones, the mRNA encoding which is found almost exclusively in the DRG and trigeminal ganglia (Caterina *et al.*, 1997). This vanilloid receptor couples to an ion channel preferentially permeable to  $\text{Ca}^{2+}$ -ions, and prolonged exposure to capsaicin kills cells expressing these receptors. (This suggests, in analogy to *in vivo* studies, that a progressive loss of responsiveness to vanilloids may reflect not only acute events but also, and ultimately, the destruction of neurones by excessive  $\text{Ca}^{2+}$ -influx). A further important feature of cloned vanilloid receptors is their activation by increases in temperature. This indicates that the vanilloid channel may transduce noxious thermal stimuli, consistent with the burning sensation provoked by cutaneous application of capsaicin, and with the co-expression of heat and capsaicin-evoked inward currents in cultures of DRG neurones (Kirschstein *et al.*, 1997; Caterina *et al.*, 1997)—although other types of (BK and/or PG facilitated) heat-sensitive channel may also exist on small calibre PAFs (Cesare and McNaughton, 1996; Reichling and Levine, 1997) (Section 3.1.1). Notably, the response of cloned vanilloid receptors both to capsaicin itself and to heat is facilitated by protons. This latter observation is consistent with an action of protons at vanilloid receptors. However, these findings do *not* exclude the putative existence of other vanilloid receptor types either directly *activated* by protons alone, or completely insensitive thereto. Indeed, it has been suggested that subtypes of vanilloid receptor may exist in several tissue types. For example, in muscle, at peripheral as compared to central terminals of PAFs and, most pertinently, on the peripheral terminals of PAFs themselves (Acs *et al.*, 1997; Griffiths *et al.*, 1996; Wood and Docherty, 1997). In addition, the *lack* of direct activation of cloned vanilloid receptors by protons suggests that other, proton-sensitive channels may exist.

Indeed, a novel, proton-gated  $\text{Na}^+$ -channel specific to sensory neurones has been cloned and termed ‘DRASIC’ (Waldmann *et al.*, 1997a,b). This channel responds to reductions in extracellular pH with both a rapidly-inactivating current

and a further, *sustained*  $\text{Na}^+$ -mediated current which clearly resembles the *prolonged* kinetics of proton-gated currents on PAF terminals. However, native, proton-gated ion channels in the DRG are *not* selective for  $\text{Na}^+$ . This difference raises the possibility of a post-transcriptional modification of 'DRASIC' ion channels *in situ*, the existence of other acid-sensitive channels or a heteromultimeric association of several different receptor subunits. Indeed, several types of acid-sensitive channel have been cloned and detected in nocisponsive PAFs (Bassilant *et al.*, 1997; Waldmann *et al.*, 1997b). Further, the assembly of functional channels from a combination of subunits of the DRASIC channel together with those from a further 'MDEG2' splice variant channel which co-exists in DRG yielded *sustained* currents discriminating *poorly* between  $\text{Na}^+$  and  $\text{K}^+$  (Lingueglia *et al.*, 1997). That is, two characteristic features of native, proton-gated channels mediating the tonic sensation of pain (Bevan and Geppetti, 1994).

It remains to be determined whether, apart from protons, other *endogenous* ligands exist for vanilloid—or proton-gated ion channels, of which additional subtypes will likely be identified.

Interestingly, NGF may modulate (up-regulate) the functional status of both proton-coupled and vanilloid-coupled ion channels on small calibre, cutaneous PAFs (Bevan and Winter, 1995; Winter *et al.*, 1993). Further, BDNF (but not NGF) modulates the capsaicin-sensitivity of sensory vagal neurones (Winter, 1998).

#### 7.4.5.4. Influence of protons (tissue acidosis) upon other receptor types

Protons may modify activity at other sites controlling PAF excitability. Thus, tissue acidosis considerably enhances nociceptor sensitivity to inflammatory mediators such as BK and 5-HT (Kress *et al.*, 1997). This synergism between protons, BK and 5-HT may be mutual inasmuch as both BK and 5-HT themselves reinforce actions at proton-(and/or vanilloid-) gated ion channels, possibly via intracellular mechanisms involving PLC (Damas *et al.*, 1997; Kress *et al.*, 1997; Steen *et al.*, 1995). An influence of tissue acidosis upon the actions of ATP has also been demonstrated inasmuch as protonation enhances the activity of agonists at recombinant  $\text{P}_{2\text{X}2}$  receptors, a subtype found on nociceptive C fibres (King *et al.*, 1997b) (Section 7.4.4). However, protons appear to *reduce* rather than increase activity at  $\text{P}_{2\text{X}3}$  sites (King *et al.*, 1997b). Further, a low pH may exert other effects *inhibiting* PAF excitability inasmuch as NMDA- and VDCC-mediated currents are reduced under some circumstances (Philippi *et al.*, 1995).

These data suggest that acidosis exerts a complex pattern of influence upon the actions of diverse agents modulating inflammatory states, PAF excitability and nociception. Nevertheless, the predominant effect of protons/low pH at nocisponsive PAF terminals is a slowly-adapting increase in excitability mediated via proton-sensitive receptors coupled to cation-permeable ion channels and provoked in

synergy with thermal stimuli and other inflammatory mediators.

It should be mentioned that vanilloid binding sites are likewise localized on the *central* terminals of fine calibre PAFs in the DH. They also exist in the thalamus and other cerebral structures involved in nociceptive processing (Acs *et al.*, 1996; Szallasi *et al.*, 1995). Further, tissue acidosis may be provoked in the CNS under conditions which are associated with pain: for example, ischaemic tissue damage and seizure-like neuronal activity. These observations suggest that localized alterations in pH may also influence nociception via the modification of synaptic transmission in the DH and supraspinal structures. An interesting potential target of protons in the CNS is provided by  $\text{GABA}_\text{A}$  receptors, the activity of which way be inhibited or enhanced by protons depending upon their subunit composition (Krishek *et al.*, 1996).

#### 7.4.6. 5-HT

DRG express mRNA encoding several types of 5-HT receptor. Correspondingly, nocisponsive PAFs may be excited by peripheral pools of 5-HT derived from platelets, mast cells and endothelial cells as well as, in the case of the cerebral vasculature, the perivascular terminals of central serotonergic fibres originating in the raphe nucleus (Millan, 1995; Pierce *et al.*, 1997) (Section 7.9). For example, 5-HT released from aggregating platelets in the diseased heart may be a source of cardiac pain (Meller and Gebhart, 1992). Sympathetic terminals may also provide a source of 5-HT inasmuch as they can take up and release 5-HT. Administration of 5-HT onto the skin (blister base) elicits pain in man. Further, the pain and pseudoaffective responses elicited by i.v. administration of 5-HT reflect pronociceptive actions in the heart and other internal organs (Lang *et al.*, 1990).

The excitation of nocisponsive, polymodal C and A $\delta$  PAFs by 5-HT appears to involve the activation of 5-HT $_3$  receptors directly gating ion channels preferentially permeable to  $\text{Na}^+$  (and  $\text{K}^+$ ). The ensuing neuronal depolarization triggers, in turn, the opening of (possibly L-type) VDCCs (Abbott *et al.*, 1996, 1997; Barann *et al.*, 1993; Ebersberger *et al.*, 1995; Grubb *et al.*, 1988; Guilbaud *et al.*, 1989a; Millan, 1995; Smith *et al.*, 1997b; Todorovic *et al.*, 1997). In analogy to  $\text{B}_2$  receptors, 5-HT $_3$  receptors are positively coupled to PLC and they may also initiate changes in PAF activity via intracellular mechanisms involving DAG-induced activation of PKC and  $\text{IP}_3$ -induced increases in  $[\text{Ca}^{2+}]_i$ . The influx of  $\text{Ca}^{2+}$  via VDCCs triggers, moreover, a further increase of  $[\text{Ca}^{2+}]_i$  levels via activation of ryanodine receptors localized on the endoplasmic reticulum: this results in a further mobilization of intracellular  $\text{Ca}^{2+}$ -stores (Rondé and Nichols, 1997) (Sections 7.5.2.8 and 10.4.1). 5-HT $_3$  antagonists possess antinociceptive properties in several models of inflammatory pain although, in clinical studies of inflammatory bowel disease and migraine, at best equivocal results have been obtained (Giordano and Sacks, 1997; Greenshaw and Silverstone, 1997; Talley, 1992). The recent discovery of mRNA



encoding many other 5-HT receptor types in DRG suggests the need for further study of the excitatory actions of 5-HT on nocisponsive PAFs (Millan, 1997; Pierce *et al.*, 1996, 1997).

#### 7.4.7. NAD Derived from the Sympathetic System

Under conditions of inflammation and nerve injury (Section 8.2.4), the release of NAD (and adrenaline) by the sympathetic system plays a role in the modulation of nociception. The release of NAD controlled by a multiplicity of mechanisms including GLU, NO, BK, PGs, 5-HT, NPY, cytokines and NAD itself (Carlton *et al.*, 1998a; Jonakait, 1993; Miao *et al.*, 1996; Munglani *et al.*, 1996; Seabrook *et al.*, 1997). Even high concentrations of NAD do not generally excite PAF neurones (Lang *et al.*, 1990), but there is functional evidence that NAD directly and indirectly enhances the activity of cutaneous, muscle and joint PAFs under inflammatory conditions (Hu and Zhu, 1989; Mense, 1993; Sato and Perl, 1991; Sato *et al.*, 1993a, 1994; Schaible and Grubb, 1993).

Several studies have implicated  $\alpha_1$ -ARs in mediating inflammatory hyperalgesia, for example, that provoked by capsaicin, and a role of the  $\alpha_{1A}$ -AR subtype was proposed to mediate formalin-induced nociception in the rat (Drummond, 1996; Drummond *et al.*, 1996; Hong and Abbott, 1996; Hunter *et al.*, 1996; Kinnman and Levine, 1995; Kinnman *et al.*, 1997; Millan, 1997; Ouseph and Levine, 1995). A pronociceptive role of  $\alpha_1$ -ARs would be consistent with their positive coupling to PLC and increases in  $[Ca^{2+}]_i$ . Further, although a direct action of NAD at  $\alpha_1$ -ARs localized on PAFs is inconsistent with anatomical evidence suggesting that PAFs express few  $\alpha_1$ -ARs, they may be up-regulated by tissue inflammation (Pieribone *et al.*, 1994). On the other hand, vascular  $\alpha_1$ -ARs might be involved in an (indirect) influence of NAD upon PAF terminals (Section 8.2.4). As concerns  $\alpha_2$ -ARs, DRG express mRNA encoding  $\alpha_{2A}$ -,  $\alpha_{2B}$ - and  $\alpha_{2C}$ -ARs (Gold *et al.*, 1997), suggesting that they might modulate the activity of PAF terminals (Dray *et al.*, 1994). However, experimental evidence for a direct, pronociceptive role of  $\alpha_2$ -ARs at PAF terminals under inflammatory conditions is *poor*, consistent with their negative coupling to cAMP and  $Ca^{2+}$ -channels. Indeed,  $\alpha_{2B}$ -ARs at PAF terminals may exert antinociceptive actions (Aley and Levine, 1997; Hunter *et al.*, 1996; Khasar *et al.*, 1995)—and a peripheral, antinociceptive action of  $\alpha_2$ -AR agonists via a local release of opioids has been reported by Nakamura and Ferreira (1988). Nevertheless,  $\alpha_2$ -ARs were recently reported to reduce  $K^+$ -currents in the terminals of damaged PAFs, providing a potential mechanism of excitation (Abdulla and Smith, 1997). Additional pharmacological characterization of the nature of  $\alpha$ -AR sites enhancing PAF activity under conditions of inflammation is needed (Section 8.2.4.2).

Recent clinical studies have provided support for a pronociceptive, peripheral role of adrenergic mechanisms in showing that the ongoing pain and mechanical allodynia associated with capsaicin application to the skin was inhibited by phentolamine

(Kinnman *et al.*, 1997; Liu *et al.*, 1996). The underlying mechanism is unclear. Some A $\beta$  fibres possessing  $\alpha_2$ -ARs and mediating mechanical allodynia may be excited by NAD (Chen *et al.*, 1996; Gold *et al.*, 1997; Liu *et al.*, 1996; Pieribone *et al.*, 1994). However, NAD may act at sensitized  $\alpha_{1/2}$ -ARs on fine calibre PAFs. This would enhance the peripheral drive to sensitized DH neurones mediating the allodynic effects of A $\beta$ -fibre stimulation (Liu *et al.*, 1996) (Section 9.1.2). In addition, C fibres themselves mediate certain forms of mechanical allodynia (Section 9.2).

Apart from direct actions at PAF terminals, the possible, indirect modulation of nociception via an influence of NAD upon inflammatory events *per se*, or via cardiovascular actions (vasoconstriction), is further discussed in Section 8.2.4. Potential, peripheral actions of NAD/ $\alpha$ -ARs are importance to clarify in the light of:

1. the potential role of sympathetic mechanisms in the pathology of inflammatory states (Miao *et al.*, 1996; Takahashi *et al.*, 1993); and
2. the involvement of 'sympathetic' mechanisms in changes in nociception accompanying PAF damage (Section 8.2.4).

Nevertheless, the *clinical* significance of sympathetic mechanisms in inflammatory nociception still requires further evaluation and, in a recent study, the pain and hyperalgesia elicited by a heat injury of skin in man was not modified by a sympathetic block (Pedersen *et al.*, 1997).

#### 7.4.8. Histamine

Although histamine, which is derived from mast cells, is a familiar component of inflammatory media, its actions are poorly understood. Generally, histamine elicits the sensation of itch rather than pain. However, higher concentrations may be painful (Carstens, 1997; LaMotte *et al.*, 1987; Levine and Taiwo, 1994; Rang *et al.*, 1991). Further, exposure to histamine may release SP and CGRP from PAF terminals (Bileviciute *et al.*, 1997b) and activate nocisponsive neurones in the DH in a manner similar to that observed with cutaneous noxious stimuli (Chapman and Besson, 1997; Yao *et al.*, 1992). The direct, excitatory (and sensitizing) actions of histamine on PAFs are likely mediated by  $H_1$  receptors positively coupled to PLC and to an increase in  $[Ca^{2+}]_i$ ; this may secondarily result in the engagement of VDCCs and an induction of NO synthesis (Hill *et al.*, 1997; Tani *et al.*, 1990). A (possibly synergistic) role of  $H_2$  receptors, which are positively coupled to AC and PKA, should also be mentioned (Hall, 1997) (Section 7.9).

#### 7.4.9. EAAs, Tachykinins and CGRP

An increase in GLU levels—derived from PAF terminals themselves and, perhaps, from immunocompetent cells—has been observed in inflamed tissue (Jeftinija *et al.*, 1991; Nordlind *et al.*, 1993; Piani *et al.*, 1991; Westlund *et al.*, 1992; Wood and Docherty, 1997). There are several reports that GLU elicits hyperalgesia via the direct exci-

tation of PAF terminals (Carlton *et al.*, 1995; Davidson *et al.*, 1997; Jackson *et al.*, 1995; Wang *et al.*, 1997b). Indeed, studies of mRNA expression in DRG, together with pharmacological analyses of responses to EAAs, have indicated that the peripheral terminals of small calibre PAFs possess NMDA, AMPA and kainate receptors (Ault and Hildebrand, 1993; Carlton *et al.*, 1995; Coggeshall and Carlton, 1997; Huettner, 1990; Lawand *et al.*, 1997b; Liu *et al.*, 1994b, 1997b; Lovinger and Weight, 1988; Sato *et al.*, 1993b; Wood and Docherty, 1997; Zhou *et al.*, 1996a). Warncke *et al.* (1997a,b) have, further, shown that local administration of the NMDA channel blocker, ketamine, inhibits primary and secondary hyperalgesia of cutaneous tissue in human subjects suggesting that peripheral NMDA receptors may participate in pronociceptive processes in man. A direct, excitatory, positive-feedback action of GLU on PAF terminals would be consistent with evidence that activation of NMDA receptors triggers SP release from their central endings (Liu *et al.*, 1994b, 1997b) (Section 3.2.4). One component of this central action of NMDA may be mediated via NO from PAF terminals (Sorkin, 1993) and NO may also intervene in the peripheral, PAF-mediated actions of GLU (Jackson *et al.*, 1995; Lawand *et al.*, 1997b; Wang *et al.*, 1997b). Further, an action of GLU at NMDA receptors vasodilates cerebral microvessels via an indirect, NO-mediated mechanism (Fergus and Lee, 1997). Thus, it would be of interest to establish whether a GLU-mediated release of NO may be involved in the vasodilation of subdural CBVs which is implicated in migraine headaches (Section 7.9.3). The discovery of NMDA receptors on postganglionic sympathetic terminals suggests that the release therefrom of NAD, ATP, PG or other mediators might also contribute to the peripheral, pronociceptive effects of GLU (Carlton *et al.*, 1998a) (Section 8.2.4).

A release of SP by GLU from PAFs (or sympathetic terminals) may also be involved in mediating its peripheral, pronociceptive actions. Indeed, in analogy to GLU, SP may activate PAFs in several tissues, including muscles, skin and CBVs—though not blood vessels—by direct actions at NK<sub>1</sub> receptors coupled to PLC/PKC and increases in [Ca<sup>2+</sup>]<sub>i</sub> (Andoh *et al.*, 1996; Carlton *et al.*, 1996; Heppelmann and Pawlak, 1997; Hu and Li, 1996; Holthusen *et al.*, 1997; Hu *et al.*, 1997; Hu and Li, 1996; Inoue *et al.*, 1995; Jonakait, 1993; Pedersen-Bjergaard *et al.*, 1989). NK<sub>2</sub> receptors and CGRP<sub>1</sub> receptors (positively coupled to AC) may also activate nocisponsive, sensory nerve terminals (Edvinsson *et al.*, 1997; Weinreich *et al.*, 1997).

It is intriguing to note evidence that A $\beta$  fibres also possess NMDA and AMPA receptors (Coggeshall and Carlton, 1997; Wood and Docherty, 1997). This raises the interesting possibility that their peripheral (or central) terminals might also be affected by EAAs. Whether such actions contribute to mechanical allodynia and/or the regenerative changes seen in PAFs following their injury would be of interest to determine (Komuro and Rakic, 1993). (Section 11.3).

Inhibitory group II—and probably other subtypes of—mGlu receptor are localized on the central terminals of fine calibre PAFs in the DH (Sections 3.2.3 and 10.3.2.3). It would be of interest to establish whether they are likewise localized on peripheral PAF terminals and corresponding play a role in the modulation of nociception at these sites (Carlton and Coggeshall, 1997).

## 7.5. Mechanisms Underlying Sensitization of PAF Terminals

### 7.5.1. Synergistic Sensitization of PAFs

The sensitization of nociceptors by tissue damage and prolonged, noxious stimulation contributes to the familiar pain, tenderness and hyperalgesia of injury and inflammation (Dray and Bevan, 1993; Dray and Urban, 1996). Sensitization refers to an increase in the responsiveness of nocisponsive fibres to pronociceptive substances and noxious stimuli. Processes of sensitization are broadly displayed by nocisponsive PAFs and are involved in the recruitment of silent nociceptors normally irresponsive to noxious stimuli (Section 3.1.3). Sensitization of PAFs may be elicited by several of the above-mentioned substances which excite sensory terminals: notably, PGs and BK (Figs 3 and 4, Table 5). Sensitizing agents (and noxious stimuli) display marked reciprocal interactions. Although certain interactions may be inhibitory, this is likely the exception and the effects of inflammatory mediators are generally expressed in a highly synergistic fashion (Dray and Bevan, 1993; Dray and Urban, 1996; Lopshire and Nicol, 1997). For example, inflammatory mediators generally potentiate the effects of tissue acidosis (protons) (Kress *et al.*, 1997; Steen *et al.*, 1996).

BK sensitizes polymodal C and A $\delta$  fibres not only to protons, but also to 5-HT and PGs as well as to thermal and, less markedly, mechanical stimuli (Kumazawa *et al.*, 1991; Khan *et al.*, 1992; Lang *et al.*, 1990; Manning *et al.*, 1991; Neugebauer *et al.*, 1989) via actions at BK<sub>2</sub> and, under long-term inflammatory conditions, BK<sub>1</sub> receptors (Davis and Perkins, 1996; Dray and Perkins, 1993; Rueff *et al.*, 1996; Rupniak *et al.*, 1997; Seguin *et al.*, 1995). BK may also increase the production of PGs via the activation of PLA<sub>2</sub> which generates arachidonic acid (the precursor of PGs) from phospholipids (Prado *et al.*, 1997) (Section 3.2.8.4).

In a reciprocal fashion, PGs can sensitize PAFs to the actions of BK, as well as several other stimuli. Thus, PGE<sub>2</sub> and PGI<sub>2</sub>, acting via (multiple) EP and IP receptors, respectively (Coleman *et al.*, 1994) (Section 3.2.8.4), have been shown to sensitize neurones to thermal and mechanical stimuli as well as to BK and capsaicin (Chahl and Iggo, 1977; Damas *et al.*, 1997; Handwerker, 1976; Khasar *et al.*, 1995; Martin *et al.*, 1988; Schepelmann *et al.*, 1992; Taiwo and Levine, 1988; Wang *et al.*, 1996a). In the light of these pronounced sensitizing actions of PGs, it is not surprising that aspirin and other anti-inflammatory drugs inhibiting COX 1 and COX 2 activity, as well as selective COX 2 inhibitors, suppress the peripheral sensitization of PAFs in inflamed tissue

(Appleton, 1997; Buritova *et al.*, 1996; Pairet and Engelhardt, 1996). However, a key—and, as yet, incompletely resolved—question is whether selective COX 2 inhibitors elicit robust, clinical analgesia without the gastric, renal and other side-effects of traditional anti-inflammatory agents which have been attributed to COX 1 inhibition (Langenbach *et al.*, 1995; Mitchell *et al.*, 1997; Pairet and Engelhardt, 1996; Smith *et al.*, 1996). Initial clinical data are promising in this respect. However, the clinical demonstration of pronounced and adequate pain relief by genuinely 'selective' COX 2 inhibition in the absence of an influence upon COX 1 or unwanted side-effects is awaited (Bakhle and Botting, 1996; Frölich, 1997; Lichtenberger *et al.*, 1995; Pairet and Engelhardt, 1996; Parnham, 1996, 1997; Seibert *et al.*, 1994). Indeed, PGs derived from COX 1 and COX 2 might both, and via different mechanisms, be involved in the phasic and tonic modulation of nociception (Dirig *et al.*, 1997; Smith and De Witt, 1996).

#### 7.5.2. Ionic and Metabotropic Mechanisms Involved in Sensitization

##### 7.5.2.1. Multiple mechanisms of sensitization

As mentioned above, the distinction between mechanisms underlying excitation and sensitization should not be regarded as absolute. Nevertheless, excitation generally involves direct activation of ion channels and the induction of APs, whereas sensitization generally reflects an increase in the likelihood of firing in response to stimulation. This increased probability of discharge is effected via the activation of intracellular transduction systems which either directly modulate activity at specific ion channels or exert long-term modifications in their activity via alterations in gene transcription (Section 7.6). Several inter-related and interactive mechanisms may be exemplified (Figs 3 and 4, Table 5).

##### 7.5.2.2. Increases in levels of cAMP

A decrease in the afterpolarization which normally follows APs increases the probability that PAFs will discharge repetitively in response to further stimuli. Such an alteration in excitability can be mediated via the activation of AC and the generation of cAMP. cAMP triggers a PKA-mediated phosphorylation of  $K^+$ -channels, thereby decreasing  $K^+$ -conductance, as well as several other changes in terminal function. Indeed, increases in PAF terminal levels of cAMP may play a generalized role in mediating the sensitization of PAFs in response to heat (and other qualities of noxious stimulus), PGs, adenosine (via  $A_{2A}$  receptors), CGRP, histamine and 5-HT (Kress *et al.*, 1996; Levine and Taiwo, 1994; Malmberg *et al.*, 1997a; Taiwo *et al.*, 1989; Wang *et al.*, 1996a, 1997h; Weinreich and Wonderlin, 1987) (Section 7.5.2.3).

As concerns 5-HT, the original proposition that 5-HT<sub>1A</sub> receptors mediate pronociceptive actions at PAF terminals is questionable since they couple *negatively* to AC; further, their activation increases and decreases  $K^+$ - and  $Ca^{2+}$ -currents, respectively (Boess and Martin, 1994). More recent data suggests that activation of 5-HT<sub>7</sub> receptors may be involved

inasmuch as they are *positively* coupled to AC and expressed in DRG cells (Abbott *et al.*, 1997; Cardenas *et al.*, 1997; Doak and Sawynok, 1997; Kress and Reeh, 1996; Kress *et al.*, 1996; Pierce *et al.*, 1996, 1997; Rueff and Dray, 1992; Taiwo and Levine, 1992; Taiwo *et al.*, 1989; Rueff and Dray, 1992). 5-HT<sub>4</sub> and 5-HT<sub>6</sub> receptors also stimulate AC. Although mRNA encoding the latter was *not* found in rat DRG, mRNA was present for 5-HT<sub>4</sub> receptors (Pierce *et al.*, 1996). Indeed, evidence that 5-HT<sub>4</sub> sites may contribute to peripheral nociception and oedema has recently been presented (Cardenas *et al.*, 1997; Doak and Sawynok, 1997).

The potential importance of cAMP/PKA in mechanisms of sensitization is underscored by the diminution in inflammatory pain and PG-induced nociception observed in mice with a targeted mutation of a regulatory subunit of PKA which is colocalized with TRK A receptors in small-calibre PAFs. Nevertheless PKA localized in the central terminals of PAFs, or in intrinsic DH neurones, might be involved in the deficits shown by these mice (Malmberg *et al.*, 1997a) (Section 10.4.3.2).

##### 7.5.2.3. Activation of a tetrodotoxin-resistant $Na^+$ -Current

It has been suggested that several substances, including PGE<sub>2</sub>, 5-HT (possibly, via 5-HT<sub>4</sub> receptors) and adenosine, facilitate a tetrodotoxin (TTX)-resistant, voltage-gated  $Na^+$ -current (termed 'PN 3') which is specific to small calibre, nocisponsive neurones. The activation threshold is decreased, while both the magnitude and the rate of activation are enhanced (Gold *et al.*, 1996a). As indicated above, the importance of an increase in cAMP/PKA activity in PAF terminals may not be restricted to an alteration in  $K^+$ -conductance and it is possible that cAMP, another soluble second messenger, or NGF may be involved in the potentiation of this  $Na^+$ -current, although this remains to be clarified (Akopian *et al.*, 1996a,b; Cardenas *et al.*, 1997; England *et al.*, 1996; Friedel *et al.*, 1997; Gold *et al.*, 1996a,b; Sangameswaran *et al.*, 1996; Wang *et al.*, 1996a).

##### 7.5.2.4. Activation of PKC via PLC

The induction of PLC by B<sub>2</sub> or NK<sub>1</sub> receptors, for example, triggers several mechanisms leading to an increased activity of PAF terminals. Thus, stimulation of PLC, via an increase in  $[Ca^{2+}]_i$  levels, may indirectly enhance the activity of AC and elevate cAMP levels. Further, stimulation of PLC increases levels of DAG which, together with  $[Ca^{2+}]_i$  activates PKC, leading to the phosphorylation and increased activity of certain, cation-permeable ion channels (including VDCCs) or receptors involved in the control of PAF activity and release (Dray and Urban, 1996).

For example, in a recent study of isolated, primary sensory neurones, BK sensitized their response to thermal stimuli by activation of PLC/PKC (Cesare and McNaughton, 1996). An activation of PLC/PKC by BK, leading to phosphorylation of synaptic, terminal-localized proteins, has also been implicated in the ability of BK to increase CGRP

and SP release from sensory terminals—although terminal depolarization and an increase in  $[Ca^{2+}]_i$  levels are also likely involved in this effect (Barber and Vasko, 1996; Geppetti *et al.*, 1991). Arachidonic acid, PGs and other metabolites, have also been suggested to enhance release from neuronal terminals via a mechanism involving PKC and, possibly, mGlu receptors. Whether such processes occur in nociceptive PAF terminals would be of interest to evaluate (Collins and Davies, 1998; Sánchez-Prieto *et al.*, 1996).

SP may itself enhance the sensitivity of PAF terminals by a facilitation in ATP-mediated currents: this action involves a PKC-mediated acceleration of the recovery of  $P_{2X3}$  receptors from desensitization (Gammon *et al.*, 1989; Hu and Li, 1996). Consistent with this possibility, the potentiation by SP (and CGRP) of responses at cloned, heterologously-expressed  $P_{2X2}$  receptors involves the activation of PLC (Hu and Li, 1996; Wildman *et al.*, 1997). Further, an induction of PLC may be involved in the inhibition of  $K^+$ -currents in PAFs by SP: this action—together with an increase in the cation-permeability of VDCCs—contributes to the sensitizing actions of SP via an increase in post-AP afterhyperpolarizations (Hu *et al.*, 1997; Inoue *et al.*, 1995; Quartara and Maggi, 1997).

#### 7.5.2.5. Inhibition of $K^+$ -Currents

PAFs possess a substantial population of 5-HT<sub>2A</sub> receptors (Carlton and Coggeshall, 1997; Pierce *et al.*, 1996, 1997), the principal 5-HT receptor type involved in the sensitization of PAFs. Activation of 5-HT<sub>2A</sub> receptors results in a cAMP-independent reduction of  $K^+$ -currents via the intervention of a G-protein, although it is unknown whether an action of PKC is involved in PAF terminals (Abbott *et al.*, 1997; Dray *et al.*, 1994; Fan *et al.*, 1994; Philippi *et al.*, 1995; Taiwo and Levine, 1992; Taiwo *et al.*, 1989; Todorovic *et al.*, 1997). This attenuation of  $K^+$ -currents reduces afterpolarization and is the basis for the potent sensitizing actions of 5-HT<sub>2A</sub> receptor agonists on the human blister base and other inflamed tissues. Correspondingly, 5-HT<sub>2A</sub> antagonists inhibit nociception associated with inflammatory states of the skin, nasal mucosa, viscera and other tissues in animals and in man (Abbott *et al.*, 1997; Damas *et al.*, 1997; Dray *et al.*, 1994; Fan *et al.*, 1994; Greenshaw and Silverstone, 1997; Langlois *et al.*, 1996; Nicol *et al.*, 1997; Philippi *et al.*, 1995; Taiwo and Levine, 1992; Taiwo *et al.*, 1989). An indirect cAMP/PKA-mediated suppression of an outward  $K^+$ -conductance may also be involved in the actions of PGs (PGE<sub>2</sub>) and other AC-activating transmitters at PAF terminals (Malmberg *et al.*, 1997a; Nicol *et al.*, 1997) (Section 7.5.2.1). Further, it is possible that a PLC-mediated decrease in  $K^+$ -currents is involved in the actions of SP (Quartara and Maggi, 1997) (Section 7.5.2.4).

#### 7.5.2.6. Activation of NO synthase

NO synthase is upregulated in DRG and immune-competent cells upon inflammation (Dickenson, 1997; Xu and Wiesenfeld-Hallin, 1997). NO released from PAFs themselves, macrophages,

vascular (endothelial) cells and other sources may sensitize the terminals of nociceptive PAFs and enhance neuropeptide release, possibly via mechanisms involving the activation of a cGMP-dependent PKG (Fozard, 1995; Laszlo *et al.*, 1995; Lawand *et al.*, 1997a; Miyasaka and Hirata, 1997; Qian *et al.*, 1996b). Correspondingly, an interruption of (peripheral) NO synthesis inhibits inflammatory hyperalgesia (Herdegen *et al.*, 1993; Kress *et al.*, 1994; Lawand *et al.*, 1997a; Meller and Gebhart, 1993; Seguin *et al.*, 1995) and s.c. injection of NO acts algescically in man (Holthusen and Arndt, 1994). An induction of NO synthase may also be involved in the sensitizing actions of BK (Holthusen and Ding, 1997), although a more complicated pattern of interactions between NO and BK at PAF terminals has also been proposed (Miyamoto *et al.*, 1997).

Notwithstanding indications for pronociceptive actions of NO at PAF terminals, in analogy to multiple actions of NO in the DH (Section 3.2.8.3), its role is likely to be more complex. Thus, several studies have suggested that the induction of NO may even participate in *antinociceptive* processes, for example, those initiated by the peripheral actions of opioids (Duarte *et al.*, 1990, 1992; Kawabata *et al.*, 1994) (Section 7.8). Indeed, although a key intracellular effector mechanism for NO is the generation of cGMP, this second messenger does *not*, as compared to cAMP, appear to be of major importance in sensitizing PAF terminals (Holthusen and Ding, 1997; Kress *et al.*, 1996). Further, via generation of cGMP, NO may even accelerate tachyphylaxis of PAF terminals to BK (MacGhee *et al.*, 1992). Quite apart from direct actions at nociceptive PAF terminals, the peripheral influence of NO upon PAF activity may also be largely *indirect*, reflecting alterations in PG synthesis, an influence upon blood flow and the modulation of inflammatory processes *per se* (Fletcher *et al.*, 1998) (Sections 4.8 and 7.9).

The multiple actions of NO mediated directly at PAFs, and indirectly via the vasculature etc, are likely of special relevance to vasoactive and neurogenic mechanisms precipitating migraine headaches (Fozard, 1995) (Section 7.9.3).

#### 7.5.2.7. A potential role of NGF

Under conditions of tissue inflammation, NGF plays a major, long-term role in modifying the activity of sensory neurones via a modulation of gene expression and a corresponding change in their phenotype (McMahon, 1996; McMahon and Bennett, 1997) [see Lexin and Barde (1996) and Section 7.6.1 for an overview of the neurobiology of NGF]. However, there is evidence from studies of central neurones that NGF—and other neurotrophins—can rapidly modify neurotransmitter release, synaptic transmission and cellular excitability via diverse processes of phosphorylation, alterations in ion flux and changes in the levels of  $[Ca^{2+}]_i$  and PKs (Berninger *et al.*, 1993; Berninger and Poo, 1996; Bevan and Winter, 1995; Greene and Kaplan, 1995; Jiang *et al.*, 1997; Kang and Schuman, 1995; Sherwood *et al.*, 1997; Toledo-Aral *et al.*, 1995; Winter, 1998) (Section 14). Should such effects occur in the terminals of C fibre, they could

contribute to the rapid induction of hyperalgesia by NGF (Dmitrieva and McMahon, 1996; Dmitrieva *et al.*, 1997; Lewin *et al.*, 1994a,b; McMahon and Bennett, 1997) (Section 7.7).

#### 7.5.2.8. General significance of an induction of PKs and of an increase in $[Ca^{2+}]_i$

To summarize, the excitation and sensitization of PAF terminals is effected via multiple transduction mechanisms, including the induction of PKA and PKC via actions of cAMP and DAG/ $[Ca^{2+}]_i$ , respectively. The activation of PKA and PKC by various inflammatory mediators may be of broad importance in modulating the activity of PAF terminals via the phosphorylation of specific proteins, such as ion channels and receptors, which control their electrical activity (*vide supra*). In addition, the production of NO in PAF terminals leads to the generation of cGMP, which can activate PKG. Although the significance of the latter intracellular cascade in nocisponsive PAFs is currently unclear, together with PKA and PKC, PKG plays a key role in events underlying the sensitization of DH neurones in response to sustained, nociceptive input (Fig. 4) (Lin *et al.*, 1996a, 1997; Wang and Robinson, 1997) (Section 10.4). A related and crucial intracellular event underlying changes in the excitability of PAF terminals (and DH neurones) is an increase in  $Ca^{2+}$ -influx and an elevation in  $[Ca^{2+}]_i$  levels. Increases in  $[Ca^{2+}]_i$  may be elicited via several mechanisms. Notably, via VDCCs, via  $Ca^{2+}$ -permeable ion channels coupled to vanilloid receptors and via the PLC-mediated mobilization of  $[Ca^{2+}]$  from intracellular stores following activation of  $B_2$  (and  $NK_1$ ) receptors. The influx of  $Ca^{2+}$  may provoke an additional increase in  $[Ca^{2+}]_i$  via activation of  $Ca^{2+}$ -dependent VDCCs and the 'feed-forward' activation of intracellular ryanodine receptors which further mobilize cellular stores of  $[Ca^{2+}]_i$  (Dettbarn and Palade, 1997; Rondé and Nichols, 1997; Usachev and Thayer, 1997). Increases in the levels of  $[Ca^{2+}]_i$  and PKs play a major role in the control of gene transcription, an alteration of which underlies longer-term changes in phenotype.

The crucial importance of increases in  $[Ca^{2+}]_i$  and PK levels in the sensitization of DH neurones by C fibre input is discussed in Section 10.4.

#### 7.5.2.9. Recruitment of silent nociceptors

The engagement of silent nociceptors provides a special case of sensitization. It is thought that silent nociceptors are chemosensitive and, once sensitized, they begin to respond to (low and high) intensity thermal and mechanical stimuli. That is, sensitization reflects the addition of *new* units rather than an amplification of the unit response. The precise mechanisms involved in the awakening of sleeping nociceptors are unclear. However, interactions between PGs and BK, key sensitizing elements, were outlined above and Stucky *et al.* (1996) have recently shown that  $PGE_2$  increases the number of SP-containing PAFs which respond to BK. This action of  $PGE_2$  is possibly mediated as  $EP_2$  sites, and may involve the formation of cAMP and an increase in  $[Ca^{2+}]_i$ , leading to an increase in SP

release and/or an augmentation in the density of  $B_2$  receptors: this remains to be clarified. Such findings are consistent with observations that, after exposure to PGs, other pro-inflammatory substances or tissue injury, up to half of mechanically-insensitive fibres begin to discharge in response to thermal or mechanical stimuli (Davis *et al.*, 1991; Handwerker *et al.*, 1991; Kress *et al.*, 1992; Meyer *et al.*, 1991).

### 7.6. Altered Phenotype of PAF Neurones

#### 7.6.1. Focus on Pronociceptive Actions of NGF at TRK A Receptor-Bearing, Small Calibre C Fibres

Changes in the activity and properties of nocisponsive C (and A $\delta$ ) fibres innervating inflamed tissue may reflect an *altered phenotype*: in particular, a modification of gene expression. Certain changes in phenotype might counter nociception. However, the most prominent components of the complex and time-dependent pattern of changes displayed by PAF neurones upon peripheral inflammation lead to a facilitation of nociception. Notably, increases in PAF levels of SP, CGRP (as well as of a structurally-related 'islet amyloid polypeptide'), NO and GLU (Cho *et al.*, 1998; Dickenson, 1997; Donnerer *et al.*, 1992, 1993; Donaldson *et al.*, 1992; Goff *et al.*, 1998; Mulder *et al.*, 1997; Sluka *et al.*, 1994b; Sluka and Westlund, 1993). Interestingly, under certain conditions, a parallel increase in the DH density of  $NK_1$  receptors may further enhance the excitatory actions of SP released from PAF terminals onto neurones therein (Abbadie *et al.*, 1996; Coggeshall and Carlton, 1997; Goff *et al.*, 1998).

Little information is available concerning the density of specific receptor types on PAFs themselves under conditions of inflammation, although it has been shown that  $GAL_1$  and  $GAL_2$  receptors on small calibre PAFs are respectively up- and down-regulated by inflammation (Puttick *et al.*, 1994; Xu *et al.*, 1996b, 1997d). Further, an increase in the density of mRNA encoding  $Y_1$  receptors in the DRG (and DH) under inflammatory conditions has been documented. This may be associated with an alteration in the *central* actions of ININ-derived NPY at  $Y_1$  receptors on small calibre PAF terminals or PNs in the DH (Ji *et al.*, 1994; Munglani *et al.*, 1996). The roles of multiple GAL and NPY receptors in the modulation of nociception is complex and the functional consequences of these changes unclear, although an increased activity of DH pools of NPY may, overall, counter nociception (Section 8.2.5) (Ji *et al.*, 1994; Kask *et al.*, 1997; Munglani *et al.*, 1996; Xu and Wiesenfeld-Hallin, 1997).

In addition to rapid functional actions (such as phosphorylation), substances involved in the sensitization of PAFs may eventually influence gene transcription under conditions of prolonged, inflammatory pain. However, little concrete information is available in this regard. Thus, the present discussion focuses on evidence that the neurotrophin, NGF, which is indispensable for the initial survival and phenotypic development of a subpopulation of fine calibre, CGRP-containing sensory neurones (Lewin, 1995; Lewin and Barde, 1996; Liebl *et al.*, 1997; Lindsay *et al.*, 1994), plays a key

role in mediating pain-related alterations in the phenotype of C fibres and, correspondingly, in the enhancement of inflammatory hyperalgesia (Lewin and Mendell, 1993; McMahon and Bennett, 1997; Woolf, 1996).

In both man and rats, the acute- or chronic administration of NGF elicits an increase in the sensitivity of cutaneous and visceral small calibre PAFs to noxious mechanical and thermal stimuli (though not spontaneous pain). Further, transgenic mice lacking NGF show a perturbation of nociceptive transmission (Akopian *et al.*, 1996b; Davis *et al.*, 1993a; Dmitrieva and McMahon, 1996; Dmitrieva *et al.*, 1997; Lewin *et al.*, 1993; McMahon and Bennett, 1997; Petty *et al.*, 1994; Smeyne *et al.*, 1994). Consistent with a pro-nociceptive role of NGF in inflammatory pain, its levels are markedly increased in inflamed cutaneous, joint and visceral tissues. These pools of NGF are derived from various sources including Schwann cells, mast cells, macrophages, fibroblasts and, in skin, keratinocytes. Multiple factors, in particular cytokines, have been implicated in the induction of NGF synthesis and secretion (Aloe *et al.*, 1992; Donnerer *et al.*, 1992; McMahon and Bennett, 1997; Safieh-Garabedian *et al.*, 1995, 1996, 1997) (Section 7.7). The influence of NGF on the activity of PAF terminals is complex and involves both indirect actions, mediated via sympathetic afferents and mast cells (Section 7.7), as well as direct, phenotype-related actions described in this section (Lewin, 1995; Lewin and Barde, 1996; Lewin and Mendell, 1993).

About 90% of CGRP-containing, capsaicin-sensitive, cutaneous small calibre C fibres bear specific TRK A receptors: that is, almost half of DRG-localized PAFs. Visceral nocisponsive afferents are also rich in TRK A receptors (McMahon and Bennett, 1997). These, and other types of PAF, also possess a low affinity, p75<sup>NTR</sup> receptor responsive to NGF (and other neurotrophins). The engagement of p75<sup>NTR</sup> sites exerts a complex, modulatory (generally facilitatory) influence upon the actions of NGF at TRK A receptors and enhances retrograde flow of NGF from PAF terminals to the DRG (Averill *et al.*, 1995; Bergmann *et al.*, 1997; Bothwell, 1995; Davies, 1997; Delcroix *et al.*, 1997; Gardano *et al.*, 1997; Hantzopoulos *et al.*, 1994; Jiang *et al.*, 1997; Kashiba *et al.*, 1995, 1996; Levi-Montalcini *et al.*, 1996; MacPhee and Barker, 1997). In the course of development, an action of NGF at p75<sup>NTR</sup> receptors on sensory neurones and certain other cell types may promote constitutive processes of apoptotic cell death, an action diametrically opposed to its prevention of programmed cell death via actions at TRK A receptors. However, p75<sup>NTR</sup> sites may be capable of autonomous signalling, and the interrelationship between p75<sup>NTR</sup> receptors on neuronal and non-neuronal cells, NGF and cellular degeneration is still under intensive discussion (Bredesen and Rabizadeh, 1997; Dechant and Barde, 1997; Ladiwala *et al.*, 1998). TRK A receptors are dimerized and activated by NGF. Although NGF is retrogradely transported to cell bodies, wherein it initiates nuclear events modifying gene transcription, this may not be the exclusive mechanisms involved in its modulation of PAF phenotype. Thus, both the

endosome-assisted dispatch of activated TRK A receptors to the DRG, as well as the transport of a NGF-TRK A complex, may also be involved in the expression of its actions (Ehlers *et al.*, 1995; Grimes *et al.*, 1996; Riccio *et al.*, 1997).

Via such mechanisms, NGF can enhance the production of many molecules occurring in the terminals of TRK A-bearing C fibres, including several involved in the induction of nociception: vanilloid receptors, certain classes of Na<sup>+</sup>-channel, proton-activated ion channels, SP, CGRP and, possibly, B<sub>1</sub> receptors (Aguayo and White, 1992; Donnerer *et al.*, 1992; Hökfelt *et al.*, 1994; Kuraischi *et al.*, 1989; Leslie *et al.*, 1995; Malcangio *et al.*, 1997a; Malcangio *et al.*, 1997b; Petersen *et al.*, 1998b; Rueff and Mendell, 1996; Sherwood *et al.*, 1997; Toledo-Aral *et al.*, 1995, 1997; Winter *et al.*, 1993; Woolf *et al.*, 1994) (Section 7.7). As concerns Na<sup>+</sup>-channels, it is of particular interest that NGF increases the expression of a 'PN 1 class'—at least in transfected cell lines (Toledo-Aral *et al.*, 1997). This PN 1 channel differs in two major respects to the 'PN 3' Na<sup>+</sup>-channel involved in the sensitization of C fibre terminals (Section 7.5.2.3):

1. it is TTX-sensitive; and
2. it occurs in both small and large calibre, DRG neurones—as well as in sympathetic neurones.

The PN 1 channel is potentially involved, thus, in the induction of hyperalgesia and mechanical allodynia—although, presumably, only Na<sup>+</sup>-channels in TRK A-bearing C fibres and sympathetic terminals can be up-regulated by NGF (Toledo-Aral *et al.*, 1995, 1997). The modulation by NGF and other factors of the expression of various Na<sup>+</sup>-channels in injured PAFs is discussed in Section 8.2.2.3.

In line with such phenotype changes, there is evidence that the delayed-onset (several hours) mechanical hyperalgesia (Lewin *et al.*, 1994b) provoked by systemic or spinal administration of NGF to rats (both of which routes can access the DRG) involves an increase in the production, transport and spinal (or peripheral) release of SP, CGRP and NKA. Thus, antibodies against NGF, or TRK A fusion products, inhibit both inflammatory hyperalgesia and the accompanying increase in PAF levels of these neuropeptides (Bowles *et al.*, 1994; Donnerer *et al.*, 1993; Lewin and Mendell, 1993; Lewin *et al.*, 1993, 1994b; Malcangio *et al.*, 1997a,b; McMahon *et al.*, 1995; Woolf *et al.*, 1994; though see Rueff *et al.*, 1996). In addition, NGF-induced hyperalgesia and wind-up of DH neurones is inhibited by NK<sub>1</sub> antagonists, consistent with a role of sensitized, SP-responsive DH neurones in the longer-term, pronociceptive actions of NGF (Lewis *et al.*, 1995; McMahon and Bennett, 1997; Thompson *et al.*, 1995). Recently, it was suggested that the ability of NGF to elicit hyperalgesia via SP release may be auto-limited by the accumulation of N-terminal SP metabolites which *inhibit* its pronociceptive actions (Larson and Kitto, 1997).

Of particular interest, NGF induces the expression of a further neurotrophin for non-C PAFs, brain-derived neurotrophic factor (BDNF) (Section 7.6.2), in TRK A-positive, cutaneous, nocisponsive C fibres. BDNF may elicit actions in the periphery,

and it is also transported anterogradely to the DH wherein it may modulate nociception (Cho *et al.*, 1997a,b; Michael *et al.*, 1997a; Apfel *et al.*, 1996; Ho *et al.*, 1997) (Section 14). A NGF-mediated increase in BDNF expression has, notably, been observed, under conditions of peripheral inflammation (Apfel *et al.*, 1996; Cho *et al.*, 1997b,c).

To summarize, NGF can enhance nociception by the sensitization of TRK A receptor-bearing, small calibre PAFs innervating skin, viscera and, probably, other tissues. These peripheral actions ultimately contribute to processes of neuronal sensitization in the DH (Section 10). The actions of NGF may involve rapid, TRK A receptor-mediated interactions with intracellular signals, such as  $[Ca^{2+}]_i$  and PKs, thereby altering the activity of other excitatory/sensitizing receptors ion channels on nocisponsive PAF terminals. In addition, NGF modulates the expression of several pronociceptive receptors, ion channels and transmitters in nocisponsive PAF terminals, resulting in a reinforcement of nociceptive transmission to the DH.

#### 7.6.2. A Potential Role of Growth Factors Other Than NGF

The above-described pattern of phenotype alterations in C fibres may be paralleled by changes in the phenotype of A $\beta$  fibres which, under inflammatory conditions, and via a so-called 'phenotypic switch', begin to synthesize and release SP (Neumann *et al.*, 1996; Woolf *et al.*, 1992). The release of SP by A $\beta$  fibres may directly (or via volume effects) stimulate DH-localized NK $_{1/2}$  receptors and contribute to processes of sensitization underlying the mechanical allodynia and hyperalgesia of inflammation (Neumann *et al.*, 1996) (Sections 11.2 and 11.4). Since large calibre PAFs do *not* bear TRK A receptors, NGF cannot be directly involved in this change of phenotype. Thus, other neurotrophins are likely implicated in mediating phenotypic changes in non-C PAFs: notably BDNF and NT-4/5, both of which express their actions via TRK B receptors, and NT-3, which expresses its actions via TRK C receptors (Acheson *et al.*, 1995; Davies, 1997; Di Stefano *et al.*, 1992; Friedel *et al.*, 1997; Lewin and Barde, 1996; Lexin and Barde, 1996; Liebl *et al.*, 1997; Yan *et al.*, 1997).

TRK C receptors (and actions of NT 3) are, in fact, primarily localized to large calibre, myelinated, proprioceptive and mechanoreceptive fibres and a role in nociception remains to be established. Nevertheless, a recent study suggested that retrograde transport of NT 3 to the DH may actually *reduce* SP release and nociception by an, as yet, unclear mechanism (Airaksinen *et al.*, 1996; Helgren *et al.*, 1997; Malcangio *et al.*, 1997b; Wilkinson *et al.*, 1996; Wright and Snider, 1995) (Section 14.5.3).

On the other hand, TRK B receptors for BDNF are found on neurones of a broad range of diameters, including a population involved in mechanical nociception (Koltzenburg *et al.*, 1995; Lewin and Barde, 1996; Wright and Snider, 1995). Thus, it would be of interest to determine whether BDNF might be involved in the phenotype changes shown by large A $\beta$  fibres under conditions of inflammation,

and to establish whether BDNF plays a peripheral role in the modulation of sensory transmission and the induction of A $\beta$  fibre-mediated mechanical allodynia (Koltzenburg *et al.*, 1995). In this light, it is of note that BDNF, like NGF, modifies  $[Ca^{2+}]_i$  levels and ionic currents in central neurones (Berninger *et al.*, 1993; Sherwood *et al.*, 1997) (Section 14.4). Further, as mentioned above, BDNF is itself synthesized in a sub-population of PAFs of various diameter, and its expression is enhanced by NGF in nocisponsive C fibres under inflammatory conditions (Apfel *et al.*, 1996; Cho *et al.*, 1997a,b; Ernfors *et al.*, 1990; Ho *et al.*, 1997; Michael *et al.*, 1997a; Zhou and Rush, 1996). In contrast to cutaneous PAFs, the majority (~90%) of visceral afferents co-express TRK A and TRK B receptors and only a few (<5%) express TRK C receptors: this provides a clear difference to cutaneous PAFs (McMahon, 1994). Inasmuch as inflammation up-regulates BDNF in visceral PAFs, a potential role of BDNF in the modulation of visceral phenotype and pain would be of interest to explore (McMahon *et al.*, 1994; Lewin, 1995; Lewin and Barde, 1996). In line with such a potential role, BDNF has been shown to enhance the sensitivity of vagal, sensory, SP-containing PAFs to capsaicin (Winter, 1998).

The above observations concerning neurotrophins and nociception clearly would justify further functional exploration and an extension to other growth factors (Acheson *et al.*, 1995; Kim *et al.*, 1994; Zhou and Rush, 1996). For example, the subpopulation of P $_{2X3}$ -receptor-bearing nocisponsive, small calibre PAFs which does *not* express CGRP/TRK A receptors is dependent upon GDNF. A potential, acute role of GDNF in the modulation of phenotype and nociception would be of interest to evaluate (Leclerc *et al.*, 1997; Molliver *et al.*, 1997; Naveilhan *et al.*, 1997) (Sections 8.2.6.2 and 11.3.4.3). Whether other types of modulatory and trophic factor are involved in the control of phenotype and nociception under conditions of inflammation also remains to be clarified. This is not unlikely inasmuch as many other molecules potentially capable of modulating neuronal phenotype, growth and activity are secreted from glia and immunocompetent cells in the vicinity of PAF terminals and inflamed tissue (Berninger and Poo, 1996; Chalazonitis *et al.*, 1992; Lo, 1995; Patterson and Nawa, 1993) (Section 4.8) (Figs 3 and 5).

#### 7.7. Modulatory Effects: Altered Activity and Phenotype of PAFs Mediated *indirectly* by Other Elements of the Inflammatory Response

The final mechanism for an enhancement in the activity of nocisponsive PAF terminals, *modulatory effects*, is a general term. It refers to a complex mesh of reciprocal interactions amongst the broad diversity of elements which directly and indirectly control the activity of nocisponsive PAFs (Figs 3 and 4) (Dray and Urban, 1996; Dray *et al.*, 1994; Reeh and Kress, 1995; Treede *et al.*, 1992b). Certain components of the inflammatory response, such as cytokines, exert principally modulatory actions and may *not* directly affect PAF terminals. Further, modulatory effects are a virtually universal mechanism for

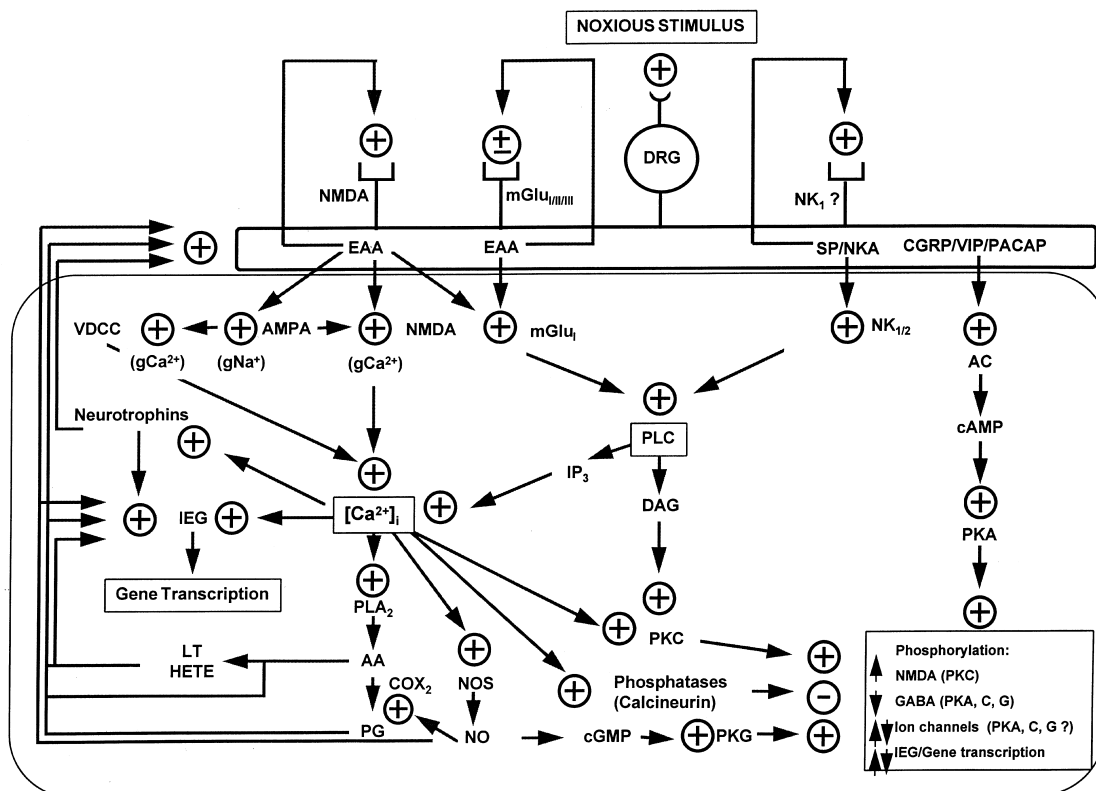


Fig. 5. Receptorial and intracellular mechanisms underlying the sensitization of WDR neurones in the DH by C fibre-mediated, nociceptive input. Abbreviations are as indicated in the general list. In addition: HETE, hydroxyecotetraenoic acid; and LT, leukotriene. For reasons of clarity, additional interactions are not shown (Sections 10.3 and 10.4). Ultimately, membrane-localized ion channels represent the final common pathway via which the electrical activity of DH neurones (and nociceptive output) is modified. This may be expressed either rapidly, via the transduction mechanisms indicated, and/or, in the long-term, by alterations in gene transcription (neuronal phenotype). Some of the actions indicated are based upon observations made in other tissues displaying NMDA receptor-mediated processes of synaptic amplification: in particular, hippocampal mechanisms of LTP. The putative role of neurotrophins is based upon a line of reasoning discussed in detail in Section 14 but not, as yet, proven to occur in DH neurones. In addition, the feedback action of SP on PAF terminals may be expressed both directly and indirectly. The following (non-illustrated), potential mechanisms should also be noted. Both PKA and a calmodulin-dependent PK may trigger the phosphorylation (activation) of AMPA receptors (Section 10.4). The anterograde transport of BDNF to PAF terminals may allow it to influence DH neurones (Section 14.5.3). NO also may be derived from PAF terminals and other neuronal and non-neuronal cell types (Section 3.2.8.3). ATP (derived from PAF terminals and other sources) may excite DH neurones via ionotropic  $P_{2X}$  receptors and metabotropic  $P_{2Y}$  receptors (Section 3.2.8.2). PGs (derived from PAF terminals and other sources) may activate DH neurones via excitatory EP receptors coupled to a variety of intracellular signals (Section 3.2.8.4).

the modification of PAF activity by algogenic substances in inflamed tissue, including SP, BK, NGF and PGs etc. Specific tissue types (such as mast cells) may release several modulatory substances, while an individual modulatory agent (such as NGF) may be derived from multiple sources. Several examples may be cited (Fig. 3): platelets (5-HT); mast cells (5-HT, histamine and NGF); polymorphic leukocytes (protons, PGs and the leukotriene, di-HETE); lymphocytes and macrophages (cytokines); Schwann cells (NGF and PGs); fibroblasts and keratinocytes (NGF); blood vessel endothelial walls (NO, cytokines and PGs) and sympathetic terminals (NAD, NPY, ATP, NO and PGs) (Fig. 3). Illustrative of such modulatory mechanisms are the following interactions.

1. Several pro-inflammatory and pronociceptive cytokines, including IL-1 $\beta$  and TNF $\alpha$ , are secreted from macrophages, fibroblasts and other immune cell types in response to infection, inflammatory stimuli and algogenic factors such as NO, SP and NGF. Cytokines and, in particular, TNF $\alpha$ , sensitize nociceptive neurones by multiple, indirect mechanisms leading to, for example, an induction of  $B_1$  receptors, possibly on PAF terminals themselves, on immune cells and on sympathetic terminals (Aloe *et al.*, 1997; Cunha *et al.*, 1991, 1992; Davis and Perkins, 1994, 1997; Hua *et al.*, 1996; Maier *et al.*, 1993; Perkins and Kelly, 1994; Petersen *et al.*, 1998b; Rueff *et al.*, 1996; Seabrook *et al.*, 1997; Wagner and Myers, 1996a; Wagner *et al.*, 1998; Wang *et al.*, 1997d; Watkins *et al.*, 1994) (see below and



Section 8.2.1). Further,  $\text{TNF}\alpha$  and IL-1 $\beta$  enhance the synthesis and release of other inflammatory mediators, including PGs (COX 2 induction) NO and, via a positive feed-back loop, NGF from fibroblasts and Schwann cells (Arias-Negrette *et al.*, 1995; Davis and Perkins, 1994; Kelly *et al.*, 1997; McMahon and Bennett, 1997; Miyasaka and Hirata, 1997; Newton *et al.*, 1997; Perkins and Kniss, 1997; Safieh-Garabedian *et al.*, 1995; Thomazzi *et al.*, 1997; Watkins *et al.*, 1995; Woolf *et al.*, 1997) (see below). Interestingly, PGs may fulfil an *inhibitory*, feed-back role since they *decrease* cytokine secretion from lymphocytes and macrophages. Paradoxically, therefore, despite relief of pain, anti-inflammatory drugs inhibiting COX activity may *exacerbate* joint disintegration in arthritis by indirectly increasing cytokine levels (Bakhle and Botting, 1996; Huskisson *et al.*, 1995; Renz *et al.*, 1995).

2. In addition to (*delayed*) hyperalgesic actions of NGF expressed *directly* upon PAFs via a change in their phenotype (Section 7.6.1), NGF can *indirectly* (and *rapidly*) sensitize nociceptive PAFs (Lewin *et al.*, 1993). This action of NGF (seen over a period of 5–30 min) reflects both:

1. the degranulation of mast cells and other types of immunocompetent cell; and
2. an activation of sympathetic neurones, for which NGF is a trophic factor (Rueff and Mendell, 1996; Tal and Liberman, 1997).

Indeed, like small calibre PAF and sympathetic terminals, mast cells possess TRK A receptors for NGF—and, possibly, also TRK B receptors for BDNF, the potential significance of which remains to be evaluated (Davis *et al.*, 1996; Horigome *et al.*, 1993; Lewin and Barde, 1996). Interestingly, further, mast cells themselves synthesize and release NGF (Leon *et al.*, 1994). Mast cell inactivation, or pharmacological blockade of serotonergic transmission, can prevent the immediate (5 min) hyperalgesic response to NGF: this suggests that NGF stimulates mast cells to release 5-HT. Sympathectomy abolishes a somewhat later (30 min) component of NGF-hyperalgesia suggesting that sympathetic terminals may be sequentially activated (Andreev *et al.*, 1995; Gentry *et al.*, 1997; Lewin *et al.*, 1994b). However, the precise temporal pattern of events remains to be further elucidated. Indeed, a recent study of inflammatory hyperalgesia over a longer observation period of several days (Woolf *et al.*, 1996) suggested that the contribution of sympathetic terminals to NGF-induced hyperalgesia may be relatively *short-lived* whereas mast cells and direct transcription-dependent actions on sensory neurones (Section 7.6.1) may later re-assume a more preponderant role. A further, recent study also suggested that mast-cell activation may be the principal mechanism involved in the long-term (several days) thermal hyperalgesia provoked by NGF in rats (Rueff *et al.*, 1996). The proximate mechanisms were suggested to be:

1. an increase in BK levels triggered by a NGF-induced degranulation of mast cells to liberate kallikrein enzymes; and

2. a consequent enhancement in cytokine ( $\text{TNF}\alpha$ /IL-1 $\beta$ ) release from macrophages mediated jointly by NGF and BK and leading to the above-mentioned upregulation of  $\text{B}_1$  receptors on PAF and/or sympathetic terminals (Petersen *et al.*, 1998b; Rueff *et al.*, 1996).

That is, cytokines mediate NGF-hyperalgesia by up-regulating  $\text{B}_1$  receptors on sympathetic and/or PAF terminals. On the other hand, there is evidence that, in an *opposite* fashion, NGF mediates the pronociceptive actions of  $\text{TNF}\alpha$ , and that NGF directly induces  $\text{B}_1$  receptors on PAF terminals via  $\text{p75}^{\text{NTR}}$  sites (Petersen *et al.*, 1998b; Watkins *et al.*, 1995) (*vide supra*). Thus, the interrelationship between NGF and cytokines in pronociceptive mechanisms (and  $\text{B}_1$  receptor induction) remains unclear. Indeed, the roles of NGF and cytokines are emerging to be increasingly complex and their multiple and reciprocal interactions require further mechanistic elucidation. The influence of sympathetic mechanisms is further discussed in Section 8.2.4.

3. As mentioned already (Section 7.4.3), leukotriene  $\text{B}_4$  (a lipoxygenase product of arachidonic acid metabolism) indirectly increases the thermal and/or mechanical sensitivity of C fibres by releasing a further leukotriene, 8*R*,15*S*-diHETE, from polymorphonuclear leukocytes (Amann *et al.*, 1996; Dray *et al.*, 1994; Levine *et al.*, 1986a; Martin, 1990; White *et al.*, 1990). A role of leukotrienes in the hyperalgesic actions of NGF has also been proposed (Amann *et al.*, 1996).
4. Principally via  $\text{B}_2$  receptors, BK induces a panoply of pronociceptive/proinflammatory effects including: degranulation of mast cells to release cytokines (*vide supra*), PGs, 5-HT and histamine; venous extravasation and vasodilation; chemotaxis of lymphocytes, and an enhancement of the release of NAD and other mediators from sympathetic neurones—via stimulation of  $\text{B}_2$  and/or  $\text{B}_1$  receptors on their terminals (Berg and Koteng, 1997; Dray and Perkins, 1993; Dray and Urban, 1996; Green *et al.*, 1997; Holthusen, 1997; Marceau, 1995; Miao *et al.*, 1996; Reeh and Kress, 1995; Seabrook *et al.*, 1997; Sorkin *et al.*, 1997; Taiwo and Levine, 1988; Wang *et al.*, 1997a; Yuan *et al.*, 1997) (*vide supra*). These multiple actions of BK add to its direct effects at PAFs in collectively enhancing nociception and inflammation. SP, a principal mediator of NI, exerts a similar, multifarious pattern of pro-inflammatory actions (Section 7.9). The actions of SP include mast cell degranulation, and it has been suggested that the activation of  $\text{A}_3$  receptors may likewise increase nociception and inflammation via the release of histamine and 5-HT from mast cells (Sawynok *et al.*, 1997; Maggi, 1991b).
5. In addition to direct actions at PAFs, NO may participate in the induction of COX 2 in other cells types, thereby increasing the production of PGs and exacerbating inflammation and nociception. However, the generality of this action has been challenged and reciprocal, tissue-dependent interactions between NO synthase and COX

synthase require further elucidation (Busija and Thore, 1997; Henrion *et al.*, 1997; Payá *et al.*, 1997; Swierkosz *et al.*, 1995; Salvemini *et al.*, 1996). An induction by NO of TNF $\alpha$  production in immunocompetent cells may also be of significance in view of the pronociceptive actions of this cytokine (Wagner and Myers, 1996a,b; Wang *et al.*, 1997e) (*vide supra* and Section 8.2.1). Indirect actions of NO also likely reflect its vascular effects. These vascular actions of NO are mediated via a complex interplay between cGMP, PKG and  $[Ca^{2+}]_i$ , the sequestration of which modifies the phosphorylation of myosin and other smooth muscle components in the vascular wall, resulting in an increase in permeability (extravasation) and contractility (vasodilation) (Lee *et al.*, 1997b; Payá *et al.*, 1997; Yuan *et al.*, 1997).

6. Finally, 5-HT may influence the activity of sympathetic nerve terminals, the ganglia of which express mRNA encoding multiple 5-HT receptor types: 5-HT<sub>1A</sub>, 5-HT<sub>1B</sub>, 5-HT<sub>2A</sub>, 5-HT<sub>2B</sub>, 5-HT<sub>3</sub> and 5-HT<sub>7</sub> (Pierce *et al.*, 1996, 1997; Newberry *et al.*, 1996). Excitatory actions of 5-HT<sub>2B</sub> and 5-HT<sub>3</sub> receptors on sympathetic terminals might, for example, contribute to the pronociceptive and proinflammatory actions of 5-HT whereas a 5-HT<sub>1B</sub> receptor-mediated inhibition of release from sympathetic terminals might decrease nociception and play a role in the vasoconstrictor/anti-inflammatory actions of 5-HT at CBVs (Jones *et al.*, 1995; Molderings *et al.*, 1996; Newberry and Gilbert, 1989) (Section 7.9). In addition, receptors for 5-HT (e.g. 5-HT<sub>2A</sub> sites) have been described on Schwann cells suggesting that they may indirectly mediate the influence of 5-HT upon the activity of PAF terminals (Yoder *et al.*, 1997).

### 7.8. Peripheral Antinociceptive Mechanisms

Although the previous paragraphs focused on the *pronociceptive* properties of inflammatory mediators following tissue damage, certain actions within inflammatory tissue may counter pathology and hyperalgesia. The existence of such mechanisms again illustrates the principle of counter-regulation whereby noxious stimulation is associated with the simultaneous activation of (preponderantly) pronociceptive, yet also counter-regulatory, antinociceptive mechanisms.

The cytokine, IL-10, can reduce inflammation and nociception via an inhibition of COX 2-mediated PG production, and by an inhibition of the production and actions of pronociceptive cytokines, such as TNF $\alpha$  (Mertz *et al.*, 1994; Poole *et al.*, 1995; Wagner *et al.*, 1998). In addition, a further endogenous mediator, the inducible polypeptide, lipocortin-1, has been proposed to mediate the peripheral, anti-hyperalgesic actions of glucocorticoids (Ferreira *et al.*, 1997). Histamine generally acts as a pro-inflammatory agent via H<sub>1</sub> and H<sub>2</sub> sites (Sections 7.4.8 and 7.9.3). However, its release from mast cells in CBVs may *reduce* nociception via an action at in-

hibitory H<sub>3</sub> sites localized on the terminals of trigeminal PAFs innervating dural vessels: a reduction in Ca<sup>2+</sup>-dependent release may be involved in this action (Dimitriadou *et al.*, 1997; Matsubara *et al.*, 1992). It has also recently been suggested that somatostatin exerts peripheral, antinociceptive properties in reducing the activity and mechanosensitivity of articular PAFs in inflamed joints (Heppelmann and Matthias, 1997).

Nevertheless, most recent attention has been directed towards reports that locally-generated opioid peptides (including  $\beta$ -endorphin derived from immune cells) may decrease nociception via actions at  $\mu$ -,  $\delta$ - and/or  $\kappa$ -receptors localized on (and upregulated in) sensory neurones, sympathetic terminals and/or other elements in inflammatory tissue (Catheline *et al.*, 1996; Eriksson-Mjöberg *et al.*, 1997; Kalso *et al.*, 1997; Khasar *et al.*, 1995; Lyons and Blalock, 1997; Stein and Yassouridis, 1997; Stein *et al.*, 1989; Stein, 1993; Taiwo and Levine, 1992; Wilson *et al.*, 1996a; see also Picard *et al.*, 1997). A disruption of the perineural blood-nerve barrier in inflamed tissue might also lead to an improved access of circulating pools of opioids to PAF terminals, a change of broader relevance to the peripheral actions of other agents (Antonijevic *et al.*, 1995; Coggeshall *et al.*, 1997). IL-1 $\beta$  has also been claimed to elicit antinociception via the release of opioids from immune cells in inflamed tissue and, in IL-1 $\beta$ -pretreated joints, des-Arg<sup>9</sup>-BK was reported to elicit *antinociception* via the local release of opioids (Davis and Perkins, 1997). However, as described earlier (Section 7.7), IL-1 $\beta$  elicits predominantly *pronociceptive* and *proinflammatory* actions and it has been suggested that its antinociceptive effects reflect a weak affinity for opioid receptors (Wang *et al.*, 1997e). CRF, derived from immune cells, sympathetic or PAF terminals, has also been proposed to elicit peripheral antinociception via a local, opioidergic mechanism (Bileviciute *et al.*, 1997a; Schäfer *et al.*, 1994, 1997). Further, CRF exerts a complex pattern of anti-inflammatory and pro-inflammatory actions, for example, via mast cell degranulation (Kiang and Wei, 1985; Schäfer *et al.*, 1997; Theoharides *et al.*, 1998). Interestingly, in analogy to mechanisms well-documented in the DH, CCK interferes with peripheral opioidergic mechanisms of antinociception, possibly via the induction of PKC and an increase in  $[Ca^{2+}]_i$  levels (Schäfer *et al.*, 1998) (Sections 3.2.6 and 8.2.5). The novel heptadecapeptide, nociceptin, has high affinity for a recently-cloned, opioid-like-receptor (Meunier, 1997). Its levels are increased in the DRG by inflammation (Andoh *et al.*, 1997). Whether nociceptin plays an anti- or pronociceptive role in peripheral inflammation would be of interest to clarify (Meunier, 1997).

### 7.9. Antidromic Activation of PAFs: NI, Vasorelaxation and Migraine Headache

#### 7.9.1. The Efferent Role of PAFs

The above paragraphs described the direct, excitatory and sensitizing actions, as well as the indirect, modulatory effects, of algogenic agents at sensory,

nocisponsive neurones under conditions of local tissue damage. Together with changes in PAF phenotype, such actions collectively increase the orthodromic input from nocisponsive PAFs to the DH. However, PAFs also transmit *antidromic* impulses, propagated via the invasion of collateral fibres and a limited degree of C fibre terminal coupling. This leads to an enhancement in the peripheral release of EAAs, CGRP SP, etc. The liberation of these substances, which is further amplified by their local, positive feedback actions on PAF terminals (Section 7.4.9), underlies processes of NI. In this respect, SP is probably the principal mediator. NI occurs in a broad variety of tissues (skin, muscle, joints and viscera) and refers to a constellation of effects including: an increase in blood flow; vasodilation; plasma extravasation; mast cell degranulation; hyperaemia; and an enhancement of leukocyte adhesion to vascular endothelium, actions expressed in interaction with immune cells, sympathetic endings, blood vessel walls and other tissues (Boolell and Tooke, 1990; Donnerer and Amann, 1993; He *et al.*, 1990; Holzer, 1988; Mantyh *et al.*, 1989; McMahon, 1994; Maggi, 1991a,b; Marchettini *et al.*, 1996; Sann *et al.*, 1996; Schaible and Grubb, 1993; Smith *et al.*, 1993).

In analogy to their *afferent*, 'warning' role in the DH, the *efferent*, peripheral role of PAFs is adaptive in promoting wound healing and counteracting local infection, actions effected via an enhancement of tissue irrigation and infiltration by immune cells, etc. (Brain and Cambridge, 1996; Holzer, 1988; Maggi, 1991a,b) (Section 2). As a more specific example of a beneficial consequence, the (proton-induced) release of CGRP in muscle during intense exercise enhances local blood flow and oxygen supply and stimulates electrogenic  $\text{Na}^+\text{-K}^+$  muscle pumps: thereby, the efficiency of muscle fibre excitability and contractility is enhanced, and performance is sustained under intense effort (Andersen and Clausen, 1993; Maggi, 1991a,b). Under certain pathological conditions, however, such as arthritis, processes of NI exacerbate tissue damage and pain by indirectly facilitating the interplay of the immune, vascular and sympathetic components of pro-inflammatory and pronociceptive events detailed above. In this light, the antidromic activation of (and release of neuropeptides from) sensory terminals may be considered a special case of those above-discussed 'Modulatory Actions' (Section 7.7) which *indirectly* potentiate the activity of nocisponsive PAFs.

Interestingly, not all classes of C fibre mediate NI, and the population(s) of C fibres which orthodromically convey nociceptive information to the DH are not identical to those antidromically eliciting NI. Indeed, in certain (non-rodent) species, a distinctive and specialised class of heat-responsive PAF may mediate cutaneous vasodilation and the axonal flare component of NI (Lynn *et al.*, 1996) (Sections 3.1.1 and 3.2.1).

#### 7.9.2. NI, Vascular Mechanisms and Migraine

Although NI is a general feature of tissue damage, processes of NI in CBVs have been specifically

implicated in the induction of migraine headaches. Thus, the theory of 'sterile NI' advocates that central mechanisms result in the antidromic invasion of trigeminal PAF terminals (Donnerer and Amann, 1993; Moskowitz, 1992), thereby provoking the release of proinflammatory (vasodilatory) and pronociceptive substances, such as SP, CGRP and EAAs. Their actions result in the vasorelaxation and inflammation of subdural CBVs (including arteries) (Dimitriadou *et al.*, 1997; Edvinsson *et al.*, 1997; Schmelz *et al.*, 1997a). An appealing feature of this neurogenic theory is that it can accommodate an involvement of 'stress' or other central 'mood' changes in the precipitation of migraine attacks. For example, the 'stress'-induced phenomenon of spreading depression underlies the aura of migraine headaches and may be involved in triggering the antidromic activation of trigeminal fibres (Olesen and Janssen-Olesen, 1997). As outlined in Section 4.8, spreading depression refers to a process whereby waves of successive hyperpolarization and depolarization in neuronal and non-neuronal cells sweep across the cortex and ultimately attain deeper structures (Olesen and Janssen-Olesen, 1997).

However, the question of the mechanism(s) underlying the induction of migraine headache is still intensely debated (Lance, 1993; Moskowitz, 1992; Olesen and Janssen-Olesen, 1997; Ferrari and Saxena, 1993). Indeed, although SP is probably the major mediator of NI, clinical results with  $\text{NK}_1$  antagonists in migraine have, to date, been disappointing. This suggests that selective blockade of—at least, the  $\text{NK}_1$  receptor-mediated component of—NI is *not* sufficient to interrupt migraine attacks (Clayton *et al.*, 1997; Cutrer *et al.*, 1995; Williamson *et al.*, 1997). Further, although the serotonergic agent, sumatriptan, and other drugs effective in terminating migraine attacks, inhibit NI via actions on the terminals of trigeminal PAFs in CBVs, the *rapidity* of their actions in relieving migraine attacks has been incorporated as evidence into an alternative, vascular hypothesis of migraine (Ferrari and Saxena, 1993; Williamson *et al.*, 1997). This vascular theory posits that the *primary* event in migraine is a vasodilation of CBVs (arteries) which secondarily activates trigeminal PAFs. A vascular trigger would, thus, be analogous to the role of injury to the skin in initiating excitatory and sensitizing events in cutaneous PAFs. Via actions at  $\text{CGRP}_1$  receptors coupled to AC, CGRP may play a role in the vasodilation of CBV arteries inasmuch as the levels of this powerful vasorelaxant increase during migraine attacks. Further, sumatriptan, via an action at  $5\text{-HT}_{1B}$  receptors, suppresses the release and synthesis of CGRP in trigeminal pathways (Buzzi *et al.*, 1991; Durham *et al.*, 1997; Merhi *et al.*, 1998; Olesen and Janssen-Olesen, 1997).

It is arguable that both neurogenic *and* vascular mechanisms are involved in the induction of migraine headaches and that they reciprocally reinforce each other. In any case, via direct, neuronal (decreased PAF activity) or indirect, vascular (vasoconstriction of CBVs) mechanisms, the inhibition of trigeminal input to the brain by sumatriptan and other serotonergic agents can interrupt migraine attacks. Their actions are mediated by  $5\text{-HT}_{1B}$ ,

5-HT<sub>1D</sub> and/or 5-HT<sub>1F</sub> receptors on trigeminal terminals in the CBV (Bouchelet *et al.*, 1996; Bruinvels *et al.*, 1994; Gupta *et al.*, 1995; Johnson *et al.*, 1997; Lucaites *et al.*, 1996; Phebus *et al.*, 1996; Rebeck *et al.*, 1994; Yu *et al.*, 1997), and by 5-HT<sub>1B</sub> and/or other 5-HT receptor types on CBVs themselves (Bouchelet *et al.*, 1996; De Vries *et al.*, 1996; Ferrari and Saxena, 1993; Gross, 1995; Hamel *et al.*, 1993; Moskowitz, 1992; Razzaque *et al.*, 1997; Saxena and Ferrari, 1989; Ferreira *et al.*, 1997). Central actions at 5-HT<sub>1B</sub> receptors localized on intrinsic PNs and/or on the central terminals of trigeminal afferents in the trigeminal nucleus may also be involved (Castro *et al.*, 1997; Cumberbatch *et al.*, 1997; Goadsby and Hoskin, 1996; Hoskin *et al.*, 1996). In addition, 5-HT<sub>1B</sub> agonists may counter vasoconstriction of CBVs via their inhibitory influence upon the activity of sympathetic terminals innervating dural vessels (Jones *et al.*, 1995; Molderings *et al.*, 1996). Apart from 5-HT<sub>1B</sub> and the other, above-specified classes of 5-HT receptor, other, as yet unidentified, 5-HT receptor types may also be involved in attenuating NI and/or vasodilation: in this regard, the possibility of species differences should be borne in mind (Gupta *et al.*, 1995; Shepherd *et al.*, 1997).

Despite the importance of actions at CBV-localized 5-HT<sub>1B</sub> receptors in alleviating migraine attacks, it must be mentioned that stimulation of 5-HT<sub>1B</sub> receptors on coronary vessels may lead to their vasoconstriction and cardiac side-effects (Terron, 1996). Further, action at 5-HT<sub>1D</sub> receptors on the terminals of sympathetic fibre innervating the heart may likewise modify cardiac function (Molderings *et al.*, 1996).

### 7.9.3. Vasorelaxation as a Trigger of Migraine Headaches: a Role for NO and 5-HT?

As mentioned above, the vascular theory of migraine proposes that the vasodilation of CBVs (arteries) triggers migraine attacks. A multiplicity of factors may be involved in modulating the tone of CBVs and in precipitating their vasorelaxation, including CGRP derived from trigeminal afferents (Section 7.9.2), adrenergic mechanisms, endothelin, EAAs, thromboxanes and histamine (Bockman *et al.*, 1996; Edvinsson, 1982; Kalaria *et al.*, 1989; Matsubara *et al.*, 1992; Merhi *et al.*, 1998; Paul and Page, 1997; Raffa *et al.*, 1996). In addition, serotonergic mechanisms may be of special importance in provoking the vasodilation of CBVs.

Serotonin in the CBVs is derived from central, raphe-localized serotonergic neurones, circulating platelets, endothelial cells, mast cells and, following 5-HT reuptake, perivascular sympathetic elements (De Keyser *et al.*, 1993; Maruki *et al.*, 1984; Mathiau *et al.*, 1994; Stanley *et al.*, 1993). The 5-HT receptor type(s) involved in eliciting migraine attacks remain unclear. Certain authors have proposed a principal role for 5-HT<sub>2C</sub> or, more likely, 5-HT<sub>2B</sub> receptors, though based on a rather cavalier interpretation of the evidence (Fozard and Kalkman, 1994). As mentioned in Section 7.9.2 5-HT<sub>1F</sub>, 5-HT<sub>7</sub> and/or other, as yet unidentified, 5-HT receptor types may also be of significance in modulating the functional status of

CBVs (Cohen and Hamel, 1996; Connor and Beattie, 1996).

It has been suggested that an activation of central sources of 5-HT by 'stress', and/or the mobilization of peripheral pools of 5-HT, may trigger migraine attacks by an (endothelium-dependent) release of NO (Olesen *et al.*, 1993; Olesen and Janssen-Olesen, 1997). NO may also be involved in the NMDA receptor-mediated vasodilation of cerebral microvessels by GLU, a phenomenon of potential relevance to vascular processes in CBVs underlying headache (Fergus and Lee, 1997). CBVs contain mRNA encoding both H<sub>1</sub> and H<sub>2</sub> receptors and a role of NO in the vasodilatory actions of histamine at CBVs has also been proposed. Thus histamine relaxes CBVs by activating both:

1. endothelium-dependent H<sub>1</sub> receptors triggering (via PLC/[Ca<sup>2+</sup>]<sub>i</sub>) the synthesis and release of NO which subsequently elicits vasodilation and NI; and
2. endothelium/NO-independent H<sub>2</sub> receptors coupled to increases in cAMP in smooth muscle cells (Gimeno *et al.*, 1998; Janssen-Olesen *et al.*, 1997; Olesen and Janssen-Olesen, 1997; Olesen *et al.*, 1993; Yuan *et al.*, 1997).

In support of the hypothesis that NO is involved in the induction of migraine headache, it can trigger smooth muscle relaxation (CBV arterial vasodilation) and extravasation via the generation of cGMP and, ultimately, a decrease in free [Ca<sup>2+</sup>]<sub>i</sub> (Lee *et al.*, 1997b; Payá *et al.*, 1997; Yuan *et al.*, 1997) (Section 7.7). In addition, several other actions of NO might synergistically aggravate vasorelaxation and pain. For example, NO may interact with trigeminal terminals to facilitate neuropeptide release (Section 7.5.2.5), it increases PG levels via the induction of COX 2 and it enhances TNF $\alpha$  production from immunocompetent cells (Cohen *et al.*, 1996; Fozard, 1995; Salvemini *et al.*, 1996; Taiwo and Levine, 1988; Valentin *et al.*, 1996; Verheggen *et al.*, 1996; Wang *et al.*, 1997e) (Section 7.7). The supersensitivity of migraine patients to the vasodilatory effects of NO on CBVs has been advanced in support of the argument that NO plays a key role in provoking the vasodilation of CBVs and migraine headaches (Olesen *et al.*, 1993; Olesen and Janssen-Olesen, 1997).

Interestingly, a *vasoconstriction* of *extracranial*, non-CBV vessels (such as the temporal artery) also contributes to migraine pain in *ca* 30% of patients. 5-HT<sub>2A</sub> and 5-HT<sub>1B</sub> receptors mediate vasoconstriction of these extracranial CBVs—an effect *counteracted* by NO. These vessels also contain several other 5-HT types, including 5-HT<sub>4</sub> and 5-HT<sub>7</sub> receptors. However, it is unclear whether a perturbation of the function of 5-HT receptors is involved in provoking the vasoconstriction of extracranial vessels (Salamone *et al.*, 1997; Verheggen *et al.*, 1996, 1997).

Notwithstanding the role of neurogenic and central processes, as well as muscular mechanisms (pericranial muscle tenderness), migraine headaches provide a distinctive illustration of the involvement of vascular mechanisms in the generation of pain (Lipchick *et al.*, 1996; Procacci *et al.*, 1994).

## 8. NEUROPATHIC PAIN: PERIPHERAL PROCESSES

### 8.1. Experimental Models of Neuropathic Pain

Neuropathic pain refers to the pain caused by damage to nervous tissue (Tables 1, 3 and 6, Fig. 2). Although pain elicited by peripheral nerve injury is sometimes used synonymously with ‘neuropathic’ pain, this latter term also incorporates the ‘central’ pain associated with damage to the CNS: for example, the thalamic syndrome which (albeit rarely) may be a sequel of stroke (Boivie *et al.*, 1989) (Section 13). Paradoxically, in addition to a disturbance of sensory and motor function and a disruption of RFs, one prominent feature of peripheral nerve damage may actually be an *enhancement* in pain ‘sensation’. Indeed, partial damage to—and even destruction of—peripheral nerves may be associated with a variety of syndromes including an increase in the sensitivity to noxious stimuli (hyperalgesia), a painful response to normally innocuous mechanical and cold stimuli (allodynia), parasthesic and dythesic sensations and spontaneous pain (Table 1). Of these changes, mechanical allodynia comprises the most striking perturbation of sensation. Thresholds to respond to *innocuous* heat stimuli are *not* invariably modified—although a thermal *hyperalgesia* is seen in several models of PAF damage (Hunter *et al.*, 1996, 1997b; Shir and Seltzer, 1990). On the other hand, a hyperalgesia/allodynia to cold may be pronounced, in particular in sympathetically-maintained painful states (Cervero and Laird, 1996b; Frost *et al.*, 1988; Lindblom, 1985) (Section 8.2.4). This pattern of altered sensitivity in neuropathic pain clearly differs to the *primary* (heat) hyperalgesia of nociceptive pain, in which cooling of the site of injury may even reduce pain, and more closely resembles the secondary hyperalgesia which accompanies tissue damage,

in particular as concerns the occurrence of mechanical allodynia (Section 9.1.2).

As explained in Section 7, peripheral mechanisms integrated in the terminals of nocisponsive PAFs appear to be the principal cause of primary hyperalgesia. In contrast, neuropathic pain—and secondary hyperalgesia—may largely be attributed to changes occurring *downstream* of PAF terminals. Extensive experimental studies of neuropathic pain, involving axotomy, or various models of sub-total nerve damage (‘mononeuropathies’), have allowed for a detailed exploration of mechanisms underlying neuropathic pain due to PAF injury (Coyle, 1996).

An important question concerning the induction of prolonged, clinical pain is how damaged nerves trigger changes in the DH and higher structures. A related issue is whether input from injured PAFs needs to be *maintained* for pain to persist (Section 9.1.3) (Fig. 2 and Table 6). In this regard, it is of note that PAF injury is associated with the rapid, intense, central discharge of both A $\beta$  and C fibres for a period of minutes—and even several days for some individual fibres (Seltzer, 1995). This pronounced discharge of PAFs upon their injury mimics their intense physiological stimulation (via nociceptor activation) and may elicit central processes of sensitization (Sections 10 and 12). Indeed, for several animal models, an initial discharge of damaged PAFs post-injury is a critical factor in the development of allodynia and other pain-related behaviours. In other models, it may play a minor role and subsequent events are of greater importance (Dougherty *et al.*, 1992a; Seltzer, 1995). In any case, injury to PAFs may be followed by their ‘ectopic’ firing (independently of nociceptor stimulation) both spontaneously and in response to sympathetic, mechanical and other modes of stimulation (Babbedge *et al.*, 1996; Devor *et al.*, 1994; Kajander and Bennett, 1992; Sheen and Chung, 1993) (Sections 8.2.2 and 8.2.4).

Table 6. Summary of principal mechanisms underlying the induction of prolonged, painful states due to PAF injury (see Sections 8 and 11)

#### A. Peripheral mechanisms

1. Activation of damaged (and adjacent, intact) PAFs by inflammatory mediators (see Table 5, Peripheral Events)
2. Increase in the spontaneous excitability and responsiveness of damaged PAFs. Mediated by changes in the expression levels and operating characteristics of multiple ion channel subtypes localized in the DRG and/or neuroma of PAFs: various classes of Ca<sup>2+</sup>-, K<sup>+</sup>- and, in particular, Na<sup>+</sup>- channel are involved
3. Abnormal patterns of inter-neuronal communication in the DRG and/or neuroma: ‘Crossed-after-discharge’ (possibly mediated via a diffusible mediator) and ‘ephaptic transmission’ (reflecting direct, interneuronal current flow)
4. Increased sympathetic innervation and excitation of the DRG and/or neuroma of PAFs. Mediated via actions of NAD at  $\alpha_2$ - (and  $\alpha_1$ -) adrenergic receptors, as well by the release of other mediators, such as PGs
5. Altered phenotype of damaged, small calibre C fibres: for example, an induction of pronociceptive mediators such as VIP and NO
6. Altered phenotype of damaged, large calibre A $\beta$  fibres: notably, an induction of SP
7. Aberrant patterns of peripheral regeneration of damaged PAFs, and alterations in their functional properties. In addition, sprouting of intact, collateral PAFs into areas of denervated, peripheral tissue

#### B. Central mechanisms

1. Reorientation of the DH terminals of A $\beta$  fibres—‘primed’ by PAF injury—into alien territories: in particular, migration from *non*-nocisponsive laminae III/IV into lamina II<sub>0</sub>, a region involved in the reception and transmission of nociceptive information. C fibres and descending pathways may also invade inappropriate regions of the DH
2. Functional reduction in the activity (or physical degeneration) of those ININs which normally suppress the supraspinal flow of nociceptive information via inhibitory actions at PNs, EXINs and PAF terminals
3. Other central events specified in Table 5

In a representative model of damage to the sciatic nerve, such questions were addressed quantitatively and it was shown that the mechanical sensitivity of certain, neurectomized A $\beta$  fibres developed rapidly over hours and peaked within weeks, thereafter declining to a low level (Babbedge *et al.*, 1996; Devor, 1994, 1995). On the other hand, the onset of their *spontaneous* firing took some days to occur, peaked (30% of neurones) within a week and returned to a level of 3–4% after a month (Babbedge *et al.*, 1996). C fibres revealed a different pattern, with spontaneous firing emerging later and totalling 2–3% of neurones. Apparently, then, under some conditions, activity in a relatively small population of affected PAFs may suffice to maintain changes in nociception which can be blocked by destruction of the injured nerve or application of anaesthetics thereto (Kajander and Bennett, 1992; Seltzer, 1995) (Section 9.1.3).

In fact, such quantitative and temporal aspects of the sensory disruption provoked by PAF damage are complex, model-dependent and difficult to relate to the clinical situation. Indeed, the characteristics of sensory deficits resulting from PAF injury, the delay to their appearance, the time required for resolution of symptomatology and the underlying mechanisms all may depend on the type of lesion and the precise experimental paradigm employed (Coyle, 1996). Further, the relative importance of input from injured and intact PAFs in mediating alterations in nociception may be variable. Nevertheless, it is possible to identify several important, peripheral and central events common to various models of PAF injury and which likely contribute to the clinical features of neuropathic pain due to peripheral nerve damage (Bennett and Xie, 1988; Coderre, 1992; Coderre *et al.*, 1993; Coyle, 1996; Guilbaud and Benoist, 1995; Kim and Chung, 1992; Koltzenburg, 1995; Na *et al.*, 1996; Woolf and Doubell, 1994; Yoon *et al.*, 1996) (Section 11).

## 8.2. Peripheral Mechanisms Underlying Neuropathic Pain

### 8.2.1. Inflammatory Events: Focus on Cytokines

Certain of those mechanisms described in Section 7 which underlie inflammatory pain may contribute to rapid changes in nociception resulting from peripheral nerve injury (Michaelis *et al.*, 1997; Tracey and Walker, 1995). Chronic constriction-induced nerve injury is accompanied by a pronounced, local inflammatory response and chronic, nerve ligatures (which release chemicals) are more effective in eliciting hyperalgesia than non-chronic sutures. Further, hyperalgesia can be attenuated by blocking the inflammatory response to ligation (Clatworthy *et al.*, 1995; Maves *et al.*, 1993). In line with these observations, degenerating, nocisponsive neurones release pro-inflammatory mediators (SP, CGRP, etc). Further, at the site of nerve damage and in neighbouring injured tissue, there is a local, inflammatory response which involves acidosis and infiltration by mast cells, macrophages and other immunocomponent cells releasing 5-HT, ATP, NO, leukotrienes,

PGs, NGF and cytokines etc (Perry *et al.*, 1993; Silver *et al.*, 1996; Yoder *et al.*, 1997; Wagner and Myers, 1996b). Proliferating Schwann cells in the vicinity of damaged nerves provide an important source of PGs, NGF, other neurotrophins, NO and the cytokine, LIF (Bolin *et al.*, 1995; Fu and Gordon, 1997; Wagner and Myers, 1996b; Zochodne *et al.*, 1997). LIF may modify nociception and plays an important role in modifying the phenotype and growth of injured PAFs and (intact) sympathetic fibres (Sections 8.2.6.2 and 11.3.4). The sympathetic innervation of damaged nerves is also intensified, and sympathetic terminals constitute a further source of PGs, ATP, NAD and other potential pro-inflammatory and pronociceptive mediators (Section 8.2.4).

Evidently, where the appropriate receptors and transduction mechanisms are available on damaged—and intact—PAF terminals, inflammatory mediators may exert direct and indirect actions contributing to an increase in nociception (Frisén *et al.*, 1993; Michaelis *et al.*, 1997; Tracey and Walker, 1995). Indeed, the prostaglandin, PGI<sub>2</sub>, and the leukotriene, di-HETE, has been shown to enhance ectopic (non-terminal) discharges of damaged C (but not A) afferents in neuromas and to excite otherwise-silent C fibres, suggesting that they increase the afferent barrage to the DH (Devor *et al.*, 1992b; Wagner and Myers, 1996a). Recently, PAF injury was shown to up-regulate B<sub>2</sub> receptors and to induce the '*de novo*' expression of B<sub>1</sub> receptors in the DRG, suggesting a role for BK in the excitation of damaged PAFs (Petersen *et al.*, 1998a).

Macrophages are of particular interest since they are the principal effector cells involved in processes of 'Wallerian' degeneration following injury to myelinated nerves (Fu and Gordon, 1997) (Section 11.3.4.1). By removing axonal myelin, this mechanism plays an important role in generating conditions permitting the successful regeneration of damaged PAFs. Possibly due to a relative absence of macrophages, genetic strains of mice in which Wallerian processes are defective show a delayed time-course of hyperalgesia following nerve injury (Myers *et al.*, 1996; Ramer *et al.*, 1997). Indeed, macrophages secrete several pro-inflammatory and pronociceptive cytokines. One important example, TNF $\alpha$  (Section 7.7), is involved in demyelination processes (Redford *et al.*, 1995) and exerts trophic or toxic effects dependent on the cell type targeted and several other factors (Chao *et al.*, 1996; Shen *et al.*, 1997). Levels of TNF $\alpha$  are increased by nerve injury (Wagner and Myers, 1996a,b; Wagner *et al.*, 1998; Wells *et al.*, 1992). Notably, then, TNF $\alpha$  induces ectopic (burst) firing in nocisponsive PAFs, while its local injection into the sciatic nerve elicits mechanical allodynia and associated pathophysiological changes resembling those provoked by PAF injury (Sorkin *et al.*, 1997; Wagner and Myers, 1996a,b). Further, inhibition of the actions of TNF $\alpha$  reduces hyperalgesia due to PAF injury (Redford *et al.*, 1995; Safieh-Garabedian *et al.*, 1995). These data suggest a pronociceptive function of TNF $\alpha$  at damaged PAFs. There are several potential mechanisms. TNF $\alpha$  enhance the activity of COX 2 and increases the density of B<sub>1</sub> receptors on PAFs and

sympathetic terminals. Further, it elevates tissue levels of IL-1 $\beta$  which, in turn, stimulates the synthesis and release of NGF from Schwann cells, and NGF may *intervene* in the induction of B<sub>1</sub> receptors on PAF terminals by TNF $\alpha$  (Hikawa and Takenaka, 1996; Horie *et al.*, 1997b; Lindholm *et al.*, 1987; Petersen *et al.*, 1998b; Ramer *et al.*, 1997; Rueff *et al.*, 1996; Watkins *et al.*, 1995) (Section 7.7). The complex role of NGF in the modulation of nociception at intact and damaged PAFs is described in Sections 7.6.1, 7.7, 8.2.4 and 8.2.6. A final, intriguing aspect is that cytokines, such as TNF $\alpha$  and ILs, may actually be induced in PAF *themselves* following their injury. A putative functional role of such intrinsic PAF pools of cytokines would be of interest to delineate (Murphy *et al.*, 1995).

### 8.2.2. Alterations in the Density and Function of Ion Channels in Sensory Neurones

#### 8.2.2.1. Ectopic activity of damaged PAFs

Injured small and large diameter PAFs show marked alterations in their patterns of excitability and conduction properties, both spontaneously and in response to excitation. Such changes reflect alterations in the density and/or operating characteristic of multiple ion channels and result in the generation of abnormal patterns of electrical impulses and afferent input to the DH (Fields *et al.*, 1997; Won *et al.*, 1997; Zhang *et al.*, 1997a). Thus, following injury, nerve endings may seal off to form an end-bulb or attempt, unsuccessfully, to sprout, resulting in a confused growth termed a neuroma. Together with their soma in the DRG, neuromas become the site of 'ectopic' (non-terminal) firing (Amir and Devor, 1997; Devor, 1994; Devor and Dubner, 1988; Fields *et al.*, 1997; Han *et al.*, 1994; Kajander and Bennett, 1992; Kajander *et al.*, 1992; Xie *et al.*, 1995b). Such discharges are seen for C and A $\beta$  fibres in each case and occur both spontaneously and in response to stimulation (Amir and Devor, 1992, 1993; Babbedge *et al.*, 1996; Study and Kral, 1996). Indeed, neuromas develop a marked hypersensitivity to mechanical stimuli (and sympathetic input) (Babbedge *et al.*, 1996; Burchiel, 1984; Devor *et al.*, 1994; Matzner and Devor, 1987). Of particular pertinence to mechanical allodynia, the discharge pattern of low threshold, mechanosensitive PAFs is modified (Na *et al.*, 1993). The significance of multiple classes of ion channels in controlling electrical activity in injured PAFs may be summarized as follows.

#### 8.2.2.2. Ca<sup>2+</sup>-Channels

Voltage-sensitive, N-type Ca<sup>2+</sup>-channels are the principal class involved in controlling release from the terminals of sensory, central and sympathetic neurones (Diaz and Dickenson, 1997; Diversé-Pierluissi *et al.*, 1997; Wright and Angus, 1996). Their blockade by verapamil and conopeptide  $\omega$ -toxin analogues reduces neuropathic pain (for example, mechanical allodynia) and inhibits spontaneous, electrical activity in ectopically-active DRG cells. These findings are consistent with a role of overactive N-type, Ca<sup>2+</sup>-channels in the induction

of ectopic firing and nociception upon PAF injury (Bowersox *et al.*, 1996; Chaplan *et al.*, 1995; Devor, 1994; Xiao and Bennett, 1995; Wright and Angus, 1996; Zhang *et al.*, 1994b). Nevertheless, in addition to actions at peripheral populations of N-type channels on injured PAFs, blockade of DH-localized N- (and P-type) Ca<sup>2+</sup>-channels localized on the central terminals of damaged PAFs—and on intrinsic DH neurones—may also be of significance (Bowersox *et al.*, 1996; Chaplan *et al.*, 1995; Miljanich and Ramachandran, 1995; Nebe *et al.*, 1997; Neugebauer *et al.*, 1996; Sluka, 1997). In contrast to N-type Ca<sup>2+</sup>-channels, selective blockade of L-type Ca<sup>2+</sup>-channels may be less effective in moderating nociception provoked by PAF injury. However, the comparative significance of specific classes and discretely-localized populations of various Ca<sup>2+</sup>-channel types in the mediation of neuropathic—as compared to nociceptive—pain remains under investigation (Bowersox *et al.*, 1996; Chaplan *et al.*, 1995; Diaz and Dickenson, 1997; Malmberg and Yaksh, 1994; Miljanich and Ramachandran, 1995; Nebe *et al.*, 1997; Neugebauer *et al.*, 1996; Sluka, 1997). The ability of the anti-convulsants, carbamazepine and gabapentin, to reduce mechanical allodynia, both in the clinic and in experimental models of neuropathic pain, may involve, amongst other mechanisms, an interaction with Ca<sup>2+</sup>-channels localized on the DRG, neuroma and central terminals of injured PAFs (Abrams, 1996; Field *et al.*, 1997; Fields *et al.*, 1997; Galer, 1995; Gee *et al.*, 1996; Hunter *et al.*, 1997b; Stanfa *et al.*, 1997; Todorovic and Lingle, 1998) (Section 13.4).

In line with a pathological role of Ca<sup>2+</sup>-channels in controlling the electrical activity of injured PAFs, a facilitation of Ca<sup>2+</sup>-currents and an elevation of [Ca<sup>2+</sup>]<sub>i</sub> levels contributes to the increase in excitability of damaged PAFs elicited by NGF (Jiang *et al.*, 1997; Sherwood *et al.*, 1997).

#### 8.2.2.3. Na<sup>+</sup>-Channels

The multiplicity of Na<sup>+</sup>-channels present in the DRG of PAFs may, in terms of operational characteristics, be classified into two types.

1. TTX-sensitive, low threshold channels which rapidly activate and inactivate; and
2. TTX-resistant, high threshold channels with slower kinetics of activation and inactivation.

The distribution of these different classes of Na<sup>+</sup>-channel on various populations of PAFs is still under evaluation, but certain interesting differences between small calibre, TRK A-bearing, CGRP-positive PAFs and large, TRK C-bearing PAFs have, for example, been established (Friedel *et al.*, 1997). It is likely that a differential alteration in the density and/or properties of specific Na<sup>+</sup>-channels upon injury to PAFs is of functional importance in determining changes in their discharge properties and AP profiles (Schild and Kunze, 1997). Overall, as outlined below, a relative *increase* in the ratio of kinetically-rapid, TTX-sensitive vs kinetically-slow, TTX-resistant channels may be elicited by PAF injury (Akopian *et al.*, 1996a,b; Black *et al.*, 1996; Friedel *et al.*, 1997; McGiven *et al.*, 1997; Kobayashi *et al.*,

1996; Oyelese *et al.*, 1997; Schaller *et al.*, 1995; Sangameswaran *et al.*, 1996, 1997).

The accumulation of Na<sup>+</sup>-channels in damaged sensory fibres, in particular in areas of demyelination, leads to hyperexcitability and electrical instability: indeed, irrespective of their class, the total density of Na<sup>+</sup>-channels is proportional to the likelihood of repetitive firing in response to mild stimuli. Further, in line with the presence of a high proportion of TTX-sensitive Na<sup>+</sup>-channels, TTX inhibits ectopic impulses from damaged nerves and their DRG (Devor *et al.*, 1992a; Devor *et al.*, 1993; Matzner and Devor, 1994; Omana-Zapata *et al.*, 1997a,b). As concerns individual classes of Na<sup>+</sup>-channel, the C fibre-localized, TTX-resistant PN 3 channel (also termed the 'SCN 10A' gene or the 'α-SNS' transcript)—which is involved in inflammatory pain (Section 7.5.2.3)—is down-regulated upon PAF damage (Akopian *et al.*, 1996a,b; Dib-Hajj *et al.*, 1996; Cummins and Waxman, 1997; Friedel *et al.*, 1997; Oaklander and Belzberg, 1997). On the other hand, a novel, TTX-sensitive ('α-III') channel which is not usually encountered in adult neuronal tissue, appears in fine calibre C fibres following their injury (Black *et al.*, 1996, 1997; Cummins and Waxman, 1997; Kobayashi *et al.*, 1996; Oyelese *et al.*, 1997; Waxman *et al.*, 1994). This Na<sup>+</sup>-channel quickly reprimers (recovers from inactivation) and may predispose nerves to rapid and abnormal firing (Cummins and Waxman, 1997). Further, damage to large diameter Aβ fibres provokes a similar increase and decrease in TTX-sensitive and TTX-resistant Na<sup>+</sup> channels, respectively (Rizzo *et al.*, 1994). A recently-cloned, 'PN 1' TTX-sensitive channel is found both in small and large diameter DRG neurones—as well as sympathetic neurones—suggesting a possible role in mechanical allodynia (Toledo-Aral *et al.*, 1997) (Section 7.6.1). Its relationship to the above-mentioned up-regulation of TTX-sensitive Na<sup>+</sup>-channels would be of interest to establish.

In addition to changes in the expression levels of specific Na<sup>+</sup>-channels, their *activity* (passage of current and inactivation kinetics etc) may be rapidly modified by processes of phosphorylation elicited by inflammatory agents (Sections 7 and 8.2.1), NGF and other modulators of [Ca<sup>2+</sup>]<sub>i</sub> levels and PK activity (Berninger and Poo, 1996; Colbert and Johnston, 1998). Indeed, the alteration of access to NGF and other neurotrophins which results from their injury may play an important role in modifying the expression and operating properties of multiple classes of Na<sup>+</sup>-channel and, thereby, modulating the electrical properties of PAFs (Black *et al.*, 1997; McMahon and Bennett, 1997; Toledo-Aral *et al.*, 1997) (Section 7.6.1).

Systemic administration of Na<sup>+</sup>-channel antagonists/local anaesthetics, such as lidocaine and mexilitine, relieves experimental and clinical neuropathic pain. Their actions may, at least partially, reflect blockade of peripheral (TTX-sensitive) Na<sup>+</sup>-channels in damaged PAFs (Barann *et al.*, 1993; Boas *et al.*, 1982; Calcutt *et al.*, 1996; Chapman *et al.*, 1997; Cummins and Waxman, 1997; Kastrup *et al.*, 1987; Khandwala *et al.*, 1997; Kingery, 1997; McGiven *et al.*, 1997; Nishiyama and Sakuta, 1995; Tanelian and MacIver, 1991). A blockade of voltage-depen-

dent (TTX-resistant and -sensitive) Na<sup>+</sup>-channels in the neuroma and DRG of injured PAFs may also be involved in the anti-allodynic actions of anti-convulsants, such as lamotrigine and phenytoin (Abrams, 1996; Blackburn-Munro and Fleetwood-Walker, 1997; Galer, 1995; Hunter *et al.*, 1997b; Rush and Elliott, 1997; Trezise *et al.*, 1997; though see Chapman *et al.*, 1997) (Section 13.4). Further, the analgesic actions of local anesthetics are expressed *without* an apparent interference with axonal conductance, consistent with the argument that they act at DRG-localized, Na<sup>+</sup>-channels mediating processes underlying ectopic activity (Devor *et al.*, 1992a). Nevertheless, in analogy to Ca<sup>2+</sup>-channels, an additional blockade of Na<sup>+</sup>-channels localized on the central terminals of PAFs—or on intrinsic DH neurones—might also be involved in the reduction of neuropathic pain by such agents (Calcutt *et al.*, 1996; Fraser *et al.*, 1992; Omana-Zapata *et al.*, 1997a,b; Pertovaara *et al.*, 1996).

#### 8.2.2.4. K<sup>+</sup>-Channels

In addition to changes in the density and properties of cation-permeable channels in damaged PAFs, a reduction in the density, or an alteration in the functional properties, of K<sup>+</sup>-channels may also increase excitability (Gold *et al.*, 1996b; Rasband *et al.*, 1998). Indeed, it has been shown that the excitation of damaged nerves by NAD involves a decrease in K<sup>+</sup>-conductance (Abdulla and Smith, 1997) (Section 8.2.4). It is not, as yet, clear whether changes in K<sup>+</sup>-channel activity are a primary response to injury, or whether they are contingent upon changes in the properties of Ca<sup>2+</sup>- and Na<sup>+</sup>-channels (Devor, 1983; Elliott, 1997). In fact, it has been suggested that a Ca<sup>2+</sup>-dependent *increase* in K<sup>+</sup>-conductance may be triggered by ectopic firing leading to a period over which burst firing is suppressed (Amir and Devor, 1997). In addition to Na<sup>+</sup>-channel blockade (Section 8.2.2.3), a facilitation in K<sup>+</sup>-currents may be involved in the attenuation of neuropathic pain by the anaesthetic agent, mexilitine (Khandwala *et al.*, 1997; Kingery, 1997; Sato *et al.*, 1995). Sensory neurones possess multiple, voltage-gated K<sup>+</sup>-currents, the significance of which would be of interest to examine (Gold *et al.*, 1996b).

#### 8.2.2.5. Spontaneous electrical activity, ion currents, [Ca<sup>2+</sup>]<sub>i</sub> and PAF regeneration

One final and intriguing aspect of the electrical activity of damaged PAFs should be mentioned. Although excessive [Ca<sup>2+</sup>]<sub>i</sub> can kill cells (Choi and Rothman, 1990; Lerea, 1997), a certain level of [Ca<sup>2+</sup>]<sub>i</sub> may be required for DRG survival. Indeed, [Ca<sup>2+</sup>]<sub>i</sub> plays a diverse and key role in controlling the activity and growth of injured PAFs, and their electrical activity may act as a mode of 'trophic' support for DRG cells independently of NGF and other neurotrophins (Benowitz and Routtenberg, 1997; Bito *et al.*, 1997; Ghosh and Greenberg, 1995; Gu and Spitzer, 1995; Hegarty *et al.*, 1997; Sjaastad and Nelson, 1997). Thus, inasmuch as damaged PAFs (transiently) lose access to NGF and other trophic factors, a continued ionic flux-maintained



spontaneously and/or in response to stimulation—may *itself* be of significance in processes underlying PAF survival and regeneration (Section 11.3).

### 8.2.3. *Abnormal Patterns of Inter-neuronal Communication*

The ectopic activity of DRG cells and neuromas may be intensified (and hyperexcitability accentuated) by ‘non-synaptic’ interactions between neurones. This refers to the phenomenon whereby activity in an individual neurone (or a group of neurones) modifies activity in adjacent neurones. One mode of inter-neuronal communication, termed ‘crossed-after-discharge’, involves the depolarization of neurones upon the repetitive firing of their neighbours (Amir and Devor, 1996; Devor, 1994, 1995; Fried *et al.*, 1993; Lisney and Devor, 1987). This process, which primarily drives *large* calibre neurones, is seen at the level of the DRG. Therein, under normal conditions, the consequences of minor depolarizations are limited but, following nerve damage, they may exaggerate ectopic activity, set up reverberating (bursting) circuits and recruit silent neurones (Amir and Devor, 1997). The mechanisms underlying cross-excitation in the DRG are unclear, although there is evidence that diffusible factors, such as ATP or, more likely, an elevation in extracellular  $K^+$ -concentrations, may be involved (Amir and Devor, 1996, 1997; Shinder and Devor, 1994; Utschneider *et al.*, 1992). Notably, following injury, neurones and neuromas become more accessible to diffusible substances owing to a loss of their normal insulation (Shinder and Devor, 1994).

Electronic coupling has been recorded in peripheral neurones, and a further mode of excitatory cross-talk is termed ‘ephaptic’ (Lekan *et al.*, 1996). This is seen both at neuromas and at axons in areas of demyelination. It may develop both transiently and rapidly following injury, or several weeks thereafter. The apposition of the membranes of adjacent axons, leading to direct current transfer from one to another, has been implicated (Amir and Devor, 1992; Blumberg and Jänig, 1982; Seltzer and Devor, 1979) (Section 4.7).

These modes of inter-neuronal communication are of particular interest since they might occur between fibres of *different* classes. Should low threshold A $\beta$  fibres activate high threshold C fibres, this mechanism could contribute to the mechanical allodynia whereby a normally innocuous touch stimulus would be perceived as painful (Section 9.1.2). [Interestingly, an alternative theory suggests that, where PAFs are *intact*, A $\beta$  fibres may evoke allodynia by indirectly recruiting C fibres at the level of the DH (Cervero and Laird, 1996a,b; Sluka *et al.*, 1993) (Section 9.2.3).]

### 8.2.4. *Sympathetic Excitation of Damaged Sensory Neurones*

#### 8.2.4.1. *Increased sympathetic innervation and excitation of the DRG upon PAF injury*

The sympathetic nervous system may be involved in sensory changes resulting from damage to peripheral nerves (Coyle, 1996; Drummond, 1996; Fields and Rowbotham, 1994; Kinnman and Levine, 1995;

Hu and Zhu, 1989; Koltzenburg, 1995; Raja, 1995; Raja *et al.*, 1996; Treede *et al.*, 1990b). Under normal conditions, sympathetic fibres exert little direct influence upon peripheral, sensory nerve endings (Section 7.4.7). However, following injury, PAF responsiveness to sympathetic stimulation is markedly augmented. Such changes are apparent for both the neuroma and the DRG. In addition, some intact, PAF endings in their vicinity may also manifest a (less pronounced) increase in sympathetic sensitivity. Affected PAFs develop a pronounced response to stimulation of the appropriate sympathetic nerve trunk and to (topical or systemic) administration of  $\alpha$ -AR agonists, such as NAD (Davis *et al.*, 1991; Devor *et al.*, 1994; Sato and Perl, 1991).

The sympathetic innervation of the DRG normally terminates within the surrounding vasculature and its role is largely limited to the control of blood supply. However, upon nerve damage, sympathetic afferents—with a time-course corresponding to the appearance of mechanical allodynia—extend into the DRG to form basket-like structures around cell bodies, in particular large soma corresponding to low threshold A $\beta$  (and proprioceptive) fibres. Smaller neurones may also—at least transiently—be affected (Chung *et al.*, 1996; McLachlan *et al.*, 1993; Ramer and Bisby, 1997a,b; Zhou *et al.*, 1996b). Following PAF injury, electron microscope studies have also revealed close contacts between sympathetic endings and sensory neurones in the DRG (Chung *et al.*, 1997). As a consequence, both NAD—and, in theory, other transmitters released by stimulation of sympathetic terminals—can now modulate the activity of DRG cells. While some hitherto-silent soma in the A $\beta$  fibre range are recruited, it is the activity of spontaneously firing cells which is most markedly accelerated.

The above observations suggest that, following injury to PAFs, the development of an aberrant sympathetic input to the DRG amplifies both their spontaneous and evoked activity and, correspondingly, enhances the ectopic barrage to the DH. Correspondingly, chemical or surgical sympathectomy (which is more effective if performed prior to nerve injury) can alleviate mechanical allodynia and other symptoms of neuropathic pain in the majority—though *not* all—experimental models (Chung *et al.*, 1996; Coyle, 1996; Kim and Chung, 1991; Lee *et al.*, 1997a). Further, guanethidine, which depletes peripheral catecholamines and other sympathetic transmitters, can relieve the pain of sympathetic-dependent painful states in some—but not all—human subjects (Torebjörk *et al.*, 1995). Similar results are, generally, obtained with adrenergic antagonists (Ghostine *et al.*, 1984; Raja, 1995; Raja *et al.*, 1996; Xie *et al.*, 1995a; Wahren *et al.*, 1995). Contrariwise, pain can be rekindled by local administration of NAD into the injured tissue (Coyle, 1996; Torebjörk *et al.*, 1995; Wallin *et al.*, 1976; Xie *et al.*, 1995a).

Irrespective of the mechanisms underlying sympathetic activation of damaged PAFs (Section 8.2.4.2), the ability of chemical sympathetic blockade to *rapidly* alleviate sympathetically-maintained pain (even within minutes) is consistent with the concept that the central sensitization underlying

pain is maintained by peripheral input (Section 9.1.3) and, in analogy to other painful states, C fibres likely fulfil this role (Cervero and Laird, 1996a,b; Chen *et al.*, 1996; Gracely *et al.*, 1992; Woolf and Wall, 1986). Thus, while an excitation by NAD/ $\alpha$ -ARs—and other sympathetic mechanisms (Section 8.2.4.2)—of large calibre A $\beta$  fibres may directly provoke mechanical allodynia, the concurrent facilitation of a continuous, low level of C fibre input into the DH contributes to the maintenance of permissive, central processes of sensitization (Andersen *et al.*, 1995; Choi and Rowbotham, 1997; Koltzenburg *et al.*, 1994) (Section 7.4.7).

An interesting question concerns those factors which permit and encourage the extension of sympathetic fibres into the DRG and neuroma of damaged nerves. In this regard, there is evidence that NGF (a trophic factor for sympathetic nerves) and cytokines may be involved (Cowen and Gavazzi, 1998; Davis *et al.*, 1997a; Kawaja and Crutcher, 1997). Following PAF damage (and Wallerian degeneration of myelinated neurones), proliferating Schwann cells and fibroblasts release NGF, and an increase in the levels of mRNA encoding NGF has been detected in the DRG, in parallel with an increase in levels of p75<sup>NTR</sup>, the low affinity NGF receptor, in glial cells (Ramer and Bisby, 1997a,b). Thus, NGF may attract and initiate the sprouting of sympathetic fibres (Davis *et al.*, 1994, 1996). This action is presumably exerted in co-operation with other extrinsic, trophic factors, and with growth-associated substances contained in sympathetic terminals (Cowen and Gavazzi, 1998; Heumann *et al.*, 1987a; Heumann *et al.*, 1987b; Michael and Priestley, 1995; Ramer *et al.*, 1997; Sebert and Shooter, 1993) (Section 11.3). Interestingly, evidence for a reciprocal interaction between sympathetic neurones and NGF under conditions of neuropathic nerve damage was provided by the observation that the activation of  $\beta$ -ARs enhances the synthesis of NGF in a model of diabetic neuropathy (Devor *et al.*, 1994; Riaz and Tomlinson, 1997; Xie *et al.*, 1995a,b). Sympathetic fibres also bear TRK C receptors and a potential, synergistic role of NT 3 with NGF in encouraging sympathetic sprouting would be of interest to evaluate (Tafreschi *et al.*, 1998). As regards cytokines, the release of ILs, such as IL-6, by immunocompetent cells involved in Wallerian degeneration may also encourage the sprouting of sympathetic terminals into damaged PAFs and their DRG (Bolin *et al.*, 1995; Ludlam *et al.*, 1995). Further, the cytokine, LIF, can also provoke the sprouting of sympathetic fibres into the DRG and it is massively induced in Schwann cells following PAF injury (Thompson and Majithia, 1997) (Sections 8.2.6.2 and 11.3.4). Intriguingly, ILs can also elicit LIF synthesis in sympathetic terminals themselves (Jonakait, 1993), suggesting that they might further 'auto-enhance' their own sprouting.

Notwithstanding the extension of sympathetic terminals into regions where they may directly access injured (and intact) PAFs, there is little or no evidence for an increase in local sympathetic outflow into the circulation. On the contrary, under certain conditions, there may even be a *diminution* in sym-

pathetic tone (Blumberg and Jänig, 1994; Devor, 1994, 1995; Drummond *et al.*, 1991; Harden *et al.*, 1994; Wallin *et al.*, 1976) (Section 8.2.4.3).

#### 8.2.4.2. Mechanisms underlying sympathetic excitation of damaged nerves: a role for $\alpha$ -ARs on PAFs or sympathetic terminals

It is currently unclear how damaged PAFs develop an increase in their sensitivity to sympathetic input. One possibility is an upregulation in the density of  $\alpha$ -ARs (Bossut *et al.*, 1996; Cho *et al.*, 1997a; Nishiyama *et al.*, 1993; Perl, 1994; Petersen *et al.*, 1996; Sato *et al.*, 1993a, 1994). Such an increase could be triggered by a reduction of local, sympathetic outflow which has, in analogy, been suggested to provoke a supersensitivity (up-regulation) of vascular  $\alpha$ -ARs (Arnold *et al.*, 1993) (Section 8.2.4.3). Further, in line with this possibility, although sympathetic terminals may eventually sprout into the DRG and re-access injured PAFs (Section 8.2.4.1), this may not occur immediately following PAF injury and only a subpopulation of PAFs are affected. In addition to an increase in the density of  $\alpha$ -ARs, their responsiveness to stimulation may be enhanced. Indeed, it was recently shown that PAF injury modifies the activity of a population of  $\alpha_2$ -ARs coupled to N-type Ca<sup>2+</sup>-channels and a topographically-linked, Ca<sup>2+</sup>-dependent K<sup>+</sup>-channel (Abdulla and Smith, 1997). Thus, following PAF injury, the activation by NAD of  $\alpha_2$ -ARs on small DRG neurones ultimately leads to a reduction in K<sup>+</sup>-currents. This results in an increase in PAF excitability and an enhancement in the probability of firing upon stimulation.

The findings of this latter study are consistent with the majority—though not all—reports that  $\alpha_2$ -ARs are involved in the excitation of PAFs following injury (Campbell *et al.*, 1992; Chen *et al.*, 1996; Gold *et al.*, 1997; O'Halloran and Perl, 1997; Hong and Abbott, 1996; Leem *et al.*, 1997; Millan, 1997; Nicholas *et al.*, 1996; Roberts and Elardo, 1985; Sato and Perl, 1991; Xie *et al.*, 1995a; Zhang *et al.*, 1997b). A role of  $\alpha_2$ -ARs in the activation of damaged PAFs would, further, be consistent with the presence of mRNA encoding  $\alpha_{2A}$ -,  $\alpha_{2B}$ - and predominantly,  $\alpha_{2C}$ -AR in DRG (Gold *et al.*, 1997; Millan, 1997; Nicholas *et al.*, 1996). Indeed it is of interest that an increase and decrease in levels of  $\alpha_{2A}$ - and  $\alpha_{2C}$ -ARs, respectively, was documented in the DRG of rats with peripheral nerve damage (Cho *et al.*, 1997a). However, the respective role(s) of peripheral  $\alpha_{2A}$ -,  $\alpha_{2B}$ - and  $\alpha_{2C}$ -AR subtypes is difficult to experimentally determine in view of the confounding antinociceptive actions of  $\alpha_2$ -AR agonists at central  $\alpha_{2A}$ -ARs (Hayashi and Maze, 1993; Hunter *et al.*, 1997a; Millan, 1997; Millan *et al.*, 1994). Anatomical support for the existence of  $\alpha_1$ -ARs in PAFs is weak (Nicholas *et al.*, 1996; Pieribone *et al.*, 1994) and there is only limited clinical and pharmacological evidence for a role of  $\alpha_1$ -ARs on (damaged or intact) sensory neurones in mediating the excitatory actions of NAD (Chen *et al.*, 1996; Choi and Rowbotham, 1997; Davis *et al.*, 1991; Drummond *et al.*, 1991; Hong and Abbott, 1996; Pieribone *et al.*, 1994; Ouseph and Levine, 1995) (Section 7.4.7).

Thus, although the pharmacology of the actions of NAD on the neuroma and DRG of damaged nerves requires further exploration, currently, the data favour a principal role of  $\alpha_2$ - rather than  $\alpha_1$ -ARs (Section 7.4.7).

Apart from actions at  $\alpha_1$ - and  $\alpha_2$ -ARs on PAFs, NAD may also control the activity of injured PAFs *indirectly* via actions at *sympathetic* terminals themselves. Indeed, like PAFs, sympathetic terminals express multiple  $\alpha_2$ -AR subtypes (Campbell *et al.*, 1992; Chen *et al.*, 1996; Gold *et al.*, 1997; Hong and Abbott, 1996; Hunter *et al.*, 1997a; Roberts and Elardo, 1985; Nicholas *et al.*, 1996; Sato and Perl, 1991; Tracey *et al.*, 1995). Such mechanisms may involve:

1. modulation of NAD release by  $\alpha_{2A}$ -AR (and  $\beta$ -AR) autoreceptors; and
2. an increase in the release of PGs elicited by  $\alpha_{2C}$ -ARs (Burnstock, 1996; Davisson *et al.*, 1996; Khasar *et al.*, 1995; Levine and Taiwo, 1994; Levine *et al.*, 1986b; Tracey *et al.*, 1995) (Section 7).

However, the generality of this latter mechanism has been challenged by observations that  $\alpha_2$ -AR agonists elicit ectopic discharges in intact and injured A $\beta$  and C fibres of DRG even in the *absence* of an intact sympathetic innervation (Rubin *et al.*, 1997; Zhang *et al.*, 1997b) (Section 8.2.4.3).

To summarize, it appears that the predominant mechanism for the excitation of damaged PAFs by NAD is a direct action of NAD at upregulated and/or oversensitive  $\alpha_2$ -ARs on PAFs, through the underlying molecular mechanisms remain unclear.

#### 8.2.4.3. Other sympathetic mechanisms potentially modulating the activity of PAFs

Several other general mechanisms whereby the sympathetic system may modulate the activity of both injured- and intact-PAFs are most appropriately considered here.

Sympathetic fibres may indirectly affect the activity of PAFs via changes in vascular permeability and blood flow—and a role of the sympathetic system in the modulation of plasma extravasation and other inflammatory events has been proposed (Miao *et al.*, 1996; Takahashi *et al.*, 1993). Specifically, the vascular (vasoconstrictor) actions of sympathetically-released NAD may encourage pain by:

1. reducing dispersion of inflammatory substances; or
2. provoking an oedema which activates pressure-sensitive nociceptors (Blumberg and Jänig, 1994; Drummond, 1996).

Such actions may be of importance in diabetic neuropathies and sympathetically-maintained painful states in which an exaggerated vasoconstrictor response to NAD has been observed (Arnold *et al.*, 1993; Blumberg and Jänig, 1994; Drummond, 1996; Paul and Page, 1997; Vo and Tomlinson, 1997). This probably reflects an above-mentioned compensatory overactivity of vascular  $\alpha$ -ARs provoked by a decrease in sympathetic tone (Arnold *et al.*, 1993). Nevertheless, vascular mechanisms *cannot* fully account for the hyperalgesic actions of NAD and

the pronociceptive influence of sympathetic transmission since the hyperalgesic actions of NAD (in inflamed tissue) are *greater* than those provoked by ischaemia alone (Drummond, 1996; Paul and Page, 1997).

The trophic factor for sympathetic fibres, NGF, increases the gene expression of NPY in sympathetic neurones (Sabol and Higuchi, 1990; Tracey *et al.*, 1995). Thus, a NGF-induced increase in the release of NPY from sympathetic terminals may be involved in the modulation of nociception, either via actions on small calibre PAFs or via feedback actions to release NAD, PGs and other mediators from sympathetic terminals themselves (Munglani *et al.*, 1996). In addition, the release of other trophic and/or vasoactive factors from sympathetic terminals, such as PACAP, VIP, GAL and SP, may modify PAF activity as well as vascular and immune function, thereby indirectly altering both the electrical activity and the regenerative capacity of injured PAFs (Brandenburg *et al.*, 1997; Munglani *et al.*, 1996). In addition, the release of NO and ATP from sympathetic terminals may directly (and indirectly) modify the activity of damaged nerves in a manner similar to that described for inflamed tissue (Sections 7.4.4 and 7.5.2.5).

The above discussion focuses on events integrated in the peripheral terminals of sympathetic fibres. However, the activity of sympathetic neurones may be modulated *centrally* at the level of preganglionic, sympathetic neurones in the intermediolateral cell column of the spinal cord. Therein, several receptorial mechanisms may potentially modify nociception via an enhancement of sympathetic outflow, including facilitatory mGlu,  $\alpha_1$ -AR and 5-HT<sub>2A</sub> receptors activated by descending pathways (Hao *et al.*, 1996b; Helke *et al.*, 1997; McCall and Clement, 1994; Millan, 1997; Nicholas *et al.*, 1996; Spanstick *et al.*, 1995; Yaksh *et al.*, 1995).

It should, finally, be recalled that increases in systemic, arterial pressure provoked by i.v. administration of NAD can *decrease* nociception via activation of sinoaortic baro-receptors and vagal afferents, subsequently activating brainstem mechanisms engaging descending inhibitory pathways to the DH (Lovick, 1993; Millan, 1997; Thurston and Helton, 1996).

#### 8.2.4.4. Sympathectomy-Induced pain

The above discussion provides evidence that sympathetic mechanisms contribute to neuropathic pain by facilitating the abnormal pattern of input from damaged PAFs onto sensitized neurones in the DH. It should, nevertheless, be mentioned that neuropathic, painful states are *not* invariably sympathetic-dependent. Indeed, a generalized role of sympathetic mechanisms in their induction has been questioned by some authorities and, at least clinically, 'sympathetic' and 'non-sympathetic' painful states can be differentiated (Blumberg and Jänig, 1994; Campbell *et al.*, 1994; Kingery, 1997; Schott, 1995; Verdugo and Ochoa, 1994; Verdugo *et al.*, 1994). Further, surgical sympathectomy can *itself* trigger a painful syndrome in *some* patients. Several mechanisms may be involved:

1. As described in Section 8.2.4.2, a decrease in sympathetic tone may provoke a compensatory increase in the density and/or responsiveness of  $\alpha_2$ -ARs on PAFs and blood vessels, that is, a perturbation of sensory and vascular function.
2. Sympathectomy may interrupt visceral nocisponsive afferents in sympathetic trunks and inadvertently damage other types of adjacent sensory fibre. Conceivably, then, processes underlying nerve damage-related pain may actually be *triggered* by sympathectomy.
3. Sympathectomy may lead to abnormal growth patterns and alterations in the phenotype of PAFs, including an induction of SP, CGRP and intrinsic trophic factors: these changes possibly involve the induction of NGF in non-neuronal cells (Aley *et al.*, 1996; Baron and Maier, 1996; Bolden *et al.*, 1997; Cowen and Gavazzi, 1998; Kramis *et al.*, 1996; Schott, 1995) (Sections 8.2.5. and 11.3).
4. Damage to sympathetic nerves results in marked alterations in their *own* phenotype, including increases in the expression of neuropeptides such as VIP and PACAP: such changes are mediated by IL-1 $\beta$ , LIF, NGF and several other factors.

Although this response to injury may play a trophic role in assisting sympathetic regeneration, neuropeptides, and other mediators may exert actions at nocisponsive PAFs leading to phenotype changes and functional effects provoking nociception (Cowen and Gavazzi 1998; Jonakait, 1993; Moller *et al.*, 1997a,b; Rao *et al.*, 1993) [Section 7.6]. Thus, paradoxically, surgical sympathectomy may *itself* elicit several pronociceptive mechanisms resembling those triggered by PAF injury. Such effects of sympathectomy require additional clarification.

#### 8.2.5. Altered Phenotype of Damaged PAFs: Functional Consequences

The level of many neuropeptides (and certain neuropeptide receptors) changes in small and large calibre primary afferent neurones following their injury. Species differences, time-dependent patterns of changes and differences between various subpopulations of small and large calibre fibres should be emphasized in this regard (Goff *et al.*, 1998; Hökfelt *et al.*, 1994; Rydh-Rinder *et al.*, 1996; Xu *et al.*, 1997d; Zhang *et al.*, 1993a,b). The importance of an *increase* in tissue levels of NGF in determining alterations in C fibre phenotype under conditions of inflammation was described in Section 7.6.1. Contrariwise, a *decrease* in the provision of NGF to the DRG of damaged C fibres, due to an—at least transient—loss of TRK A receptors on their peripheral terminals and a reduction in axonal flow, results in a pattern of phenotype changes broadly opposite to inflammation (Section 8.2.6) (McMahon and Bennett, 1997). Such phenotype changes in injured PAFs may have major, functional consequences at their central (nociception) and peripheral (nociception and trophic effects) terminals. In this regard, certain changes in PAF phenotype occurring upon injury have deleterious consequences, while others may be favourable. Indeed, some authors have interpreted the overall pattern of alterations in the phe-

notype of axotomized neurones as a globally adaptive response to injury inasmuch as such changes contribute to their recovery by promoting protective and regenerative mechanisms (Fu and Gordon, 1997; Hökfelt *et al.*, 1994; Lieberman, 1971; Tanaka *et al.*, 1997a) (but see Section 2.2). Further, certain—though *not* all—changes in PAF phenotype may palliate the sensory (hyperalgesia and allodynia) consequences of injury as concerns transmission in the DH. That is, certain excitatory (pronociceptive) and inhibitory (antinociceptive) neuropeptides are down- and up-regulated respectively in damaged PAFs (Hökfelt *et al.*, 1994).

An interesting example is provided by GAL, the trophic actions of which may encourage nerve regeneration in the periphery (Kask *et al.*, 1997). Although GAL generally enhances nociceptive reflexes in intact animals, it exerts predominantly *inhibitory*, antinociceptive actions in the DH following PAF injury and it is up-regulated in both small and (to a lesser extent) large PAFs following their damage (Luo and Wiesenfeld-Hallin, 1995; Ma and Bisby, 1997; Villar *et al.*, 1989; Wiesenfeld-Hallin *et al.*, 1989 and 1992). The release of GAL in superficial DH is, correspondingly, elevated ipsilateral to a peripheral mononeuropathy (Colvin *et al.*, 1997). Interestingly, the levels of both GAL<sub>1</sub> and GAL<sub>2</sub> receptors in damaged neurones are *decreased* (Xu *et al.*, 1996b, 1997d). This reduction in their density may limit the excitatory, pronociceptive actions of GAL on PAFs (Shi *et al.*, 1997). Thus, the antinociceptive properties of GAL at intrinsic DH neurones may be privileged, actions probably mediated by GAL<sub>1</sub> receptors which are *negatively* coupled to AC and which enhance and inhibit Ca<sup>2+</sup> and K-currents, respectively (Kask *et al.*, 1997; Xu *et al.*, 1997d). Nevertheless, the receptorial mechanisms underlying the complex role of GAL at PAFs and intrinsic DH neurones requires further clarification (Section 3.2.6). The levels of a GAL-related neuropeptide, 'GMAP', which may likewise play a role in the modulation of nociception, are augmented in parallel to those of GAL upon PAF injury (Xu *et al.*, 1995a).

The level of mRNA encoding PACAP is similarly increased in small DRG neurones containing GAL—as well as a subpopulation of large neurones containing NPY (Zhang *et al.*, 1996b) (see below). Like GAL, PACAP may express antinociceptive actions in the DH (Yamamoto and Tatsuno, 1995; Zhang *et al.*, 1993c) and, peripherally, it elicits extravasation, promotes neuronal survival and differentiation and is implicated in repair processes post-injury (Cardell *et al.*, 1997; Deutsch and Sun, 1992; Tanaka *et al.*, 1997a).

Less favourable than the above changes may, however, be the induction of CCK in as many as 30% of DRG neurones, and of CCK<sub>B</sub> receptors in both small and large calibre PAFs (Hökfelt *et al.*, 1994; Xu *et al.*, 1993b, 1994, 1997d). CCK interferes with the central antinociceptive actions of opioids, probably via the induction of PLC and an increase in [Ca<sup>2+</sup>]<sub>i</sub> levels. There is evidence from experimental models in rodents that the activation at CCK<sub>B</sub> (CCK<sub>A</sub>) receptors contributes to the relative inefficacy of opioids in clinically managing neuropathic

pain, and blockade of CCK<sub>A</sub> receptors increases nociception in man (Arnér and Meyerson, 1993; Benedetti, 1997; Nichols *et al.*, 1995; Portenoy *et al.*, 1990; Stanfa *et al.*, 1994; Xu *et al.*, 1993b, 1994; Wiesenfeld-Hallin *et al.*, 1990; Zhang *et al.*, 1993a, 1998b). In line with these observations, CCK<sub>B</sub> antagonists enhance opioidergic antinociception in rodent models of neuropathic pain (Idänpään-Heikkilä *et al.*, 1997; Nichols *et al.*, 1995, 1996). Their actions reflect the blockade of upregulated pools of CCK not only in PAFs, but also in intrinsic DH neurones and, possibly, descending fibres. In parallel to the appearance of CCK, levels of somatostatin are decreased in injured, small calibre fibres (Höckfelt *et al.*, 1994). This reduction may also be disadvantageous inasmuch as somatostatin exerts antinociceptive actions in the DH and periphery (Heppelmann and Matthias, 1997; Mollenholt *et al.*, 1990).

Interestingly, despite observations of a decrease of SP and CGRP levels in damaged C fibres, nociceptive transmission may be maintained (Höckfelt *et al.*, 1994; Mulder *et al.*, 1997). In addition to peripheral mechanisms discussed in Sections 8.2.1, 8.2.2, 8.2.3 and 8.2.4, this finding may reflect the actions of residual stores of SP and CGRP at up-regulated NK<sub>1</sub> and CGRP receptors on sensitized DH neurones (Abbadie *et al.*, 1996; Carlton and Coggeshall, 1997; Goff *et al.*, 1998) [note, also, that recent studies of the evolution of changes in neuropeptide levels post-injury suggest that SP levels may not be reduced at all time periods post-injury (Goff *et al.*, 1998)]. A further intriguing explanation is that VIP assumes a major, excitatory role in nociceptive transmission at neurones in the DH following its induction by PAF injury (Höckfelt *et al.*, 1994; Shehab and Atkinson, 1986a,b). Indeed, VIP antagonists attenuate the induction of central hyperexcitability from injured (but not intact) PAFs (Wiesenfeld-Hallin *et al.*, 1992). This central, 'deleterious' effect of VIP may be secondary to its beneficial, vasodilatory, trophic and glyconogenic actions in the periphery which encourage nerve survival and regeneration (Cardell *et al.*, 1997; Colbert *et al.*, 1994; Höckfelt *et al.*, 1994; Tanaka *et al.*, 1997a; White and Mansfield, 1996).

A further neuropeptide, NPY, mimics the trophic actions of VIP on blood vessels and nerves and its gene expression can be enhanced by VIP (Kashiba *et al.*, 1997; Shigeri and Fujimoto, 1993; White and Mansfield, 1996; Youn *et al.*, 1997). However, it remains to be elucidated whether VIP plays a role in the modest increase in NPY levels shown by injured C fibres. mRNA encoding NPY shows, in fact, a more marked increase in large calibre fibres following peripheral nerve injury (Noguchi *et al.*, 1993; Wakisaka *et al.*, 1991). Irrespective of its origins, PAF injury markedly enhances the spontaneous release of NPY in the DH (Mark *et al.*, 1998). Further, levels of Y<sub>1</sub> and Y<sub>2</sub> receptors on large (but not small) calibre neurones are increased following PAF damage (Mantyh *et al.*, 1994; Zhang *et al.*, 1997e). It has been suggested that NPY exerts antinociceptive actions in the DH, possibly via Y<sub>2</sub> receptors negatively coupled to AC and localized on intrinsic DH neurones and PAF terminals (Munglani *et al.*, 1996). Thus, an inhibitory action

of increased release of NPY at up-regulated Y<sub>2</sub> receptors on central A $\beta$  fibre terminals might, theoretically, moderate mechanical allodynia (Zhang *et al.*, 1994c, 1997e). In addition, NPY modulates nociception by multiple actions in the periphery, certain of which are expressed in interaction with NAD released (like NPY) from sympathetic neurones. In fact, the prevailing peripheral action of NPY may be an increase in nociception via a Y<sub>2</sub>-receptor mediated release of PGs from sympathetic terminals (Munglani *et al.*, 1996). Evidently, the relationship between multiple receptors for NPY and its spectrum of peripheral and central actions is still poorly understood. However, this issue would be of interest to explore further within the framework of the changes in NPY levels provoked not only in PAFs, but also in intrinsic DH neurones, by peripheral nerve injury (Ji *et al.*, 1994; Munglani *et al.*, 1996) (Sections 10.4 and 10.6).

Neurotensin generally exerts antinociceptive actions at intrinsic DH neurones and, possibly, PAF terminals. Inhibitory 'neurotensin' receptors (negatively coupled to AC) may be involved in these effects. However, neurotensin receptors in the DH are down-regulated by PAF injury revealing additional, excitatory actions of neurotensin on C (and A $\beta$ ) fibres, effects which are presumably mediated via a further, unknown neurotensin receptor type, which is possibly coupled to PLC (Carlton and Coggeshall, 1997; Xu *et al.*, 1997d).

Simultaneous to the loss of SP in fine calibre C fibres, SP actually appears in axotomized, large calibre A $\beta$  fibres upon their injury (Miki *et al.*, 1998; Neumann *et al.*, 1996; Noguchi *et al.*, 1994). The consequences of this induction of SP synthesis in A $\beta$  fibres is compounded by:

1. their release of EAAs;
2. concurrent, structural changes whereby they now sprout into superficial laminae of the DH to make inappropriate contacts with nocisponsive neurones; and
3. an upregulation of NK<sub>1</sub> receptors in the DH (Abbadie *et al.*, 1996; Woolf and Doubell, 1994) (Section 11.2).

Further, A $\beta$  fibres display an increase in levels of VIP and NO following injury (Höckfelt *et al.*, 1994). This induction of VIP and NO may, thus, further contribute to abnormal, pro-nociceptive actions of migrated A $\beta$  fibres at NS neurones in the superficial DH laminae (Section 11.2). Large calibre A $\beta$  fibres projecting to the gracile nucleus of the PSDC pathway (Section 6.1) may play a role in the mediation of dyesthesias and mechanical allodynia following PAF injury. Thus, it is of interest that an increase in CGRP levels was detected in large, myelinated PAFs projecting to the gracile nucleus following peripheral axotomy. This increase may, at least partially, reflect its induction in A $\beta$  fibres (Miki *et al.*, 1998). Further, this study showed that the increase in mRNA encoding CGRP was restricted to the  $\alpha$ -vs  $\beta$ -isoform suggesting that they can be differentially regulated.

To summarize, damage to PAFs elicits a complex pattern of phenotype changes, of which certain are involved in the induction of neuropathic painful

states, while others may contribute to their attenuation.

### 8.2.6. *The Significance of a Reduction in DRG Access to NGF and Other Trophic Factors in Modifying the Phenotype of Damaged PAFs*

#### 8.2.6.1. *Phenotypic consequences of a loss of DRG access to NGF for C fibres*

An—at least temporary—loss of DRG access to NGF likely plays a major role in determining altered patterns of gene expression in injured, fine calibre PAFs (Woolf, 1996). Indeed, in addition to a generalized reduction in axonal transport, both diabetic neuropathies and PAF lesions are characterized by decrease in the DRG density of mRNA encoding TRK A and p75<sup>NTR</sup> receptors: this further compromises delivery of NGF to the DRG—although a compensatory increase in mRNA encoding TRK A receptors may eventually occur (Delcroix *et al.*, 1997; Heumann *et al.*, 1987a,b; Maeda *et al.*, 1996; McMahon and Bennett, 1997; Vergé *et al.*, 1992a, 1995a; Zhou *et al.*, 1996b). Certain of the phenotype changes displayed by C fibres can be pre-empted by administration of NGF (Delcroix *et al.*, 1997; Funakoshi *et al.*, 1993; Fernyhough *et al.*, 1994; Gold *et al.*, 1991; McMahon and Bennett, 1997; Ren *et al.*, 1995; Vergé *et al.*, 1992a, 1995a,b) and the accompanying hyperalgesia/allodynia may be reduced in parallel (Dray and Urban, 1996; Herzberg *et al.*, 1997; Thomas *et al.*, 1993). The argument that a reduction in the availability of NGF to the DRG of injured PAFs plays a role in mediating phenotype changes in injured C fibres is well illustrated by GAL, SP and CGRP.

Thus, consistent with observations that NGF exerts a suppressive influence upon the gene expression of GAL, the levels of mRNA encoding GAL increase in C fibres following injury (Section 8.2.5). This increase can be reversed by intrathecal administration of NGF which, via intact TRK A receptors on the *central* terminals of damaged PAFs, regains access to the DRG (Vergé *et al.*, 1995a,b; Xu *et al.*, 1996b; Zhang *et al.*, 1995). High doses of NGF also decrease GAL levels in cultured DRG neurones (Kerekes *et al.*, 1997).

NGF normally enhances the expression of mRNA encoding SP, levels of which generally decrease upon nerve damage (Goff *et al.*, 1998; Hökfelt *et al.*, 1994; Maeda *et al.*, 1996; Munglani *et al.*, 1996; Vergé *et al.*, 1995a,b). This action of NGF may be explained by the presence in the promoter region of the preprotachykinin gene (which encodes SP) of a NGF-responsive element controlling SP transcription (Heumann, 1994; Watson *et al.*, 1995). Thus, whereas an *accumulation* of NGF contributes to an *increase* of SP synthesis in C fibres in *inflammatory* pain (Donnerer *et al.*, 1992; Kuraischi *et al.*, 1989; Woolf *et al.*, 1994), a *reduction* in the DRG access of damaged nerves to NGF leads to a *decrease* in SP production in *neuropathic* pain (Cameron *et al.*, 1997; Hökfelt *et al.*, 1994; Marchand *et al.*, 1994; Nahin *et al.*, 1994; Wong and Oblinger, 1991). Indeed, the application of NGF to DRG and the administration of anti-NGF

antibodies, respectively, up-regulates (cf inflammation) and down-regulates (cf nerve injury) SP synthesis (Donnerer *et al.*, 1992; Lindsay and Harmar, 1989; Woolf *et al.*, 1994). Further, NGF treatment corrects the reduction in DRG levels of mRNA encoding SP and CGRP seen in diabetic neuropathies (Diemel *et al.*, 1994). As regards this influence of NGF upon SP expression, one remarkable indication of PAF plasticity and of the role of NGF is revealed by the surgical re-routing of muscle nerves to skin—the latter tissue contains far higher level of NGF. These reoriented muscle nerves display a marked increase in their content of SP—and develop an intensification of synaptic contacts in the spinal cord. (Lewin and McMahon, 1991; McMahon and Gibson, 1987). Such findings indicate that, if damaged nerves are allowed to regenerate to their normal peripheral targets, certain pathological changes in their phenotype and other changes may, at least partially, be normalized (Lisney, 1983) (Section 11).

Interestingly, despite *opposite* changes in SP synthesis in the DRG, NK<sub>1</sub> receptor levels *increase* in superficial laminae of the DH following both PAF injury and (generally) inflammation. The underlying mechanisms are unclear, but SP may itself elicit this increase. Thus, in the former case, the increase may reflect the initial and transient intense discharge of PAFs which follows their damage (Abbadie *et al.*, 1996; Coggeshall and Carlton, 1997; Goff *et al.*, 1998). In any case, increases in DH levels of NK<sub>1</sub> receptors are temporally correlated with the time-course of those changes in nociception which accompany both PAF injury and peripheral inflammation (Goff *et al.*, 1998).

The gene encoding CGRP similarly possesses a promoter element for NGF. Thus, it is likely that a reduction in the DRG provision of NGF is involved in the decrease in CGRP levels provoked by injury to C fibres, although changes in CGRP levels following peripheral nerve injury are more variable than those of SP (Cameron *et al.*, 1997; Watson *et al.*, 1995).

In analogy to GAL, administration of NGF can reduce the number of small calibre PAF neurones displaying an upregulation in mRNA encoding CCK and NPY following their injury (Vergé *et al.*, 1995b).

#### 8.2.6.2. *A potential role of other trophic factors: focus on LIF*

Upon nerve damage, VIP is co-expressed and co-induced with GAL in a subpopulation of C fibres, a change probably reflecting a reduction in access to NGF, the application of which reverses this increase (Kashiba *et al.*, 1992; Vergé *et al.*, 1995b).

However, changes in fine calibre PAF phenotype do *not* all reflect a reduction in access to NGF. Indeed, a further pool of VIP is present in a subpopulation of somatostatin-containing C fibres *lacking* TRK A receptors. The increase and decrease, respectively, in VIP and somatostatin levels in these neurones following injury is, thus, probably NGF-independent (Kashiba *et al.*, 1996; Mulderry and

Lindsay, 1990; Noguchi *et al.*, 1993; Vergé *et al.*, 1995b).

One interesting candidate for mediating changes in VIP expression in such somatostatin-containing C fibres *lacking* TRK A receptors is the cytokine, LIF, which encourages VIP synthesis in sympathetic neurones (Jonakait, 1993; Rao *et al.*, 1993). Thus, the expression of LIF, which is normally very low, is markedly induced in Schwann cells upon peripheral nerve injury via factors derived both from injured PAFs and from macrophages (Banner and Patterson, 1994; Livesey *et al.*, 1997). Further, although LIF does *not* induce VIP expression in small diameter, TRK A-positive PAFs (Matsuoka *et al.*, 1997) (*vide supra*), it may contribute—together with the loss of NGF—to the induction of GAL in these neurones (Corness *et al.*, 1996; Curtis *et al.*, 1993; Southall *et al.*, 1996). In line with a modulatory influence of LIF on gene expression in PAFs, it has recently been shown that LIF is retrogradely transported to cell bodies of small calibre, nociceptive C fibres containing CGRP (Thompson *et al.*, 1997). Furthermore, as described in Section 11.3.4, LIF (derived from Schwann cells or sympathetic terminals) may induce the expression of specific proteins in damaged PAFs, the secretion of which reciprocally encourages further Schwann cell proliferation (Jonakait, 1993; Livesey *et al.*, 1997). Additional support for a modulatory role of LIF is also available. Thus, in analogy to NGF, the peripheral administration of LIF induces mechanical allodynia (Thompson *et al.*, 1996, 1997). Further, the recent discovery that mRNA encoding LIF is present in superficial DH laminae I/II, and that it is upregulated by inflammation and PAF injury, raises the possibility of central actions of LIF in the modulation of nociception (Heppenstall *et al.*, 1997).

These findings underscore the fact that NGF is *not* the only element responsible for changes in the phenotype of damaged C fibres (Aldskogius *et al.*, 1992; Kerekes *et al.*, 1997; Raivich *et al.*, 1991). A reduction of axonal flow upon nerve injury limits access to the DRG of multiple trophic factors and an interruption of axonal flow *per se*, in the *absence* of damage to PAFs, has been shown to markedly modify their phenotype (Kashiba *et al.*, 1992; Knyihar-Csillik *et al.*, 1991) (Section 8.2.2.5). It would be of interest to clarify the role of GDNF in the response of NGF-independent, fine calibre PAFs to injury (Section 3.2).

#### 8.2.6.3. Gene transcription factors: immediate early genes

The levels of transcription factors, such as NF- $\kappa$ B, and of immediate early genes (IEGs), such as c-jun and jun-d, are altered in injured PAFs. A putative role of these factors in the modulation of gene expression by NGF, LIF and other trophic molecules is an interesting issue (Doyle and Hunt, 1997; Herdegen *et al.*, 1991, 1997; Jenkins *et al.*, 1993; O'Neill and Kaltschmidt, 1997; Vergé *et al.*, 1995b). Axonal damage induces the expression of c-jun, enhances its phosphorylation by specific kinases and encourages its functional dimerization with jun-d, c-

fos and other transcription factors. These conformational changes enable c-jun to modify the transcription of several effector genes which act in synergy with other regulatory elements to control the precise pattern of phenotype changes initiated by nerve injury (Fiallos-Estrada *et al.*, 1993; Herdegen *et al.*, 1997; Hughes and Dragunow, 1995). One interesting illustration of the role of c-jun is provided by the increase in GAL synthesis detected in damaged C-fibres possessing TRK A receptors (Section 8.2.5). C-jun stimulates the transcription of GAL and a reduction in the suppressive influence of NGF upon c-jun expression in damaged nerves may underlie a secondary increase in GAL gene expression (Gold *et al.*, 1993; Herdegen *et al.*, 1991, 1997; Vergé *et al.*, 1995a,b). Further, inasmuch as NGF activates the transcription factor, NF- $\kappa$ B, in the DRG, a loss of access to NGF may explain the reduction in NF- $\kappa$ B levels observed in damaged PAFs (Dechant and Barde, 1997; Doyle and Hunt, 1997; O'Neill and Kaltschmidt, 1997). The role of other elements, such as BDNF and the cytokines, TNF $\alpha$  and LIF, in modulating the expression of c-jun, NF- $\kappa$ B and other transcription factors in injured PAFs, would be of interest to establish (Cheema *et al.*, 1994; Doyle and Hunt, 1997). However, damage to PAFs proximal to the DRG can *also* induce c-jun expression, even though DRG cells do *not* degenerate and trophic factors are still available to their PAF terminals. This observation, and the induction of c-jun in many cell types upon PAF injury, suggest that the induction of c-jun and several other regulators of gene expression may be a generalized response to their injury (Kenney and Kocsis, 1997).

#### 8.2.6.4. Factors involved in phenotype changes in large calibre A $\beta$ fibres

As concerns phenotype changes in damaged, large A $\beta$  fibres, since these lack TRK A receptors, the above-mentioned increases in levels of SP, NPY and, to a less marked degree, VIP and GAL, are unlikely to directly involve NGF. Rather, they may be due to alterations in the provision of other growth factors for large neurones such as BDNF, NT 3, LIF or fibroblast growth factor (Fu and Gordon, 1997; Lewin and Barde, 1996; Neumann *et al.*, 1996; Ma and Woolf, 1996b; Sterne *et al.*, 1997). Indeed, direct evidence that a loss of access to fibroblast growth factor and BDNF may be involved in the upregulation of GAL in injured, large PAFs has been provided by Kerekes *et al.* (1997). Further, the availability of LIF from Schwann cells may also contribute to the increase in GAL synthesis therein (Southall *et al.*, 1996). These mechanisms require considerable further clarification.

#### 8.2.6.5. Functional considerations

Notwithstanding the wealth of information discussed above concerning the relationship between NGF and the phenotype of injured C fibres, the precise functional and clinical significance of these observations remain unclear. Some authorities have suggested, in line with the above-described changes in phenotype triggered by a loss of NGF to DRG

loss, that the provision of exogenous NGF to injured PAFs might be beneficial in restoring a normal phenotype (Dray and Urban, 1996; McMahon and Priestley, 1995). However, *pronociceptive* effects of NGF at damaged (and intact) PAFs may be expressed independently of changes in phenotype via mechanisms discussed in Section 7. Further, it has been reported that the acute neutralization of NGF (by specific antibodies) can *reduce* neuropathic pain due to PAF injury (Dray and Urban, 1996; Herzberg *et al.*, 1997).

The acute and long-term functional effects of NGF, BDNF, LIF and other trophic factors under conditions of PAF injury require considerable further clarification before the therapeutic exploitation of such strategies can realistically be envisaged.

#### 8.2.7. Phenotype Changes in Damaged PAFs: Neuromodulators other than Neuropeptides

Damage to PAFs provokes changes in the levels of many substances other than neuropeptides. For example, the cytoskeletal protein, tubulin, which plays a role in growth cone support and other regenerative mechanisms of damaged PAF terminals (Fournier and McKerracher, 1997; Wong and Oblinger, 1990, 1991) (Section 11.3).

Concerning nociception, the spinal release of EAAs may be enhanced by nerve injury, a change which enhances nociceptive transmission in the DH (Al-Ghoul *et al.*, 1993; Cui *et al.*, 1997b; Dickenson, 1997—but see Xu *et al.*, 1995b).

An induction of NO synthase has also been seen in the DRG following PAF injury—particularly in small calibre, CGRP-containing neurones—whereas, in a model of diabetic neuropathy, NO levels were not changed (Fiallos-Estrada *et al.*, 1993; Sasaki *et al.*, 1998; Vergé *et al.*, 1992b; Zhang *et al.*, 1993b). NO may play a role in modulating (primarily in facilitating) nociception via both central (DH) and peripheral actions following PAF injury (Sections 3.2.8.3 and 7.7). Interestingly, a loss of access to NGF has been speculated to underlie this increase in NO synthase—in analogy to these changes in neuropeptide levels in C fibres detailed in Sections 8.2.5 and 8.2.6. (Thippeswamy and Morris, 1997). In addition to alterations in nociceptive transmission via actions at PAFs, the peripheral (trophic) actions of NO should also be mentioned: for example, its ability to increase vascular flow (Section 7.9.2) (Höckfelt *et al.*, 1994; Vergé *et al.*, 1992b; Wiesenfeld-Hallin *et al.*, 1993; Zhang *et al.*, 1993b).

As discussed in Section 3.2.8.2, adenosine may play an important role in modulating nociception in the DH. Notably, the engagement of spinal A<sub>1</sub> receptors suppresses both the allodynia and the activation of DH neurones which is associated with PAF injury (Section 3.2.2). Whether the release of adenosine from central or peripheral terminals of damaged PAFs is modified would, thus, be of interest to determine. In line with such a possibility, nerve damage is clinically associated with a *decrease* in CSF levels of adenosine, the administration of which alleviates the accompanying pain. These observations raise the possibility that a deficiency in the central release of adenosine from damaged

PAFs may be involved in certain neuropathic, painful states (Cui *et al.*, 1997a; Guieu *et al.*, 1996; Sollevi *et al.*, 1993).

Finally, changes in the density of multiple opioid receptors elicited by PAF injury are of potential significance, in particular a decrease in the levels of  $\mu$ -opioid receptors on PAF terminals and intrinsic neurones in the DH. This reduction in  $\mu$ -opioid receptor availability may dampen endogenous, antinociceptive mechanisms and contribute to the poor responsiveness of opioids in treating neuropathic pain states (Goff *et al.*, 1998; De Groot *et al.*, 1997; Zhang *et al.*, 1998b).

A further exploration, thus, of alterations in the synthesis and release of substances other than neuropeptides in damaged PAFs would be of interest. In addition, the role(s) of NGF, BDNF, LIF and other trophic factors in mediating such changes would profit from examination.

## 9. NOCICEPTIVE AND NEUROPATHIC PAIN: CENTRAL MECHANISMS AND ALLODYNIC STATES

### 9.1. Evidence for Central Mechanisms of Sensitization

#### 9.1.1. The Significance of Central Events

The previous sections illustrate the complexity of peripheral events involved in the generation and maintenance of painful states provoked by tissue inflammation or PAF injury. An enhanced, C fibre-mediated, afferent barrage from sensitized nociceptors (including the recruitment of silent nociceptors) is involved in the induction—and maintenance—of inflammatory pain states. Moreover, following an initial, intense discharge of injured PAFs, the generation of abnormal (ectopic) impulses is involved in the initiation—and maintenance—of neuropathic, painful states. Correspondingly, interference with peripheral inflammatory events by, for example, inhibition of COX 2 (and 1) synthase, or antagonism of B<sub>2</sub> receptors, may attenuate nociceptive pain (Appleton, 1997; Dray and Urban, 1996). On the other hand, sympathetic blockade, or systemic administration of local anesthetics, may alleviate neuropathic pain (Arnér *et al.*, 1990; Koltzenburg *et al.*, 1994). Indeed, peripheral events certainly contribute to two principal features of tissue damage. That is, spontaneous pain and an exaggerated (hyperalgesic) response to heat and other modes of noxious stimulation (primary hyperalgesia). However, adaptive events in the CNS, which amplify the consequences of an abnormal and/or excessive PAF input, also play an important role in determining changes in pain sensation. Indeed, an additional *key* element of clinical pain, mechanical allodynia, which is displayed by *uninjured* tissue surrounding the area of inflammation (secondary hyperalgesia), and which accompanies injury to PAFs, *cannot* be satisfactorily explained without taking into account *central* mechanisms (Cervero and Laird, 1996b; Simone *et al.*, 1991; Woolf *et al.*, 1994). Likewise, the phenomenon of spatially-referred ('remote') pain cannot be convincingly ascribed to peripheral processes. The fol-



lowing paragraphs consider, thus, evidence that processes integrated in the CNS contribute to the induction of chronic, painful states.

Implicit to many discussions of central sensitization is the assumption that an increase in the excitability of nociceptive pathways in the periphery, DH and higher structures is deleterious. However, certain events underlying central sensitization are triggered very rapidly (over minutes) and a normalization of neuronal activity may occur once peripheral input is terminated. Such shorter-term, reversible states of sensitization, maintained by peripheral input and correlating temporally with, for example, acute, peripheral noxious stimulation, may not involve permanent phenotypic/morphological changes. They likely play a role in encouraging protective behaviours and avoiding aggravation of tissue injury (Traub, 1997; Wiertelak *et al.*, 1994c) (Section 2, Table 2). Thus, transient processes of sensitization may be related to the adaptive role of subchronic pain. On the other hand, chronic, clinical pain may reflect long-term, possibly irreversible, processes of central sensitization which become at least partially independent of peripheral input, and which ultimately involve morphological/phenotype changes in pathways mediating and modulating nociceptive transmission (Table 2) (Section 10.2.1).

#### 9.1.2. Mechanical Allodynia: Evidence for Mediation by A $\beta$ Fibres

As indicated above, mechanical allodynia is a prominent feature of secondary hyperalgesia and, in particular, of neuropathic, painful states due to PAF or CNS injury. There is compelling evidence that the activation of mechanosensitive, low threshold A $\beta$  fibres, which normally mediate sensations of touch or vibration etc, but *not* pain, underlies the mechanical allodynia associated with, for example, light brushing of the skin. This is the major, clinical form of allodynia (Ma and Woolf, 1996b; Woolf and Doubell, 1994).

1. First, as described in Section 8.2.2, PAF injury is associated with abnormal firing patterns in both fine calibre C fibres *and* large diameter, A $\beta$  fibres.
2. Following their injury, A $\beta$  fibres become particularly responsive to sympathetic stimulation, and chemical or surgical sympathectomy often relieves (though not invariably) clinical, mechanical allodynia (Ghostine *et al.*, 1984; Handwerker and Kopal, 1993; Raja *et al.*, 1991; Treede *et al.*, 1992b; Wallin *et al.*, 1976) (Section 8.2.4).
3. Clinical and experimental studies of secondary hyperalgesia indicate that, despite the marked increase in pain elicited by mechanical stimulation under conditions of chemical irritation (e.g. application of capsaicin to the skin), the transduction sensitivity of individual, nocisponsive, fine calibre *mechanoreceptors* is *not* markedly modified (Gracely *et al.*, 1992; Handwerker and Kopal, 1993; Koltzenburg *et al.*, 1992, 1994; LaMotte *et al.*, 1991; Meyer *et al.*, 1994; Torebjörk *et al.*, 1992; Treede *et al.*, 1992b). High threshold, mechanosensitive, nocisponsive C (or A $\delta$  fibres) do *not*, thus, seem to be primarily involved. Further, the unchanged transduction

sensitivity of mechanosensitive PAFs implicates *central* events in the altered perception of A $\beta$  fibre input and the induction of allodynia.

4. The delay between cutaneous, mechanical stimulation and the onset of allodynia corresponds to the rapid conduction velocity of myelinated, A $\beta$  fibres (Handwerker and Kopal, 1993; Lindblom, 1985; Treede *et al.*, 1992b).
5. In line with this argument, under condition of nerve injury (or capsaicin treatment), selective electrical activation of A $\beta$  fibres elicits pain and dyesthesias, while selective blockade of A $\beta$  fibres suppresses brush-evoked allodynia (Koltzenburg, 1995; LaMotte *et al.*, 1991; Simone *et al.*, 1989b; Torebjörk *et al.*, 1992; Wallin *et al.*, 1976).
6. A $\beta$  fibres exert their actions, at least partially, via the activation of DH-localized AMPA receptors, the pharmacological blockade of which reduces tactile allodynia in rats. Although it is difficult to completely exclude a role of AMPA sites coupled to C fibres, AMPA receptors activated by A $\beta$  fibres are likely involved in this action (Millan, 1995; Sang *et al.*, 1997; Sherman and Loomis, 1996; Xu *et al.*, 1993a; Zhang *et al.*, 1994a) (Section 3.2.7).
7. Following peripheral nerve injury, the density and Ca<sup>2+</sup>-permeability of AMPA receptors is enhanced in the DH with a time-course paralleling mechanical supersensitivity and allodynia (Hargett *et al.*, 1997; Harris *et al.*, 1996) (Section 10.3.2.1).
8. Non-noxious touch and electrical stimulation of A $\beta$  fibres modifies gene expression in DH neurones *only* under conditions of inflammation (Molander *et al.*, 1992; Ma and Woolf, 1996a).

The above observations provide convincing evidence for a role for A $\beta$  fibres in mediating (at least some forms of) mechanical allodynia. It is conceivable that damage to PAFs allows for the transactivation of C fibres by A $\beta$  fibres via processes of interneuronal communication in the DRG and neuroma (Section 8.2.3). This could lead to the perception of an innocuous stimulation as noxious. However, this mechanism is of little relevance to the allodynia (secondary hyperalgesia) which manifests itself *independently* of nerve injury. Further, although it has been proposed that A $\beta$  fibres activate sensitized WDR neurones via the indirect recruitment of C fibre terminals in the DH (Cervero and Laird, 1996b) (Section 9.2.3), this mechanism may be of limited pertinence to the allodynia elicited by PAF injury. In any case, the indirect recruitment of C fibres would *not* question the crucial role of A $\beta$  fibres—and mechanisms of *central* sensitization—in the mediation of mechanical allodynia.

#### 9.1.3. Secondary Hyperalgesia: Peripheral Maintenance of Central Sensitization

The secondary hyperalgesia encountered in the zone circumferential to the area of injured tissue (primary hyperalgesia) is characterized by an enhanced sensitivity to mechanical rather than heat stimuli (Ali *et al.*, 1996; Treede *et al.*, 1992a).

It might be argued that peripheral events underlie this secondary, mechanical hyperalgesia. Indeed,

many years ago, Lewis (1942) hypothesized that a peripheral mechanism was involved whereby APs triggered in PAFs by a noxious stimulus travelled both orthodromically to the DH and also *antidromically*, via a network of branches or current spread amongst coupled fibres, to invade nerve terminals: these terminals would then release sensitizing substances, such as CGPP and SP. In fact, the interconnected network of fibres imagined by Lewis has not been demonstrated to exist. Further, although inter-neuronal communication may occur between injured nerves (Section 8.2.3), such processes are uncommon for intact, peripheral fibres (Meyer *et al.*, 1985, 1994) (Section 3.1.1). The antidromic activation of PAFs which occurs within regions of tissue damage/primary hyperalgesia is involved in processes of NI and the axonal 'flare' response of the skin to injury (Dray and Urban, 1996; Gamse and Saria, 1987; Lynn, 1990; Reeh and Kress, 1995) (Section 7.9). However, it is unclear whether the population of PAFs which mediates the flare response is identical to that which mediates an increase in nociception (Lynn *et al.*, 1996). Further, the boundary of secondary hyperalgesia generally extends *beyond* the flare zone, and there is no spatial correlation between the flare response and the mechanical hyperalgesia elicited by application of capsaicin to human skin. In addition, antidromic nerve stimulation in the rat does *not* elicit mechanical hypersensitivity or nociceptor sensitization (Reeh *et al.*, 1986; Treede *et al.*, 1992b). As mentioned above, moreover, the transduction sensitivity of small calibre, mechanosensitive fibres is not changed in secondary hyperalgesia. Finally, histamine can produce a flare response with little or no pain and does not, in general, excite mechanosensitive PAFs (Ali *et al.*, 1996; LaMotte *et al.*, 1991). In conclusion, there is little evidence that antidromic activation of PAFs contributes to the secondary, mechanical allodynia of uninjured tissue.

The observations in Section 9.1.2 provide compelling evidence that stimulation of A $\beta$  fibres mediates the mechanical allodynia of secondary hyperalgesia. They also suggest that central mechanisms are required for its expression: such mechanisms are discussed in detail in Sections 10 and 12. Assuming that central processes underlie secondary hyperalgesia and altered responsiveness to A $\beta$  fibre stimulation, it is reasonable to ask whether they are phasically triggered by tissue injury and persist in the absence of additional peripheral input, or whether they require a continuous, peripheral drive for their maintenance.

Following early work by Hardy *et al.* (1950), LaMotte *et al.* (1991) showed that the hyperalgesia and allodynia to mechanical stimuli provoked in human subjects by application of capsaicin to the skin extends outside the region of injection. The hyperalgesia could be prevented by anaesthetic blockade of the peripheral nerve innervating the injected site *before* capsaicin administration whereas, *following* the induction of pain, cooling of the capsaicin-treated region was only partially effective in its relief (Dahl *et al.*, 1993; LaMotte *et al.*, 1991; Treede *et al.*, 1992b). Similar data have been found employing electrical stimulation (Torebjörk *et al.*,

1992). Thus, under some conditions, central changes and a corresponding induction of secondary hyperalgesia, may become at least partially *independent* of subsequent C (and A $\beta$ ) fibre input (Baron and Saguer, 1993). Nevertheless, under other conditions, a sustained, low level of PAF drive appears to maintain those persistent states of central sensitization which contribute to the cutaneous and visceral hyperalgesia/allodynia provoked by tissue damage (Andersen *et al.*, 1995; Cervero, 1995a; Cervero and Laird, 1996b; Cervero *et al.*, 1994; Dickenson, 1997; Gracely *et al.*, 1992; Koltzenburg *et al.*, 1994; LaMotte *et al.*, 1991). For example, as mentioned in Sections 8.2.2 and 8.2.4, local anaesthesia (or sympathectomy) can *rapidly* alleviate some forms of secondary hyperalgesia and neuropathic pain due to PAF injury. In addition, these interventions can even prevent the re-appearance of pain upon intense A $\beta$  fibre stimulation (Gracely *et al.*, 1992; LaMotte *et al.*, 1991; Treede *et al.*, 1992b).

In analogy to clinical investigations, experimental studies have shown that capsaicin enhances the responsiveness of WDR neurones to low intensity, mechanical stimuli and A $\beta$  fibre stimulation *outside* the region of tissue injury in rats. Further, their responsiveness to A $\delta$  fibre stimulation may also be enhanced (Simone *et al.*, 1989a). Both in rats and in primates, heat injury of the skin leads to a facilitation in the response of DH (including STT) neurones to adjacent, non-noxious, tactile stimuli (Dougherty *et al.*, 1992b; Kenshalo *et al.*, 1982; Lin *et al.*, 1997; McMahon and Wall, 1984). In parallel, a reorganization or expansion in the RFs of individual DH neurones may be seen—including those in the cuneate nucleus of the PSDC pathway (Laird and Cervero, 1989; Pettit and Schwark, 1996). Such changes, which are considered to reflect central sensitization, are most pronounced for WDR PNs, in particular, those in deep laminae. However, it is possible that WDR and NS classes of PNs and EXINs in superficial and deeper laminae become sensitized and responsive to low-threshold, A $\beta$  fibre input. Indeed, studies of intracellular markers of neuronal activity bear out the possibility that neurones throughout the DH can be sensitized by nociceptive input (Cervero, 1995b; Chapman and Besson, 1997; Simone *et al.*, 1991; Treede and Magerl, 1995) (Section 10.4.2.5). In analogy to several, above-discussed clinical studies, there is evidence that central, sensitized states in the rat may be further facilitated by a persistent, peripheral input from injured tissue (Dickenson, 1997; Taylor *et al.*, 1995).

To summarize, then, one component of central sensitization may be expressed independently of further PAF input, whereas a further, superimposed component (mediated by contrasting mechanisms) may be maintained by a persistent peripheral drive. Nevertheless, the quantitative relationship between the duration, intensity, temporal patterns and other characteristics of peripheral input to the DH and the maintenance of central, sensitized states requires further elucidation.

### 9.1.4. Referred Pain

#### 9.1.4.1. Characteristics of referred pain

Injury to superficial and (more markedly) deep nerves, as well as noxious stimulation of cutaneous C fibres and (more effectively) nocisponsive muscle afferents, increases both ipsilateral *and* contralateral flexor reflexes. This increased excitability of contralateral reflexes is maintained even after interruption of input from the ipsilateral (affected) paw (Wall and Woolf, 1984; Woolf and McMahon, 1985; Woolf and Wall, 1986) and is independent of changes in the excitability of motoneurons and PAFs innervating the region of referred pain (Cook *et al.*, 1986). These observations point to a role of *central* mechanisms in the mediation of potentiated reflexes from 'remote' tissue regions. Tissue damage may also elicit a hypersensitivity to innocuous, mechanical stimuli in remote regions (cf allodynia) and increase the RF size of the corresponding population of DH neurones (Cook *et al.*, 1987; McMahon and Wall, 1984; Ness and Gebhart, 1990; Neugebauer and Schaible, 1990). In analogy, localized noxious stimulation of a single paw in rats can elicit a hyperalgesia of the contralateral paw which is prevented, but not reversed, by anaesthesia of the stimulated paw (Coderre and Melzack, 1991; Coderre *et al.*, 1993; Wiertelak *et al.*, 1994a). These data suggest that noxious stimulation has triggered persistent changes in the *central* processing of nociceptive input from other regions.

Many other examples of referred pain involving tenderness, allodynia and hyperalgesia of intact tissues are seen clinically. In general, referred pain develops *slowly*, like secondary hyperalgesia, and, clinically, it is triggered by deep somatic and visceral rather than superficial pain (Graven-Nielsen *et al.*, 1997; Mohammadian *et al.*, 1997; Procacci and Zoppi, 1983). Examples include the referred pain which is felt segmentally upon stimulation of the viscera, and the referral of muscle pain to other muscle groups, tendons or joints. The most familiar illustration is, however, the referred pain from the heart which is experienced in the inner aspect of the left arm and shoulder, and which may signal cardiac infarction (Graven-Nielsen *et al.*, 1997). This example conforms to a 'dermatomal' rule whereby pain is often referred to regions derived from the same embryonic segment, and which possess nerves entering the spinal cord at the same level—an observation consistent with a role of convergent DH neurones in the mediation of remote pain (Section 9.1.4.2). A classic illustration is provided by pain in the diaphragm which is often referred to the shoulder. PAFs supplying these tissues share a common embryonic origin and, in each case, enter the DH via the third and fourth cervical DRG to target a common population of neurones. Nevertheless, referred pain can *exceed* segmental boundaries and its referral may be idiosyncratic. For example, some subjects display referred heart pain exclusively in the abdominal region. The non-stereotyped nature of referred pain is also illustrated by the frequent referral of pain to sites of previous painful trauma: for example, a surgical scar in abdominal disease, or previously-operated teeth during dental surgery.

This 'learnt' and variable component of pain is consistent with a role of central (cerebral) processes in its mediation.

Although the issue is still somewhat controversial, referred pain in the absence of long-term changes in tissue pathology (Section 9.1.4.2), is generally prevented or interrupted by anaesthesia of the region exposed to noxious stimulation, rather than by anaesthesia of the region where pain is experienced (Vecchiet *et al.*, 1993). Further, intact tissue regions usually do *not* display alterations in the transduction sensitivity of their nociceptors. These observations, together with the above-mentioned findings, point to a role of *central* mechanisms in the mediation of referred pain. There are several, possible mechanistic explanations which should be regarded as complementary rather than mutually exclusive.

#### 9.1.4.2. Potential mechanisms underlying referred pain

1. Referred pain has been attributed to the peripheral branching of PAFs. This hypothesis assumes that individual sensory nerves send collaterals both to deep tissues and to the skin. However, little anatomical support for this possibility is available inasmuch as dichotomizing fibres are rare and there is considerable inter-individual variability in their occurrence (Bahr *et al.*, 1981; Dawson *et al.*, 1992; Häbler *et al.*, 1988; Mense *et al.*, 1981; Takahashi *et al.*, 1993). Further, the peripheral branching of sensory afferents cannot satisfactorily account for either the temporal *delay* in the onset of referred as compared to local pain nor for its *differing* characteristics.
2. A minor population of PAFs projecting to the *contralateral* DH (Culbertson *et al.*, 1979; Light and Perl, 1979; Sugimoto *et al.*, 1987; Sugiura *et al.*, 1986) might be involved in instances of segmentally-referred contralateral pain, but this mechanism is not relevant to referred pain from other regions.
3. In many cases of segmentally-referred pain, the underlying mechanisms may involve convergent (e.g. visceral/cutaneous) input onto a common population of sensitized DH neurones (Al-Chaer *et al.*, 1996a,b; Berkley *et al.*, 1993; Cervero, 1995a; Cook *et al.*, 1987; McMahon, 1994; Mense, 1993; Ness and Gebhart, 1990; Schaible *et al.*, 1987). Indeed, all DH neurones receiving input from the viscera and deep somatic regions are also targetted by PAFs innervating the skin. However, a role of convergent neurones cannot provide a complete explanation inasmuch as sensation may be *differentially* modified in the region of referred as compared to local pain (Graven-Nielsen *et al.*, 1997). Further, referred pain may exceed segmental boundaries and it also occurs between muscle and deep tissues for which convergence of sensory input at a common population of DH neurones is rare (Hoheisel and Mense, 1990; Mense, 1993). Thus, at least under certain conditions, additional mechanisms may also intervene.
4. The engagement of (ipsilateral or contralateral) DH neurones corresponding to remote tissue

regions may occur via a supraspinal loop. That is, a strengthening and weakening of descending facilitation and inhibition, respectively (Section 10.8). The putative implication of supraspinal structures in mediating referred pain is reinforced by observations that the noxious stimulation of PAFs is associated with distinctive patterns of adaptive changes in neuronal properties in the thalamus and cortex: notably, the appearance of neurones with *bilateral* RFs (Apkarian, 1995b; Apkarian *et al.*, 1995; Guilbaud and Benoist, 1995) (Section 12). Further, in models of unilateral, inflammatory and neuropathic pain, a hyperalgesia may develop in the *opposite, untreated* limb in parallel with the appearance of a corresponding subpopulation of sensitized neurones in the thalamus and cortex (Guilbaud and Benoist, 1995). One anatomical substrate permitting such changes would be the convergence of both ipsi- and contralateral cutaneous, muscle and visceral nociceptive input from multiple ascending pathways in specific, cerebral processing centres: for example, the VPL and other thalamic nuclei, the nucleus gracilis of the PSDC or the cortex itself (Al-Chaer *et al.*, 1997a; Apkarian, 1995b; Apkarian *et al.*, 1995; Brüggemann *et al.*, 1997) (Section 6). Indeed, thalamic neurones have been identified which display increased responsivity to mechanical stimuli in RF regions remote from the locus of injury (Apkarian *et al.*, 1995; Guilbaud *et al.*, 1986). Further, interhemispheric communication of sensory information—including sensitized states—can occur at the level of the cortex and other supraspinal structures, possibly via the engagement of intracortical and reciprocal corticothalamocortical circuits (Sections 6.3.2 and 12). As concerns the role of individual, ascending pathways, Apkarian *et al.* (1995) have, intriguingly, suggested that ‘true’ and ‘referred’ visceral pain are predominantly mediated by the PSDC and STT, respectively. Within the context of referred pain, the present discussion focuses on remote *increases* in nociception. However, C fibre input from damaged tissue can heterotopically activate descending inhibitory mechanisms. This may account for certain instances of modality-specific *decreases* in nociception (Bouhassira *et al.*, 1995; Graven-Nielsen *et al.*, 1997; Le Bars, 1988; Romita and Henry, 1996). Although mechanisms of heterotropic inhibition do *not* necessarily require a supraspinal loop (McGaraughty and Henry, 1997; Romita and Henry, 1996), these observations are consistent with the notion that cerebral mechanisms may be involved in remote alterations in nociception.

5. Persistent, intense nociceptive input—or PAF injury—may lead to generalized and widespread increases in DH excitability via mechanisms involving sensitization, disinhibition and possibly, the emergence of ‘generalized, reverberating’ circuits (Coghill *et al.*, 1991) (Section 10.6). Such excited neuronal states, and corresponding alterations in RF properties, could be communicated intrasegmentally, intersegmentally and contralaterally by ININs and propriospinal neurones

(Willis and Coggeshall, 1991). In addition, a supraspinal loop (*vide supra*) and the minor population of PAFs with collaterals running to the contralateral DH may also be involved. Following disinhibition, normally-subthreshold stimuli may elicit frank APs in DH neurones innervated by remote tissues (Cook *et al.*, 1987; McMahon and Wall, 1984; Pettit and Schwark, 1996). In line with this concept of spreading sensitization, SP released from PAF terminals persists in the DH wherein it may be widely dispersed and act via volume transmission (Section 4.7). Moreover, a localized, noxious stimulus has been observed to elicit a widespread, ‘non-topographic’ upregulation of NK<sub>1</sub> receptors in the DH (Abbadie *et al.*, 1996; Goff *et al.*, 1998). In addition, *unilateral* PAF stimulation or damage can elicit a variety of *bilateral* changes including alterations in:

1. nociceptive thresholds and the influence of drugs upon nociception;
2. sensitivity and RF characteristics of DH neurones; and
3. levels of various transmitters in the DH (Ji *et al.*, 1994; Leah *et al.*, 1992; Leslie *et al.*, 1995; Löfgren *et al.*, 1997; Mao *et al.*, 1992b, 1993a; Millan, 1993; Mohammadian *et al.*, 1997; Presley *et al.*, 1990; Sugimoto *et al.*, 1990; Takaishi *et al.*, 1996) (Section 10.6).

In this light, it is of note that central, DH-integrated mechanisms can modify the activity of sensory fibres via an influence upon their central terminals. This leads, in turn, to the antidromic invasion of their peripheral branches. Indeed, as described in Section 7.9, the efferent activation of polymodal C fibres provokes extravasation and other processes of NI. For example, there is evidence that peripheral inflammation and the accompanying nociception can be modified via DH-localized, GABA<sub>A</sub>- and non-NMDA receptor-mediated mechanisms eliciting ‘dorsal root potentials’ (DRP) (or ‘dorsal root reflexes’) in fine calibre PAFs (Bagust *et al.*, 1997; Cervero and Laird, 1996b; Sluka *et al.*, 1993, 1994a,b, 1995; Thompson and Wall, 1996; Wall and Lidieth, 1997). The engagement of such mechanisms might underlie the *contralateral* vasodilation seen in response to *unilateral* sciatic ligation in rats, a procedure which is accompanied by bilateral changes in neuronal activity the DH (Kurvers *et al.*, 1996; Mao *et al.*, 1992c). Further, unilateral, arthritic joint inflammation may be accompanied by *bilateral* DRPs and hyperalgesia (Rees *et al.*, 1996), while the eventual transfer of unilateral, arthritic joint inflammation of the paw to the contralateral side may well involve such DH-integrated events (Millan and Colpaert, 1991). In addition to the antidromic activation of peripheral PAF terminals via actions mediated in the DH, sympathetic mechanisms may also modulate the activity of PAF terminals, providing a *sixth* potential mechanism underlying referred changes in nociception. Changes in sympathetic outflow to regions of referred pain might be mediated either via:

Table 7. Summary of mechanisms potentially involved in the induction of referred (remote) pain (see Section 9.1.4)

*A. PAF organization*

1. Peripheral branching of PAFs: collaterals to both deep (e.g. visceral) and cutaneous tissue
2. PAFs projecting to the *contralateral* as well as ipsilateral DH

*B. Central mechanisms*

1. Convergent PAF input from different tissues (e.g. muscle *and* skin) onto a *common* population of (sensitized) DH neurones
2. Development of heterosegmental, excited circuits in the DH leading to a generalized pattern of disinhibition and sensitization over widespread regions of the DH
3. Convergent input of nociceptive information from different tissues (e.g., muscle and skin), and transmitted by multiple, ascending pathways, onto a common populations of neurones in the thalamus or other supraspinal structures involved in second order, nociceptive processing
4. Exchange of nociceptive information amongst specific, supraspinal pain-processing regions via corticothalamic loops, interhemispheric links etc: activation of cortical neurones with large and/or bilateral receptive fields
5. Triggering by ascending nociceptive information of a supraspinal loop leading to a heterosegmental modulation of descending inhibition (reduction) or descending facilitation (reinforcement). Regions of the DH affected include both those receiving PAF input from damaged tissue as well as *other* areas

1. spinal reflexes directly connecting the DH to pre-ganglionic sympathetic neurones in the intermediolateral cell column; or
2. engagement of a supraspinal loop leading to activation of descending pathways innervating pre-ganglionic neurones (Jänig, 1993; Miao *et al.*, 1996; Millan, 1997; Takahashi *et al.*, 1993).

Within this context, it is also of note that unilateral injury to PAFs elicits *bilateral* alterations in their phenotype, possible by DH-integrated mechanisms comparable to those evoked above (Oaklander and Belzberg, 1997; Petersen *et al.*, 1998a).

Alterations in the sensitivity and activity of PAFs innervating regions of referred pain (whether antidromically- or sympathetically-mediated) are of particular interest. They may, thus, underlie the above-mentioned, rare cases where anaesthesia of the intact region, rather than the site of injury, reduces referred pain. Further, changes in the activity of PAFs from areas of remote pain may underlie not only changes in nociception but also slowly-developing trophic phenomena, such as a perturbation of blood flow, oedema and alterations in skin texture (Jänig, 1993).

To summarize (Table 7), there is considerable evidence that *central* events integrated in the DH and/or higher structures contribute to alterations in nociception from remote, intact tissue regions. These involve: sensitization of convergent neurones in the DH (and higher structures), widespread, non-topographical increases in DH excitability, modulation of the activity of descending pathways and, in certain cases, secondary, spinally- or sympathetically-mediated changes in the activity of PAFs innervating the region of referred pain.

## 9.2. C Fibres and Allodynic States

### 9.2.1. Involvement of C Fibres in Allodynic States

The above-discussed observations suggest that mechanical allodynia is predominantly mediated by large calibre, A $\beta$  fibres. However, they do *not* necessarily exclude a role of C fibres in the induction or maintenance of central sensitized states underlying mechanical allodynia, or in the development of

clinical, neuropathic painful states. For example, a recent study revealed a deep, C fibre-mediated component of clinical, neuropathic pain which was *not* affected by manipulations of A $\beta$  fibre/sympathetic fibre activity, despite the disappearance of tactile allodynia (Mailis *et al.*, 1997). The following points underline the potential importance of C fibres in mediating and/or maintaining painful states.

1. As discussed in Section 9.1.3, an afferent barrage from C fibres triggers the sensitization of WDR neurones in the DH and a persistent, low level of C fibre-mediated afferent drive may be necessary for maintaining central mechanisms underlying certain hyperalgesic and allodynic states (Andersen *et al.*, 1995; Cervero *et al.*, 1993; Cervero, 1995b; Dickenson, 1997; Gracely *et al.*, 1992; Koltzenburg *et al.*, 1994; LaMotte *et al.*, 1991; Qian *et al.*, 1996; Xu *et al.*, 1995b). Mechanisms involved in *maintaining* a background state of central neuronal excitation may not be identical to those responsible for the effects of phasic superimposition of further, intense stimulation (Hoheisel *et al.*, 1995). Thus, C fibre input to the DH may indirectly facilitate A $\beta$  fibre-mediated allodynia by inducing and accentuating central processes of sensitization. Further, at C fibre-excited DH neurones, A $\beta$  fibre stimulation may be able to elicit processes of further sensitization (Section 10.5). In addition, excitatory C and A $\beta$  fibre input may even synergize at the level of WDR DH neurones (Andersen *et al.*, 1995; Choi and Rowbotham, 1997; Hoheisel *et al.*, 1995, 1997).
2. Several, different forms of mechanical allodynia exist and it has been proposed that a non-A $\beta$  class of PAF is involved in mediating a specific form of 'punctate' mechanical allodynia (Ali *et al.*, 1996; LaMotte *et al.*, 1991) (Section 9.2.2).
3. A recent theory has suggested that A $\beta$  fibres elicit mechanical allodynia (secondary hyperalgesia) by the (indirect) recruitment of C fibre terminals in the DH (Cervero and Laird, 1996b) (Section 9.2.3).
4. There is evidence that a disinhibition of small calibre, 'cooling-sensitive', C fibres mediates *cold* allodynia, a process involving adaptive changes

- integrated at the level of the thalamus (Craig, 1995; Craig *et al.*, 1996) (Sections 9.2.4 and 13.4).
5. It is of note that CNS damage or PAF injury may be accompanied by a C fibre-mediated hyperalgesia to heat which occurs simultaneously with a A $\beta$  fibre-mediated, mechanical allodynia (Dickenson, 1997; Hao *et al.*, 1996a,b; Hunter *et al.*, 1997b; Kim *et al.*, 1997b; Qian *et al.*, 1996a; Shir and Seltzer, 1990; Wegert *et al.*, 1997).

Irrespective of the relative roles of C and A $\beta$  fibres, it should be emphasized that central, sensitized states are a precondition for *each* of the possible mechanisms underlying allodynia summarized in the following paragraphs.

#### 9.2.2. 'Punctate' Hyperalgesia/allodynia

The discussion in Section 9.1.2 focused on the role of A $\beta$  fibres in mediating the mechanical allodynia which accompanies nerve injury, and which can be elicited from the area surrounding a region of peripheral tissue damage. This form of allodynia is evoked by normally innocuous, mechanical stimulation, such as light touch or brushing of the skin, and has been termed 'dynamic hyperalgesia'. It may be distinguished from a further form of mechanical allodynia, termed 'punctate', which is elicited by non-noxious, localized, mechanical stimuli: for example, Von Frey hairs (Koltzenburg *et al.*, 1992; LaMotte *et al.*, 1991; Warncke *et al.*, 1997a). Like its dynamic counterpart, punctate allodynia requires the induction of central sensitization for its manifestation. However, punctate allodynia develops more rapidly, is more persistent and occupies a larger tissue region.

It has been proposed that punctate allodynia is mediated by *small* calibre fibres (Cervero *et al.*, 1993, 1994; Treede and Cole, 1993; LaMotte *et al.*, 1991). However, if polymodal C receptors were involved, a thermal allodynia should also be apparent, yet this is not so. Further, the distribution of punctate allodynia might be anticipated to correspond to the zone of axonal flare, which is also not the case (Ali *et al.*, 1996)—and the population of PAFs which mediates axonal flare may not be the same as that which mediates nociception (Lynn *et al.*, 1996). One possible explanation would be the involvement in punctate allodynia of a 'mechanoselective channel': that is, of mechanospecific, small calibre (possibly type I A $\delta$ ) fibres projecting onto sensitized WDR neurones—which may, in turn, selectively respond to mechanical input (Ali *et al.*, 1996; Fitzgerald and Lynn, 1977; Treede and Magerl, 1995; Willis and Coggeshall, 1991) (Section 3.1.1). A further proposition by Ali *et al.* (1996) is that mechanical stimuli activate not only the same population of polymodal C fibres as thermal stimuli but also large diameter, mechanosensitive afferents which normally activate ININs in the DH, thereby counterbalancing the activation of WDR neurones. Under conditions of PAF injury, the activity of these ININs is reduced (by mechanisms discussed in Section 10.6) and mechanical nociception is selectively enhanced (Fig. 2). However, as discussed in Section 10.6, inflammatory tissue injury is *not* accompanied by a decrease in ININ tone in the DH,

questioning the pertinence of this hypothesis to secondary hyperalgesia. A related proposition of Treede and Magerl (1995), which also provides a more general explanation for selective, secondary mechanical vs thermal hyperalgesia, proposes that a generalized sensitization of *all* PNs may *not* occur in the DH. Rather, mechanosensitive, but not thermosensitive, afferents may impinge upon a subset of sensitized EXINs which themselves project onto PNs.

Thus, although the precise mechanisms involved in punctate allodynia require further elucidation, central, adaptive events emerge as of key importance in its expression. Further, consistent with a role of C fibres in its mediation, the NMDA receptor channel blocker, ketamine, was recently shown to suppress punctate, secondary hyperalgesia in man (Bouhassira *et al.*, 1997; Warncke *et al.*, 1997b).

#### 9.2.3. An A $\beta$ -C Fibre Link in the DH Underlying Allodynia?

As mentioned above, the absence of thermal allodynia presents a challenge for all theories of the mechanical allodynia (whether dynamic or punctate) which accompanies secondary hyperalgesia and peripheral nerve damage, since it is difficult to understand why WDR neurones in the DH should be selectively sensitized to specific, sensory modalities. Further, notwithstanding a key role of mechanoselective A $\beta$  fibres, *the rapidity* with which mechanical allodynia can be induced by, for example, capsaicin treatment of human skin, suggests that this phenomenon occurs within a time-scale too rapid to allow for the establishment of novel patterns of A $\beta$  connectivity in the DH (Section 11.2). Based on a series of studies in hyperalgesic human skin, Cervero and Laird (1996b) have recently proposed a model of mechanical allodynia which helps account for these observations.

The hypothesis suggests, in principle, that mechanical allodynia depends upon activity in both A $\beta$  and C fibres, and that the former indirectly enhance input of the latter onto sensitized WDR (or NS) neurones. This is achieved by a mechanism involving A $\beta$  fibre-mediated activation of a population of ININs in the DH which interact with the central terminals of small calibre, C fibres. This theory is, thus, based upon older studies showing that DRPs (that is, antidromic activity) can be evoked in the central terminals of C fibres by stimulation of INs interacting with their terminals (Section 9.1.4.2). The mild, depolarizing action of INs at C fibre terminals, termed 'primary afferent depolarization' (PAD), results in presynaptic inhibition of neurotransmitter release and, under normal conditions, antinociception (Melzack and Wall, 1965; Schmidt, 1971; Wall, 1995). This action is mediated via the activation of both GABA<sub>A</sub> receptors (coupled to chloride channels) and of non-NMDA (kainate or AMPA) ionotropic receptors (Cervero and Laird, 1996a; Rees *et al.*, 1995a; Rudomin, 1990; Sluka *et al.*, 1993, 1994a,b, 1995). The model of Cervero and Laird (1996a) assumes that these INs also possess a C fibre input. Thus, following tissue injury and inflammation, DH-localized INs are excited by C

fibres originating in the region of primary hyperalgesia. Activation of these INs triggers DRPs in the terminals of C fibres emanating from the neighbouring, uninjured zone of *secondary* hyperalgesia (Rees *et al.*, 1995a). As indicated above, this low level of C fibre terminal depolarization normally discourages propagation of APs and decreases transmitter release. However, the superimposition of an *additional* volley of excitatory input onto pre-excited INs by activation of A $\beta$  fibres from the region of secondary hyperalgesia results in spike activity in C fibre terminals. This, in turn, results in:

1. a localized C fibre-mediated flare response peripherally (antidromic transmission); and
2. activation of DH neurones and the misinterpretation of A $\beta$  fibre-triggered, yet C fibre-mediated, excitation of WDR and NS as noxious.

This mechanism provides a more *rapid* mechanism for A $\beta$  fibre-mediated activation of sensitized DH neurones than that of the reorganization of A $\beta$  input in the DH following PAF injury (Section 11.2). Further, an (indirect) activation of the central terminals of C fibres by A $\beta$  fibres would be consistent with the sensitization of DH neurones provoked by A $\beta$  fibre stimulation in inflamed states (Section 10.5), and with the induction of DH gene expression by A $\beta$  fibre stimulation *only* following PAF nerve injury (Ma and Woolf, 1996a; Molander *et al.*, 1992) (Section 11.2). The hypothesis is also consistent with the spontaneous activity, and increased sympathetic responsiveness, of large calibre A $\beta$  fibres following PAF injury (Section 8.2.4). Moreover, under conditions of inflammation, there is evidence for an increase in the activity of GABAergic INs which mediate PAD via GABA<sub>A</sub> receptors on PAF terminals (Cervero and Laird, 1996a; Coggeshall and Carlton, 1997) (Sections 9.1.4.2 and 10.6). Nevertheless, several points require clarification.

1. Following PAF injury, notwithstanding the occurrence of allodynia, there is an—at least transient—decrease in the functional activity of GABAergic INs in the DH, and DRPs may also be reduced by nerve injury (Laird and Bennett, 1992; Wall and Devor, 1981) (Sections 9.1.4.2 and 10.6).
2. A pronounced depolarization of C fibre terminals could result in a *resistance* to invasion by APs: that is, a shunt resulting in the *termination*—rather than potentiation of—forward transmission onto DH neurones (Cattaert *et al.*, 1994; Wall, 1995).
3. As mentioned in Section 9.1.3, there is evidence from other studies that *different* areas of hyperalgesic skin present flare responses *or* allodynia and that the underlying neuronal mechanisms may not be identical (Ali *et al.*, 1996; Lynn *et al.*, 1996).
4. It might be expected that, even in the absence of additional A $\beta$  fibre stimulation, the induction of PAD by INs should alter the effects of C fibre stimulation in the region of secondary hyperalgesia.

5. This model of allodynia, while providing an attractive, potential explanation of *rapidly-evoked* secondary hyperalgesia seems less pertinent to the allodynia associated with long-term PAF injury in which there is a reorganization of large calibre A $\beta$  input in the DH. This offers an alternative mechanism whereby normally innocuous, mechanical information can access and excite sensitized nocisponsive WDR (and NS) neurones and evoke the sensation of pain (Section 11.2).

Thus, despite the insights afforded by this novel theory, further work is required to improve our understanding of processes underlying mechanical allodynia. Irrespective of the precise underlying mechanisms, there is clearly a consensus that at least one important, clinical form of mechanical allodynia involves both the activation of A $\beta$  fibres and central mechanisms of sensitization triggered—and possibly maintained by—C fibre-input to the DH.

#### 9.2.4. Cold Allodynia

Cold allodynia refers to the induction of pain by normally non-noxious, cold stimuli. This abnormal responsiveness to cold is seen both experimentally and clinically from regions of secondary hyperalgesia and, in particular, from areas innervated by damaged nerves. It may be distinguished from the *reduction* in pain obtained upon the cooling of areas of primary hyperalgesia. Unmyelinated axons are the predominant route for the signalling of noxious, cold information in rats and, like thermal (heat) hyperalgesia, cold allodynia appears to be mediated by capsaicin-sensitive C fibres interacting with sensitized WDR neurones in the DH (Cervero *et al.*, 1994; Craig *et al.*, 1996; Hao *et al.*, 1996a; Kim *et al.*, 1995; Meller *et al.*, 1992b,c; Shir and Seltzer, 1990; Wegert *et al.*, 1997). It cannot be discounted that the population of C fibres which mediates cold allodynia is mechanosensitive and polymodal in nature, although this is unlikely.

In any case, cold-sensitive C fibres mediating allodynia appear to be independent of the population of cold-sensitive, A $\delta$  fibres which intensity-code temperature information (Sections 3.1.1 and 13.4) (Craig, 1995; Craig *et al.*, 1994; LaMotte and Thalhammer, 1982). Interestingly, cold-temperature/A $\delta$  and cold-pain/C channels normally interact at the thalamic level and this mechanism may be compromised upon damage to the thalamus. That is, a lesion-induced disinhibition of a C fibre-activated medial thalamus–cingulate cortex circuit may underlie the cold allodynia provoked by stroke damage to the thalamus (Boivie *et al.*, 1989; Craig *et al.*, 1994 and 1996; Vanhoesen, 1995) (Section 13.4).

## 10. NOCICEPTIVE AND NEUROPATHIC PAIN: PROCESSES INTEGRATED IN THE DH

### 10.1. Multiple Mechanisms Integrated in the DH

From the above-discussed observations (Section 9), the most satisfactory explanation of the phenomena of mechanical allodynia, secondary hyperalgesia and referred pain is that they involve *central*, adap-

tive changes triggered by peripheral events and involving both C and A $\beta$  fibre input.

Several processes integrated in the DH have been implicated in the induction of painful states, and each of these evolves with a distinctive time-course (Table 5):

1. Neuronal sensitization; that is, an increased excitability of WDR neurones to both C and A $\beta$  fibre input. This can occur rapidly (within minutes) and is triggered, and usually enhanced by C fibre input. NMDA receptors play a key role in both the induction and maintenance of such sensitized states.
2. As concerns pain due to PAF injury, a reduction in the activity of ININs targeting PNs, reflecting either transient functional changes or their physical degeneration.
3. Likewise for PAF damage, a reduction in excitatory A $\beta$  input onto ININs in the DH.
4. A modulation in the activity of descending pathways.

These processes, which are likely interactive and synergistic, are described below. In addition, as outlined in Section 11.2, nerve injury may trigger a structural reorganization of the DH involving the inappropriate sprouting of damaged A $\beta$  afferents from deeper into superficial laminae, a mechanism lying at the interface of central and peripheral events contributing to neuropathic pain.

## 10.2. Sensitization and Increased Excitability of DH Neurones

### 10.2.1. LTP and Neuronal Sensitization

Studies of the hippocampus and other cerebral regions have established that persistent alterations in synaptic efficacy may be produced postsynaptically by alterations in patterns of presynaptic stimulation. Correspondingly, LTP and long-term depression (LTD) refer to an increase and a decrease in synaptic strength, respectively, with changes in postsynaptic, cytosolic levels of  $[Ca^{2+}]_i$  and PKs playing a key role in their generation (Barria *et al.*, 1993; Bito *et al.*, 1997; Bliss and Collingridge, 1993; Deisseroth *et al.*, 1998; Linden and Connor, 1996; Lisman, 1994, 1997; Malenka and Nicoll, 1997; McEachern and Shaw, 1996; Wang *et al.*, 1997g; Xu *et al.*, 1997a). Recent studies have suggested that changes resembling LTD can be induced in the substantia gelatinosa by low frequency stimulation of afferent A $\delta$  fibres. On the other hand, high frequency, tetanic stimulation of C (and, probably, A $\delta$ ) fibres may elicit processes similar to LTP in DH neurones (Bouhassira *et al.*, 1997; Liu and Sandkühler, 1997; Randic *et al.*, 1993; Sandkühler *et al.*, 1997; Svendsen *et al.*, 1997; Willis, 1997). Furthermore, there is considerable evidence that intense, recurrent and/or sustained electrical or noxious stimulation of C fibres leads to an increase in synaptic efficacy and WDR neurone excitability in the DH. Such processes of 'central sensitization' also appear related to processes underlying LTP and similarly involve the engagement of NMDA receptors and alterations in levels of  $[Ca^{2+}]_i$  and PKs

(Baranauskas and Nistri, 1998; Bouhassira *et al.*, 1997; Dickenson, 1997; Liu and Sandkühler, 1997; McEachern and Shaw, 1996; Lisman *et al.*, 1997; Svendsen *et al.*, 1994, 1997; Willis, 1997) (Sections 10.3 and 10.4).

Supraspinal processes of LTP and memory formation can persist for days or longer even in the absence of additional stimulation, and they may be associated with alterations in gene expression and, ultimately, morphological changes. Further, the induction of LTP, alterations in synaptic strength and memory storage may involve a multiplicity of pre- and postsynaptic mechanisms operating in parallel and in synergy (Bliss and Collingridge, 1993; McEachern and Shaw, 1996; Schulz and Fitzgibbons, 1997; Turrigiano *et al.*, 1998). On the other hand, the sensitization of DH neurones can be expressed very rapidly and reversibly in the absence of morphological changes, and may require peripheral input for its maintenance. It might, thus, be questioned whether rapid DH sensitization can genuinely be considered as equivalent to processes of LTP. However, although DH mechanisms of neuronal sensitization are *not* invariably comparable to processes of LTP, they possess several common underlying mechanisms (*vide supra*) and recent studies have re-asserted the possibility that LTP-like phenomena can be triggered in DH neurones by nociceptive input to the DH (Baranauskas and Nistri, 1998; Dickenson, 1997; Liu and Sandkühler, 1997; Svendsen *et al.*, 1997; Wilcox, 1993b; Willis, 1997). On teleological grounds, it might be argued that LTP-like events are *inconsistent* with a physiological, reversible and short-term protective role of DH sensitization (Section 9.1.1). Indeed, the induction of prolonged—and perhaps irreversible—LTP-like states of enhanced excitability, involving structural modifications of synaptic architecture, may underlie chronic, pathological, painful states due to, for example, PAF injury (Section 10.2.1).

In analogy to processes of peripheral nociceptor sensitization and the recruitment of 'silent nociceptors' (Sections 3.1.3 and 7.5), those central processes of response amplification and sensitization which underlie prolonged, painful states may reflect both increases in synaptic efficacy as well as the transformation of synapses from a 'silent' to an 'active' mode (Isaac *et al.*, 1997; Malenka and Nicoll, 1997).

### 10.2.2. Induction of Sensitization in DH Neurones: Characteristics of Sensitized Neurones

Damage to the skin and other organs, cutaneous application of capsaicin, inflammation, intrathecal administration of GLU or brief electrical activation of C (and possibly A $\delta$ , but not A $\beta$ ) fibres elicits a state of enhanced excitability in the DH, in particular of WDR neurones in deep laminae (Clément *et al.*, 1996; Coutinho *et al.*, 1996; Dickenson, 1997; Dougherty and Willis, 1992; Ide *et al.*, 1997; King and Thompson, 1995; Kolhekar and Gebhart, 1996; Mense, 1993; Schaible and Grubb, 1993). Stimulation at 1 Hz for 20 sec, for example, elicits an increase in excitability which persists for about 1 hr (Baranauskas and Nistri, 1998; King and



Thompson, 1995; Owens *et al.*, 1992; Wall and Woolf, 1984; Woolf and Wall, 1986; Woolf, 1983; Woolf and Wiesenfeld-Hallin, 1986). Increased neuronal excitability manifests several general characteristics.

1. A transient stimulus now provokes a response of greater duration and intensity involving a greater number of APs: that is, the magnitude of the response is enhanced (cf hyperalgesia).
2. RFs are magnified such that responses can now be evoked from a larger area. Normally, only stimulation in a spatially-limited, discrete, 'trigger' region evokes APs. In contrast, stimulation of the surrounding, 'subliminal' zone, which provides a convergent but less strong input to DH neurones, is ineffective—at most eliciting EPSPs but not provoking firing. This fringe zone now *also* becomes the origin of frank discharges (cf secondary hyperalgesia).
3. The threshold for triggering firing is reduced such that neurones can be activated by lower, normally sub-noxious, stimulus intensities. There is also an increase in, and an appearance of novel, responses to A $\beta$  fibres (cf allodynia).

The relationship of these changes to experimental and clinical observations of primary and *secondary* hyperalgesia, and of A $\beta$  fibre-mediated mechanical allodynia is, thus, evident.

The increased excitability of deep DH laminae provoked by repetitive C fibre stimulation may be explained by the temporal and spatial summation of rapid and, more importantly, *slow* (many seconds) EPSPs. This process reflects the sequential yet intercalated activation of several receptor types. Thus, upon activation of C fibres, an initial and rapid EPSP lasting a few milliseconds is provoked by the engagement of AMPA receptors. This triggers the opening of VDCCs and further depolarization. Further, it is succeeded by the activation of NK<sub>1/2</sub>, group I MTB and CGRP receptors mediating sustained EPSPs over tens of seconds. The differential mechanisms underlying these various components of excitation, and their cooperative nature, is explained further in Sections 10.3 and 10.4. Evidently, where noxious stimulation is maintained and firing is rapid, EPSPs will summate, leading to an incremental depolarization, induction of APs and an increase in excitability. In this regard, two related events should be recognized.

1. C fibre-mediated 'wind-up' refers to the gradual neuronal depolarization and increased number of APs evoked by C fibre stimulation (King and Thompson, 1995).
2. 'Heterosynaptic facilitation' refers to the process whereby a progressive increase in neuronal excitability leads to an increased amplitude in the response to *other* inputs, specifically A $\beta$  fibres (Thompson *et al.*, 1993b; Woolf and Doubell, 1994).

These processes might, therefore, be considered as substrates of hyperalgesia and allodynia, respectively, and would both contribute to the expansion of RFs.

To summarize, sensitization of WDRs is associated with an increase in their spontaneous neuronal activity, an expansion of their RFs (too extensive to be accounted for by changes in the RFs of their corresponding PAFs), an increased responsiveness to noxious, C-fibre-mediated input and the induction of responses by low threshold (normally innocuous) A $\beta$  fibre input (Baranauskas and Nistri, 1998; Dougherty *et al.*, 1992c; Dubner, 1992; Hylden *et al.*, 1989; McMahon and Wall, 1984; Woolf and King, 1990). In correspondence with this schema, diverse noxious stimuli (such as capsaicin) applied to the skin within the RFs of STT and other deep WDR neurones in rodents and primates have been shown to decrease their thresholds for responding to mechanical stimuli, expand their RFs and, in particular, enhance their responsiveness to innocuous A $\beta$  fibre-mediated mechanical stimulation from the area of secondary hyperalgesia (Cook *et al.*, 1987; Dougherty *et al.*, 1992c; Laird and Cervero, 1989; Lin *et al.*, 1997; Simone *et al.*, 1991; Thompson *et al.*, 1993b).

The above description of sensitization is largely based on observations obtained from WDR neurones in deep DH laminae of rats and primates. In principle, assuming that the necessary intracellular machinery is present, sensitization might be initiated by C fibre/NMDA stimulation of other neuronal classes in the DH. Thus, although monosynaptic sensitization of PNs definitely does occur, they may also be secondarily (polysynaptically) excited and sensitized by (presensitized) EXINs. Further, ININs might themselves be sensitized by recurrent and intense C fibre input, a possibility supported by neurochemical and functional observations of increases in the activity of opiodergic (DYN-containing) and GABAergic ININs in the DH under conditions of inflammation (Chapman and Besson, 1997; Men  trety *et al.*, 1989; Millan, 1990, 1993; Todd *et al.*, 1994a) (Sections 10.4.2.5 and 10.6). In addition to WDR units, superficial or deep laminae NS neurones may also be sensitized although, to date, direct evidence in support of this possibility is limited (Chapman and Besson, 1997; Dougherty *et al.*, 1992b,c; Cervero, 1995b; Simone *et al.*, 1991; Tavares *et al.*, 1993). Thus, the following description of molecular mechanisms underlying DH sensitization concerns events documented primarily in deeper laminae WDR neurones, such as PNs of the STT. Although the following paragraphs focus on EAAs, tachykinins and CGRP, a potential role of other excitatory neuropeptides, PGs, ATP, neurotrophins, cytokines and other substances released from PAF terminals in mediating (or modulating) the sensitization of DH neurones should not be neglected (Sections 3.2.6, 4.8 and 14). In any case, all such potential mediators likely converge on common, intracellular transduction mechanisms involved in the sensitization of SH neurones and illustrated in Fig. 5 (Section 10.4).

### 10.3. The Role of EAAs, Tachykinins and CGRP in the Sensitization of DH Neurones

#### 10.3.1. Molecular Mechanisms Underlying Neuronal Sensitization: The Key Role of NMDA Receptors

Recent studies have begun to unravel the mutually-interactive pattern of cellular events which underlies the sensitization of DH neurones by C fibre input from the skin and other organs (Baranauskas and Nistri, 1998; Coderre *et al.*, 1993; Coutinho *et al.*, 1996; Dickenson, 1997; Ide *et al.*, 1997; Kolhekar and Gebhart, 1996; King and Thompson, 1995; Mense, 1993; Schaible and Grubb, 1993; Urban *et al.*, 1994a,b; Wilcox, 1991; Woolf, 1994). As mentioned above, the following account concentrates upon the actions of EAAs, tachykinins and SP, but the possible role of other neurotransmitters, in particular excitatory neuropeptides, in the sensitization of DH neurones, should not be forgotten (Baranauskas and Nistri, 1998; Coggeshall and Carlton, 1998). Indeed, the summation of multiple, slow and sustained EPSPs and depolarizations plays a key role in the sensitization of DH neurones. The underlying processes are of considerable complexity and the following key points should be emphasized.

1. The release of EAAs, tachykinins and CGRP from a subset of nocisponsive C fibres innervating the skin and other organs fulfils a key and cooperative role in eliciting DH sensitization.
2. The influence of PAF-localized transmitters upon the activity of DH neurones is mediated via:
  1. a direct alteration in ion flux at cation-permeable channels;
  2. an interaction with intracellular transduction mechanisms leading to the secondary modification of ionic currents (for example, via receptor/ion channel phosphorylation) and
  3. longer-term effects involving processes of receptor recycling and alterations in the gene transcription of receptors, transmitters and other molecules (Mantyh *et al.*, 1995; Sluka *et al.*, 1997a,b; Lin *et al.*, 1997).
3. Sensitizing mechanisms may all ultimately converge to reinforce transmission at NMDA receptors, thereby resulting in a pronounced and sustained elevation in  $\text{Ca}^{2+}$ -influx and  $[\text{Ca}^{2+}]_i$  levels.
4. NMDA receptors display several, distinctive attributes underlying their key importance in both the induction and maintenance of sensitized states (Chapman *et al.*, 1996; Chen and Huang, 1992; Coderre and Melzack, 1991, 1992a,b; Coderre *et al.*, 1993; Kolhekar and Gebhart, 1996; King and Thompson, 1995; Mayer and Miller, 1990; Seguin *et al.*, 1995; Woolf and Thompson, 1991; Yoshimura and Jessel, 1990). These properties may be summarized as follows:
  1. under resting conditions, NMDA receptors are quiescent owing to an intra-channel  $\text{Mg}^{2+}$ -block, the relief of which by depolarization is required to permit the sustained passage of current (Chizh *et al.*, 1997; Sharma and Stevens, 1996);

2. the NMDA receptor-coupled ion channel is permeable to  $\text{Ca}^{2+}$ -ions. Thus, NMDA receptor activation not only depolarizes cells, but also increases levels of  $[\text{Ca}^{2+}]_i$  (Mayer and Miller, 1990; Reichling and MacDermott, 1996);
3. the phosphorylation of NMDA receptors by PKC counteracts the  $\text{Mg}^{2+}$ -block and allows NMDA receptors to operate at more negative (hyperpolarized) potentials (Ben-Ari *et al.*, 1992; Lerea, 1997);
4. the activity of PKC is synergistically facilitated by increases in  $[\text{Ca}^{2+}]_i$  and the generation of DAG following activation of PLC by  $\text{NK}_{1/2}$  and group I mGlu receptors (Ramakers *et al.*, 1997; Zheng *et al.*, 1997);
5. activation of NMDA receptors can elicit a 'burst'-like pattern of firing in DH neurones, an action which is enhanced by the interruption of glycinergic/GABAergic ININ transmission (Grubb *et al.*, 1996) (Section 10.6). Based on studies elsewhere in the CNS (Johnson *et al.*, 1992; Lejeune *et al.*, 1997), 'burst' firing markedly enhances neurotransmitter release. Further, it may set-up reverberatory, hyperexcitable circuits and reinforce the rostral transmission of nociceptive information by PNs;
6. presynaptic NMDA receptors on central PAF terminals may enhance the release of SP and EAA, thereby further accentuating sensitizing events at PNs in the DH (Coggeshall and Carlton, 1997; Liu *et al.*, 1997b) (Section 3.2.4). This action is complemented by a further component of NMDA receptor-mediated PAF release *indirectly* mediated via NO (Sorkin, 1993). There is also evidence for an increase in PAF levels of GLU under conditions of peripheral inflammation (Sluka and Westlund, 1993; Westlund *et al.*, 1992). However, there are contradictory data concerning changes in the density of NMDA receptors in the DH in painful states. Minor reductions in NMDA receptor density might be attributable to their down-regulation by an enhanced PAF input, or to their loss upon the transynaptic degeneration of ININs triggered by PAF injury (Coggeshall and Carlton, 1997; Harris *et al.*, 1996; Dickenson, 1997; Hama *et al.*, 1995; Pellegrini-Giampietro *et al.*, 1994; Sloan *et al.*, 1991) (Section 10.6).

Overall, then, upon repetitive C fibre stimulation, activity at NMDA receptors is augmented by several mechanisms of response *amplification*. Indeed, for the above reasons, NMDA receptors and increases in  $[\text{Ca}^{2+}]_i$  levels fulfil a particularly important role in triggering and maintaining neuronal sensitization in the DH, a process underlying the development of hyperalgesic and allodynic states. In addition, under conditions of PAF injury, the increase in DH excitability mediated via NMDA receptors may contribute to the diminished antinociceptive efficacy of  $\mu$ -opioid agonists. Correspondingly, the administration of NMDA receptor antagonists potentiates

the analgesic properties of opioidergic agents (Dickenson, 1997; Felsby *et al.*, 1995; Hama *et al.*, 1995; Hoheisel *et al.*, 1997; Lewin *et al.*, 1994a; Mao *et al.*, 1993b; Smith *et al.*, 1994b; Ossipov *et al.*, 1995, 1997; Thompson *et al.*, 1995; Wiesenfeld-Hallin, 1998).

A recent study has elegantly exemplified the functional interrelationships amongst NMDA receptor activation, increases in  $[Ca^{2+}]_i$  levels and the acute modulation of neuropathic pain. Thus, Kawamata and Omote (1996) showed that PAF damage elicits an increase in the GLU content of superficial and deep laminae of the ipsilateral DH together with a parallel elevation in levels of  $[Ca^{2+}]_i$ : the NMDA channel blocker, dizolcypine, blocked both the rise in  $[Ca^{2+}]_i$  levels and the accompanying hyperalgesia.

The contribution of specific receptor types to intracellular mechanisms underlying C fibre-mediated sensitization of WDR neurones in the DH is outlined in the following paragraphs. A graphic summary of events is presented in Fig. 5. The present description is based primarily on observations acquired in DH neurones themselves. However, it also incorporates a few, speculative elements (see legend to Fig. 5) derived from LTP and other processes of synaptic plasticity and response amplification contributing to memory formation in the hippocampus and cortex (Section 10.2.1).

### 10.3.2. The Roles of AMPA, $NK_{1/2}$ , MGLu and CGRP Receptors in Neuronal Sensitization

#### 10.3.2.1. AMPA receptors

Upon C fibre stimulation, the release of GLU, aspartate or other EAAs evokes a fast (milliseconds) EPSP at ionotropic AMPA sites mediating cationic currents, predominantly to  $Na^+$  and only to a lesser degree to  $Ca^{2+}$  (Dickenson, 1997; Lerea, 1997; Wood and Docherty, 1997) (Section 3.2.3). The instantaneous engagement of AMPA receptors likely fulfils an important role in the phasic transmission of nociceptive information under 'baseline' conditions and at low frequency rates (Dickenson, 1997; Hunter and Singh, 1994). The activation of AMPA receptors leads to the secondary activation of VDCCs which further amplify depolarization and trigger an increase in  $[Ca^{2+}]_i$  (Wood and Docherty, 1997). Thus, processes which eventually lead to a relief of the voltage-dependent  $Mg^{2+}$  block at NMDA receptors are initiated via AMPA receptor stimulation. Nevertheless, the ephemeral (msec) nature of AMPA receptor-mediated currents (which may rapidly desensitize), and the topographically-restricted extent of alterations in intracellular levels of  $[Ca^{2+}]_i$ , is incompatible with a major role in the activation of NMDA receptors and the induction of sensitization (Sections 3.2.3 and 10.5). Furthermore, the gene expression of AMPA receptors (gluRI subunit) is diminished under conditions of peripheral inflammation—perhaps suggesting a decreased  $Ca^{2+}$ -permeability (Pellegrini-Giampietro *et al.*, 1994). Indeed, over a longer time-scale, sustained NMDA receptor activation may, as described below, be more convincingly be ascribed to the subsequent engagement of  $NK_1$  and other receptor

types eliciting prolonged alterations in intracellular signals in the vicinity of NMDA receptors. In line with these considerations, the balance of functional evidence suggests that AMPA receptors play a comparatively minor role in the mediation of persistent painful states (Coderre and Melzack, 1991, 1992a,b; Dickenson, 1997; Hunter and Singh, 1994; King and Thompson, 1995; Nasström *et al.*, 1992; Székely *et al.*, 1997). Further, although AMPA receptors are implicated in mediating mechanical allodynia, the population involved is likely activated by EAAs released from  $A\beta$ —rather than C-fibres onto *presensitized* WDR (or NS) neurones (Cumberbatch *et al.*, 1994; Millan, 1995; Sherman and Loomis, 1996; Xu *et al.*, 1993a; Zhang *et al.*, 1994a) (Section 9.1.2).

Notwithstanding the above observations, recent studies of the interrelationship between NMDA and AMPA receptors in the induction of hippocampal LTP suggest that the activity of AMPA receptors may be *reciprocally* enhanced via the engagement of NMDA receptors. Thus, a NMDA receptor-mediated increase in  $[Ca^{2+}]_i$  levels results in the autophosphorylation of calmodulin kinase II which subsequently phosphorylates and increases the responsiveness of AMPA receptors. Such processes, which occur over a time-scale of 10–15 min, suggest that AMPA receptors play a significant role in sustaining LTP and mediating synaptic plasticity (Barria *et al.*, 1997; Lisman, 1994; Lisman *et al.*, 1997). An exploration of a possible role of such mechanisms in the sensitization of DH neurones would be of interest. Further, the influence of PAF injury upon AMPA receptors in the DH *differs* to that of inflammatory, painful states. Thus, there may be an increase in the density of AMPA sites on intrinsic neurones in the DH while the ratio of the gluR1 to the gluR2 subunit is increased, suggestive that their permeability to  $Ca^{2+}$  is enhanced (Carlton *et al.*, 1998b; Coggeshall and Carlton, 1998; Harris *et al.*, 1996). These observations suggest that, under conditions of neuropathic pain, AMPA receptors—activated by small or large calibre fibre input—may make a more important contribution to processes of sensitization in the DH.

#### 10.3.2.2. $NK_{1/2}$ receptors

Upon activation of C fibres, SP and NKA are released in the DH. Via actions at  $NK_1$  and  $NK_2$  receptors, respectively, they together make an important contribution to the induction of DH sensitization (Abbadie *et al.*, 1997; Aicher *et al.*, 1997; Donnerer *et al.*, 1993; McCarron and Krause, 1994, 1996; Krause *et al.*, 1995; Liu and Sandkühler, 1997; Maggi and Schwartz, 1997; Noguchi and Ruda, 1992; Noguchi *et al.*, 1993, 1994; Traub, 1996). As compared to NMDA receptors, however, the *selective* engagement of  $NK_1$  and  $NK_2$  receptors likely plays a less marked role in the *maintenance* of sensitized (inflammatory) states once established (De Koninck and Henry, 1991; Liu and Sandkühler, 1997; Mantyh *et al.*, 1997; Rusin *et al.*, 1992; Thompson *et al.*, 1993a, 1994; Traub, 1996). It is possible that this lesser importance of  $NK_1$  receptors may, at least partially, reflect their rapid, PKC-mediated phosphorylation—although the signifi-

cance of this mechanism of desensitization in the DH remains unclear (Quartara and Maggi, 1997). In any case, over a time-scale of hours, the endosomal internalization of NK<sub>1</sub> receptors on neurones in superficial laminae (I/II<sub>0</sub>) of the DH and on the dendrites of neurones in deeper laminae results in their disappearance from the cell membrane. However, this process is only transient and, following degradation of SP, functionally-active NK<sub>1</sub> receptors are rapidly recycled to the cell surface. Indeed, PAF damage and—less consistently—peripheral inflammation may be accompanied by an increase in the density of NK<sub>1</sub> receptors in the DH, while the release of SP from PAFs is also enhanced by peripheral inflammation (Abbadie *et al.*, 1996; Allen *et al.*, 1997a; Coggeshall and Carlton, 1997; Garland *et al.*, 1996; Goff *et al.*, 1998; Liu *et al.*, 1997b; Mantyh *et al.*, 1995; Tao *et al.*, 1997) (Section 7.6).

The principal NK<sub>1</sub>/NK<sub>2</sub> receptor-coupled, cellular mechanism underlying the induction of slow depolarizations and sustained EPSPs by SP and NKA is the activation of PLC leading to the formation of:

1. IP<sub>3</sub>, which releases Ca<sup>2+</sup> from intracellular sequestration in the endoplasmic reticulum; and
2. DAG, which, synergistically with [Ca<sup>2+</sup>]<sub>i</sub>, activates PKC leading to the phosphorylation of NMDA receptors and a further relief of their Mg<sup>2+</sup>-block (Ben-Ari *et al.*, 1992; Chen and Huang, 1992; Mantyh *et al.*, 1989; Otsuka and Yoshioka, 1993; Quartara and Maggi, 1997; Rusin *et al.*, 1993; Urban *et al.*, 1994a,b).

As described in Section 10.2, an increase in [Ca<sup>2+</sup>]<sub>i</sub> levels may exert several other actions contributing to an enhancement of neuronal excitability, including the generation of NO, which has been implicated in the pronociceptive actions of SP on DH neurones (Radhakrishnan *et al.*, 1995; Tao *et al.*, 1997) (Section 10.4.2.2). In addition to the induction of PKC, several other intracellular transduction mechanisms may potentially intervene in the excitatory actions of SP at NK<sub>1</sub> receptors (Quartara and Maggi, 1997). For example, a component of the slow membrane depolarization which is triggered by SP in certain neuronal types is effected—possibly independently of PLC—via a decrease in an inwardly-rectifying, Ca<sup>2+</sup>-dependent K<sup>+</sup>-current (Baranauskas and Nistri, 1998; Bentley and Gent, 1995; Murase and Randic, 1984; Nowak and MacDonald, 1982; Otsuka and Yoshioka, 1993; Quartara and Maggi, 1997; Shen and North, 1992). However, the potential role of intracellular transduction mechanisms other than PLC in the actions of tachykinins at DH neurones requires clarification. In addition to effects on WDR themselves, SP exerts a (partially indirect) positive feedback action at PAF terminals to further facilitate the release of GLU and SP (Coggeshall and Carlton, 1997; Hu *et al.*, 1997; Kangrga and Randic, 1990; Skilling *et al.*, 1990; Smullin *et al.*, 1990; Sorkin, 1993).

The relative importance of NK<sub>1</sub> and NK<sub>2</sub> receptors in mediating the facilitatory, sensitizing actions of tachykinins on DH neurones is still under discussion. In fact, it has proven difficult to visualize NK<sub>2</sub> receptors in the DH. Further, although there is evidence suggesting that DH-localized NK<sub>2</sub> receptors

are involved in spinal nociceptive transmission, this role appears to be exerted *physically*. Indeed, under more prolonged conditions, behavioural and electrophysiological studies from a broad variety of tissues suggest that NK<sub>1</sub> receptors assume the major role (Coggeshall and Carlton, 1997; De Koninck and Henry, 1991; Fleetwood-Walker *et al.*, 1990; Jia and Seybold, 1997; Liu and Sandkühler, 1997; Nagy *et al.*, 1994; Neugebauer *et al.*, 1995; Parsons *et al.*, 1996; Radhakrishnan and Henry, 1997; Seguin *et al.*, 1995; Sluka *et al.*, 1997a; King and Thompson, 1995; Urban *et al.*, 1994a,b). There is substantial evidence that activation of NK<sub>1</sub> receptors reinforces excitatory actions mediated by NMDA receptors in the DH. Indeed, the *cojoint* activation of NK<sub>1</sub> and NMDA receptors may be essential for a *maximal* degree of neuronal excitation. Correspondingly, persistent painful states reflecting sensitization of DH neurones can be synergistically (or additively) blocked by *co-administration* of antagonists at NMDA and NK<sub>1</sub> receptors (Chapman *et al.*, 1996; Chizh *et al.*, 1995; Clayton *et al.*, 1997; Dougherty *et al.*, 1995; Heppenstall and Fleetwood-Walker, 1997a,b; Mjelle-Joly *et al.*, 1991; Nagy *et al.*, 1993; Ren *et al.*, 1996; Rusin *et al.*, 1992; Seguin and Millan, 1994; Xu *et al.*, 1992).

Interestingly, under conditions of PAF injury, the role of SP in nociceptive transmission and DH sensitization may, at least partially, be assumed by VIP, the levels of which are up-regulated in parallel with a decrease in those of SP. However, unlike NK<sub>1/2</sub> receptors, VIP receptors are positively coupled to AC (Hökfelt *et al.*, 1994; Vertongen *et al.*, 1997) (Section 3.2.6). The relationship between actions mediated by VIP and NMDA receptors under conditions of PAF damage would be of interest to examine.

#### 10.3.2.3. mGlu receptors

In analogy to NK<sub>1/2</sub> receptors, group I mGlu<sub>1</sub> and mGlu<sub>5</sub> receptors are positively coupled to PLC. Thus, their activation ultimately results in an increase in [Ca<sup>2+</sup>]<sub>i</sub> and a stimulation of PKC—a feedback action of which may, however, result in the rapid desensitization of mGlu receptors by their phosphorylation (Conn and Pin, 1997; Gereau and Heinemann, 1998; Stefani *et al.*, 1996; Toms *et al.*, 1996; Valerio *et al.*, 1997; Young *et al.*, 1995). Correspondingly, the activation of group I mGlu<sub>1</sub> (and mGlu<sub>5</sub>) receptors likely initiates events in DH neurones similar to those outlined above for SP (Section 10.3.2.2). Further, evidence from cerebral structures that group I mGlu receptors are involved in processes eliciting LTP under certain—though *not all*—conditions, supports the concept that they potentiate NMDA receptor-mediated processes of sensitization in the DH (Bortolotto *et al.*, 1994, 1995; Huber *et al.*, 1998; Martin and Morris, 1997; Vickery *et al.*, 1997). Studies in other tissues have shown that PKC inhibitors interfere with the ability of mGlu receptors to potentiate activity at NMDA receptors (Ben-Ari *et al.*, 1992; Kelso *et al.*, 1992).

In correspondence with these observations, there is electrophysiological and behavioural evidence that the activation of DH-localized mGlu receptors by

noxious, inflammatory stimuli elicits a slow excitation of spinal neurones (via an increase and decrease in cation- and  $K^+$ -currents, respectively) and cooperatively facilitates the excitatory actions of NMDA receptors. Interestingly, further, mGlu receptors also potentiate the excitatory actions of AMPA receptors, with which they act collaboratively in recruiting NMDA receptors (Budai and Larson, 1998; Coderre, 1993; Dickenson, 1997; Fisher and Coderre, 1996; Hunter and Singh, 1994; Meller *et al.*, 1993; Neugebauer *et al.*, 1994; Young *et al.*, 1994, 1995, 1997).

mGlu<sub>1</sub> and mGlu<sub>5</sub> receptors may, then, by virtue of their positive coupling to PLC and, possibly, NO synthase, activate DH neurones. In line with their high density in the DH—especially lamina II—pharmacological evidence for a key role of mGlu<sub>1</sub> receptors in nociceptive transmission was recently presented (Coggeshall and Carlton, 1997; Conn and Pin, 1997; Young *et al.*, 1997). The potential significance of other mGlu subtypes in modulating nociception requires further elucidation (Budai and Larson, 1998; Fisher and Coderre, 1996; Stefani *et al.*, 1996; Toms *et al.*, 1996; Young *et al.*, 1997). Indeed, group II and III mGlu receptor subtypes are all *negatively* coupled to AC. This suggests that, should they be present on WDR neurones, their activation may *counter* increases in WDR excitability provoked by other mechanisms. Nevertheless, it remains possible that certain group II mGlu receptor subtypes increase cAMP levels and activate PKA *independently* of AC (Winder and Conn, 1995). Further, an influence of certain group II and/or group III mGlu receptors upon  $Ca^{2+}$ - and  $K^+$ -currents may increase neuronal excitability (Conn and Pin, 1997). In addition, there is evidence from other tissues that group II receptors can *facilitate* the induction of PLC by group I receptors, suggesting a putative synergistic role of group I and II mGlu receptors in neuronal sensitization (Mistry *et al.*, 1998). Such potential mechanisms require direct evaluation in the DH. In a recent study of the influence of peripheral inflammation upon mRNA levels encoding various mGlu receptor types in the DH, only the density of mGlu<sub>3</sub> receptors was affected (Boxal *et al.*, 1998).

An additional level of complication is provided by observations that mGlu receptors modulate EAA release from fine calibre PAFs in the DH. For example, there is evidence for an involvement of group II mGlu<sub>7</sub> (or L-AP<sub>4</sub>-sensitive receptors). Indeed, group II (and mGlu III) receptors, which are negatively coupled to AC, exert a predominantly inhibitory influence upon presynaptic release, via actions involving a reduction in  $Ca^{2+}$ -currents and, possibly, a potentiation of  $K^+$ -currents (Conn and Pin, 1997; Crawford *et al.*, 1997; Fisher and Coderre, 1996; Pin and Duvoisin, 1995; Li *et al.*, 1997a). The identity of excitatory mGlu receptors on PAF terminals remains unclear (Coggeshall and Carlton, 1997; Sánchez-Prieto *et al.*, 1996).

#### 10.3.2.4. CGRP receptors

The role of CGRP in the DH is less well-defined than those of EAAs and SP, but it probably facili-

tates their actions. Thus, CGRP elicits slow membrane depolarizations in parallel with an increase in  $[Ca^{2+}]_i$  and an enhancement of  $Ca^{2+}$ -influx through (possibly L-type) VDCCs. These actions potentiate the effects of NK<sub>1</sub> and NMDA receptor activation and further strengthen processes of sensitization (Miletic and Tan, 1988; Oku *et al.*, 1988; Woolf and Wiesenfeld-Hallin, 1986). The mechanism(s) underlying these actions of CGRP of DH neurones are unclear, but presumably involve the positive coupling of CGRP<sub>1</sub> and CGRP<sub>2</sub> receptors to AC leading, via cAMP, to the activation of PKA. In addition, an increase in NO synthesis, leading to the formation of PKG, may be involved (Sluka and Willis, 1997; Wimalawansa, 1996).

In addition to these poorly-characterized postsynaptic actions at CGRP at DH neurones, CGRP facilitates nociception by directly retarding the metabolism of SP, thereby encouraging 'volume transmission' (Section 4.7). Further, CGRP may enhance the release of GLU and SP from PAF terminals (Kangrga and Randic, 1990; Schaible *et al.*, 1992; Wimalawansa, 1996). An involvement of CGRP in inflammatory nociception is supported by the increase in DRG and DH levels of CGRP which is elicited by chronic inflammation and by the reduction in the accompanying nociception effected both by the antagonist, GGRP<sub>8-37</sub>, and by sequestration of spinal pools of CGRP with specific antibodies (Hökfelt *et al.*, 1994; Kuraischi *et al.*, 1989; Löfgren *et al.*, 1997; Malcangio and Bowery, 1996a; Satoh *et al.*, 1992; Wimalawansa, 1996: though see Yu *et al.*, 1996) (Section 7.6).

### 10.4. Cellular Processes Underlying Sensitization of DH Neurones: Focus on $Ca^{2+}$ and PKs

As described in this section, the rapid and long-term sensitization of DH neurones by EAAs, tachykinins and other excitatory mediators reflects their influence upon multiple intracellular transduction mechanisms. In this regard, alterations in the levels of  $[Ca^{2+}]_i$  and the activity of various PKs play particularly crucial roles.

#### 10.4.1. Increases in $Ca^{2+}$ -Influx and in $[Ca^{2+}]_i$ Levels in DH Neurones

The above observations point to a critical role of  $Ca^{2+}$ -influx and increases in  $[Ca^{2+}]_i$  levels in the sensitization of DH neurones. Consistent with this contention,  $Ca^{2+}$ -channel antagonists and  $Ca^{2+}$ -ionophores, respectively, inhibit and potentiate inflammatory nociception. In distinction they do not modify the effects of transient, intense, noxious stimuli (Coderre and Melzack, 1992a,b; Coderre *et al.*, 1993; Diaz and Dickenson, 1997; Malmberg and Yaksh, 1994, 1995; Miljanich and Ramachandran, 1995; Miranda *et al.*, 1992; Neugebauer *et al.*, 1996). The activation of L-type  $Ca^{2+}$ -channels on intrinsic DH neurons may be of particular significance in the mediation of slow, summing  $Ca^{2+}$ -currents contributing to gradual and sustained increases in excitability (Baranauskas and Nistri, 1998; Morisset and Nagy, 1996). Further, L-type  $Ca^{2+}$ -channels are an important source of those intracellular pools of

$[Ca^{2+}]_i$  which modulate gene transcription via various nuclear regulatory elements (Section 10.4.2.5). On the other hand, the effects of antagonists at N- (and P-) type  $Ca^{2+}$ -channels—which are concentrated in superficial lamina I/II—also reflect actions at the terminals of PAFs (Diaz and Dickenson, 1997; Malmberg and Yaksh, 1994; Miljanich and Ramachandran, 1995; Nebe *et al.*, 1997) (Section 8.2.2). The respective roles of individual  $Ca^{2+}$ -channel subtypes requires, thus, further characterization.

To summarize the findings discussed above, increases in  $[Ca^{2+}]_i$  levels may be derived from several sources (Berridge, 1993; Bito *et al.*, 1997; Carafoli *et al.*, 1997; Ogden, 1996; Pellegrini-Giampietro *et al.*, 1997; Rodriguez-Alvarez *et al.*, 1997; Simpson *et al.*, 1995; Tsumoto and Yasuda, 1996):

1. ligand-gated ion channels, in particular, the NMDA-receptor-gated ion channel (Kawamata and Omote, 1996; Ozawa, 1996);
2. VDCCs, the operation of which is enhanced by the engagement of depolarizing AMPA and NMDA receptors, by increases in  $[Ca^{2+}]_i$  levels and by the actions of specific phosphorylating PKs (Ben-Ari *et al.*, 1992; Olivera *et al.*, 1994);
3. mobilization of  $Ca^{2+}$  from intracellular stores following activation of PLC by  $NK_1$ ,  $MGLu_1$  and  $MGLu_5$  receptors; and
4. in a 'feed-forward' fashion, an influx of  $Ca^{2+}$  may further enhance  $[Ca^{2+}]_i$  levels via the activation of  $Ca^{2+}$ -mobilizing ryanodine receptors on the endoplasmic reticulum (Dettbarn and Palade, 1997; Simpson *et al.*, 1995; Usachev and Thayer, 1997; Wang *et al.*, 1996b).

Recent studies have shown that specific pools of intracellular  $[Ca^{2+}]_i$ , for example, those which enter cells via VDCCs vs NMDA receptors, exert a contrasting influence upon modulation of neuronal activity. For example, in the generation of the cellular mediators, NO and PG (Sections 10.4.3.2 and 10.4.3.3), and in the modulation of gene expression (Carafoli *et al.*, 1997; Hughes and Dragunow, 1995; Lerea, 1997) (Section 10.4.2.5).

Unrestrained increases in  $[Ca^{2+}]_i$  are potentially dangerous and may lead to excitotoxic degeneration (Choi and Rowbotham, 1997; Lerea, 1997) (Section 10.6.2). Studies in a variety of tissues suggest that homeostatic mechanisms may be concurrently engaged by increases in  $Ca^{2+}$ -influx and  $[Ca^{2+}]_i$  levels which *counterregulate* the above processes. These include the activation of an APTase-dependent pump for the extrusion of  $[Ca^{2+}]_i$ , and the stimulation of several phosphatases leading to a reduction in neuronal excitability and  $Ca^{2+}$ -influx as outlined in Section 10.4.2.4 (Kyrozis *et al.*, 1996; Montieh and Roufogalis, 1995; Robello *et al.*, 1997; Young *et al.*, 1998).

In general, increases in  $[Ca^{2+}]_i$  levels result in an enhancement of transmitter releases (Stanley, 1997). However, an increase in  $[Ca^{2+}]_i$  levels in DH neurones may play a more specific role in their sensitization. Several of the mechanisms summarized below result in the induction of specific PKs, the significance of which for neuronal sensitization is discussed in Section 10.4.3.

#### 10.4.2. Functional Effects of Increases in $[Ca^{2+}]_i$ : Focus on Phenotype Changes in DH Neurones

##### 10.4.2.1. Enhancement of the activity of PKA, PKC and other PKs

PLC-mediated increases in levels of DAG and  $[Ca^{2+}]_i$  synergistically enhance the activity of PKC and increase its translocation to the cell membrane. Moreover, an increase in  $[Ca^{2+}]_i$  levels may directly enhance the ability of PKC to phosphorylate NMDA receptors (Chen and Huang, 1992; Coderre *et al.*, 1993; Rostas *et al.*, 1996; Zheng *et al.*, 1997). Elevations in  $[Ca^{2+}]_i$  levels generally also increase the activity of NO synthase leading, via the production of NO, to the activation of PKG (Clementi and Meldolesi, 1997). Further, they favour the generation of cAMP by AC and the subsequent activation of PKA which, together with a calmodulin-dependent PK II, has been shown to phosphorylate AMPA receptors in certain populations of neurones (Barria *et al.*, 1997; Ben-Ari *et al.*, 1992; Lisman, 1994, 1997; Section 10.3.7). As concerns longer-term events, these and other  $Ca^{2+}$ -dependent PKs play crucial roles in modulating the activity of nuclear transcription factors, IEG expression and gene transcription (Bito *et al.*, 1997; Carafoli *et al.*, 1997; Deisseroth *et al.*, 1998; Hughes and Dragunow, 1995; Lerea, 1997; Lisman *et al.*, 1997; Stevens *et al.*, 1994).

##### 10.4.2.2. Induction of NO synthesis

There is a complex pattern of interplay between intracellular pools of  $[Ca^{2+}]_i$  and NO (Clementi and Meldolesi, 1997; Horie *et al.*, 1997a; Garthwaite and Boulton, 1995) and, via an action involving calmodulin,  $[Ca^{2+}]_i$  increases the activity of neuronal NO synthase. Indeed, both peripheral tissue damage and PAF injury are associated with increases in DH levels of NO (Dickenson, 1997; Herdegen *et al.*, 1993; Lin *et al.*, 1997). The elevation in NO synthesis which follows NMDA receptor activation and an increase in  $[Ca^{2+}]_i$  levels is of particular significance inasmuch as NO plays a broad role in NMDA receptor-associated processes of synaptic plasticity in other tissues (Zhang and Snyder, 1995). NO participates in the modulation of nociceptive transmission via several mechanisms outlined in Section 3.2.8.1 and, of special note, it increases intracellular levels of cGMP which, via the activation of PKG, plays an important role in neuronal sensitization (Section 10.4.3.3). Alterations in intracellular  $[Ca^{2+}]_i$  levels may be spatially restricted. This compartmentalization reflects the differential origins of  $[Ca^{2+}]_i$ , for example via VDCCs or the activation of NMDA receptors (Allbritton *et al.*, 1992; Carafoli *et al.*, 1997; Deisseroth *et al.*, 1998; Lerea, 1997). A recent study in striatal neurones indicated that the pool of  $[Ca^{2+}]_i$  which activates NO synthase may be primarily derived from VDCCs (Rodriguez-Alvarez *et al.*, 1997). This finding was unanticipated inasmuch as the activation of NO synthase triggered by activation NMDA receptors might reasonably be assumed to reflect an accumulation of  $[Ca^{2+}]_i$  entering neurones via NMDA receptors themselves. It would be of interest to perform such studies in DH neurones. Apart from the modulation of nociception

following injury to PAFs or to the spinal cord itself, NO may, possibly independently of cGMP, also modulate processes of cell survival and degeneration (Minghetti and Levi, 1998; Nishio and Watanabe, 1998) (Section 10.6.2).

#### 10.4.2.3. Generation of PGs

$[Ca^{2+}]_i$  increases arachidonic acid production by facilitating the activity of  $PLA_2$ . There is evidence from the above-mentioned studies in striatal neurones that the major pool of  $[Ca^{2+}]_i$  which activates  $PLA_2$ , in distinction to that inducing NO synthase, enters neurones via NMDA receptors themselves (Dumuis *et al.*, 1988; Lerea *et al.*, 1997; Rodriguez-Alvarez *et al.*, 1997). The generation of arachidonic acid via  $PLA_2$  and, subsequently, of PGs via COX, provides several potential mechanisms for an increase in cellular excitability. Notably, a facilitation in the activity of PKC (Section 10.4.3.1), an action expressed both in cells of origin and, following extracellular release and diffusion, in PAF terminals from which GLU and SP release may be enhanced (Section 3.2.8.4). In intrinsic DH neurones, gene expression may also be modified (Casabona, 1997; Collins and Davies, 1998; Lerea, 1997; Lerea *et al.*, 1997; Nicholls and Attwell, 1990; Sánchez-Prieto *et al.*, 1996; Yaksh and Malmberg, 1994).

#### 10.4.2.4. Counter-regulatory processes: induction of phosphatases

In an opposite manner, however,  $[Ca^{2+}]_i$  may activate several  $Ca^{2+}$ - (and calmodulin)-dependent protein phosphatases, such as calcineurin, which has been detected in intrinsic neurones in superficial DH laminae (Strack *et al.*, 1996; Wang and Kelly, 1997). The dephosphorylation of DH-localized NMDA receptors reduces their functional activity (Kyzozis *et al.*, 1996; Lieberman and Mody, 1994; Wang and Salter, 1994). In addition, the dephosphorylation of GABA<sub>A</sub> receptors results in an increase in their activity (Robello *et al.*, 1997). As mentioned above, the relationship between NO synthesis and  $[Ca^{2+}]_i$  is complex and, under certain conditions, an increase in  $[Ca^{2+}]_i$  may, likewise via a mechanism involving activation of phosphatases, suppress NO synthesis, (Horie *et al.*, 1997a). Thus, in addition to the possible activation of a  $Ca^{2+}$ -extruding-pump (Montieh and Roufogalis, 1995; Young *et al.*, 1998), increases in  $[Ca^{2+}]_i$  may trigger several, phosphatase-mediated, mechanisms resulting in an inhibition of neuronal excitability and sensitization (Winder *et al.*, 1998). These actions clearly counterbalance the phosphorylating, PK-mediated excitatory effects of increases in  $[Ca^{2+}]_i$  levels (Section 10.4.2). The precise balance between such processes of phosphorylation/excitation and dephosphorylation/inhibition as a function of the levels of  $[Ca^{2+}]_i$  and other factors remains to be established. A perturbation of this homeostatic regulation of  $[Ca^{2+}]_i$  levels may well have grave consequences. Thus, an uninhibited increase in  $[Ca^{2+}]_i$  levels in PNs or EXINs may result in an excessive output of nociceptive information to higher centres. Further, the unrestrained accumulation of  $[Ca^{2+}]_i$  in ININs, which are particularly vulnerable to excitotoxic damage, may lead

to their degeneration following PAF or spinal cord injury (Section 10.6).  $Ca^{2+}$ -dependent phosphatases likely play a more generalized and complex role in the modulation of neuronal excitability, receptor sensitivity, gene expression (in a fashion opposite to  $Ca^{2+}$ -dependent PKs) and other events underlying sensitization and control of neuronal function: such actions remains to be further explored in the DH (Bito *et al.*, 1997; Guerini, 1997; Sandkühler *et al.*, 1997; Winder *et al.*, 1998).

#### 10.4.2.5. Modulation of IEG expression and gene transcription in DH neurones

Via multifarious mechanisms, including interactions with NO, PGs, cAMP and several PKs,  $[Ca^{2+}]_i$  plays a key role in modifying the expression of nuclear transcription factors controlling IEG and gene expression (Bito *et al.*, 1997; Carafoli *et al.*, 1997; Chapman and Besson, 1997; Chapman *et al.*, 1995, 1996; Deisseroth *et al.*, 1998; Eder, 1997; Hardingham *et al.*, 1997; Hughes and Dragunow, 1995; Lerea, 1997; Lerea *et al.*, 1997; Lin *et al.*, 1994c; O'Neill and Kaltschmidt, 1997; Roche *et al.*, 1996). The precise origin of various pools of  $[Ca^{2+}]_i$ , whether derived from VDCCs or NMDA receptors, may be important in determining their influence upon gene expression. This distinction reflects not only their differential modulation of intracellular levels of NO and PG (Sections 10.4.2.2 and 10.4.2.3) but also their differential interaction with PKs such as calmodulin-dependent PK II. This results in a contrasting influence upon the activity of the nuclear transcription factor  $Ca^{2+}$ /cAMP-response element binding protein (CREB) and, thereby, the expression of IEGs such as c-fos and, ultimately, synaptic plasticity. Intriguingly, it appears that  $[Ca^{2+}]_i$  which enters neurones via L-type  $Ca^{2+}$  channels plays a particularly significant and sustained role in triggering the phosphorylation of CREB and, thereby, modulating gene expression (Bito *et al.*, 1997; Carafoli *et al.*, 1997; Hughes and Dragunow, 1995; Lerea, 1997). A localized increase in  $[Ca^{2+}]_i$  at the level of the cell membrane triggers the translocation of calmodulin into the nucleus: calmodulin then phosphorylates a specific PK IV which subsequently phosphorylates CREB (Deisseroth *et al.*, 1998). In addition, PKA and several other PKs converge onto CREB to modify IEG expression and gene transcription (Bito *et al.*, 1997).

The CREB-activated IEG, c-fos, has been extensively exploited as a marker of neuronal activation in the DH—although DH expression of c-fos does not invariably correlate with levels of nociception (Chapman and Besson, 1997; Millan, 1993; Ossipov *et al.*, 1997; Presley *et al.*, 1990; Todd *et al.*, 1994a). The widespread appearance of c-fos in the DH in response to peripheral nociceptive input is consistent with the notion that cellular mechanisms underlying sensitization are not confined to WDR neurons in deeper laminae. In this respect, much attention has been directed toward the apparent induction by c-fos of gene expression for the endogenous opioids, enkephalin and DYN, under conditions of acute and long-term noxious stimulation and PAF damage (Chapman and Besson, 1997; Clayton *et al.*,

1997; Clément *et al.*, 1996; Coderre, 1992; Dubner and Ruda, 1992; Hunt *et al.*, 1987; Hunter *et al.*, 1995; Kawakami *et al.*, 1994; Millan, 1990, 1993; Naranjo *et al.*, 1991; Ossipov *et al.*, 1997). A c-fos complex and a further IEG upregulated by noxious stimulation, c-jun, may be involved in the alteration of the gene transcription of opioids peptides and other proteins (Wisden *et al.*, 1990). Although a subpopulation of PNs in superficial DH laminae contains DYN (Section 6.1.1), both DYN and other opioid peptides inhibitory to nociceptive transmission in the DH are preferentially localized (with c-fos) in ININs rather than WDR PN in deep laminae (Hunter *et al.*, 1995; Millan, 1993; Todd *et al.*, 1994a) (Sections 4.6 and 10.6). Thus, the question remains as to which putative transmitters are upregulated in parallel with, and possibly by, c-fos in sensitized WDR PNs. Presumably, they play a role in the ascending transmission of nociceptive information. Their characterization would be of particular interest inasmuch as a recent study reported that neutralization of c-fos expression by spinal antisense treatment decreases inflammatory nociception (Hou *et al.*, 1997). However, under other conditions, a similar approach has been shown, to *enhance* nociception, possibly via an interference with the induction of DYN (Ossipov *et al.*, 1997—though see Hunter *et al.*, 1995). The reasons underlying these contrasting results are unclear.

As concerns changes in the phenotype of DH-localized neurones, one could imagine that an increased expression of pronociceptive transmitters in EXINs might aggravate painful states and several lines of evidence might be advanced to support this possibility:

1. An increase in the synthesis and release of CCK from EXINs may be involved in the reduced antinociceptive efficacy of opioids following injury to the spinal cord or damage to PAFs (Ossipov *et al.*, 1997; Xu and Wiesenfeld-Hallin, 1997).
2. An increase in DH levels of the 'anti-opioid' neuropeptide FF under conditions of peripheral inflammation was reported by Kontinen *et al.* (1997). However, under these conditions, Pertovaara *et al.* (1998) have suggested that neuropeptide, this may actually fulfil an *antinociceptive* role.
3. Inflammatory tissue damage and PAF injury is, as mentioned above, accompanied by an increase in DH levels of DYN.

Certain authors have suggested that high concentrations of DYN *enhance* nociception by antagonist actions at NMDA receptors. However, the principal, physiological role of DYN is the inhibition of nociceptive transmission via actions at  $\kappa$ -opioid receptors in the DH (Millan, 1990, 1993; Ossipov *et al.*, 1997) (Section 10.6). Further, DH levels of ININ-localized enkephalins are also increased under conditions of PAF inflammation (Dubner and Ruda, 1992; Millan, 1993; Ossipov *et al.*, 1997) and there is additional evidence that phenotype changes in DH-localized ININs may counter nociception. Thus, inflammation also elicits an increase in the synthesis of GABA in the DH, while DH levels of GAL and NPY, which are colocalized with GABA

and which may also inhibit nociception, are likewise elevated (Mantyh *et al.*, 1994; Munglani *et al.*, 1996; Xu and Wiesenfeld-Hallin, 1997) (Section 10.6). Further, Stanfa *et al.* (1994) suggested that a *reduction* in CCK generation by EXINs may account for the potentiation of opioidergic antinociception in inflammation. The relationship of such changes to alterations in c-fos, other regulators of gene expression and  $[Ca^{2+}]_i$  levels remains to be clarified.

To summarize, the induction of c-fos in PNs and EXINs may, in theory, trigger events leading to the upregulation of pronociceptive transmitters in the DH. However, there is, to date, *little* evidence that neuronal phenotype changes in the DH contribute to the induction of *inflammatory*, painful states, in which GABAergic ININ activity is enhanced (Section 10.6.2.2) and the activity of CCK (probably) decreased. On the other hand, an increase and decrease in DH levels of CCK and GABA, respectively, may be involved in the induction of *neuropathic*, painful states due to PAF or spinal injury. Further, the increase in the DH density and  $Ca^{2+}$ -permeability of AMPA receptors should also be mentioned in this regard (Section 10.3.2.1), as well as the elevation in the DH density of NK<sub>1</sub> and CGRP receptors (Abbadie *et al.*, 1996; Coggeshall and Carlton, 1997).

A further exploration of changes in the phenotype of various classes of DH neurones in relationship to alterations in levels of  $[Ca^{2+}]_i$ , IEGs and other intracellular signals controlling gene expression would be of considerable interest. Along these lines, it has recently been speculated that a reduction in activity at tonically-active, antinociceptive cannabinoid receptors in the DH may be involved in the induction of certain painful states (Richardson *et al.*, 1998).

#### 10.4.3. The Roles of Specific PKs

##### 10.4.3.1. Actions of PKC

As indicated above, one particularly important action of  $[Ca^{2+}]_i$  in nocisponsive DH neurones is (together with DAG) the induction of PKC (Newton, 1997; Ramakers *et al.*, 1997). The following observations support the concept that PKC plays a pivotal role in processes underlying neuronal sensitization and an enhancement of nociception.

1. Stimulation and inhibition of spinal pools of PKC respectively enhances and reduces the inflammatory hyperalgesia provoked by intraplantar injection of formalin (Coderre, 1992; Coderre and Yashpal, 1994; Munro *et al.*, 1994).
2. PKC inhibitors attenuate the capsaicin-induced sensitization of WDR STT cells to mechanical stimuli (Lin *et al.*, 1996a,b; Sluka *et al.*, 1997a,b). In addition, the PKC inhibitor, staurosporin, blocks the facilitatory influence of NK<sub>1</sub> receptors upon NMDA receptor-mediated currents in DH neurones whereas phorbol esters, which enhance PKC activity, mimic the facilitatory influence of PKC on NMDA receptor-mediated ion currents (Gerber *et al.*, 1989; Rusin *et al.*, 1992; Urban *et al.*, 1994a,b).
3. Activation of PKC excites and sensitizes WDR PNs of the STT (Lin *et al.*, 1996a; Palecek *et al.*, 1994; Sluka and Willis, 1997; Sluka *et al.*, 1997b)



and inhibits opioidergic mechanisms of antinociception (Zhang *et al.*, 1990).

4. Levels of membrane-bound (translocated) PKC are increased in superficial and deep DH laminae during inflammatory hyperalgesia (Mao *et al.*, 1992d; Yashpal *et al.*, 1995).
5. Gangliosides may reduce pain due to PAF injury by interfering with the translocation of PKC (Hayes *et al.*, 1992; Mao *et al.*, 1992a; Vaccarino *et al.*, 1987).

Together with  $\text{Ca}^{2+}$ , a key role has been established for PKC in modulating the activity of c-fos and other mechanisms controlling gene expression: such actions are of importance to long-term increases in DH neuronal excitability (Hughes and Dragunow, 1995). Further, over a more rapid time-scale, PKC is strongly implicated in NMDA-receptor dependent mechanisms of synaptic plasticity underlying memory formation (LTP). Indeed, the most important sensitizing action of PKC in WDR neurones is undoubtedly the phosphorylation of NMDA receptors (Rostas *et al.*, 1996; Lisman, 1994; Zheng *et al.*, 1997). This leads to a relief of  $\text{Mg}^{2+}$ -block, thereby permitting their operation at lower potentials and enhancing passage of current. Although the underlying molecular mechanisms remain unclear, PKC likely fulfils a more general contribution to the control of ionic currents and intracellular  $\text{Ca}^{2+}$ -homeostasis. For example, PKC can also increase cellular excitability via a prolongation of the  $\text{Ca}^{2+}$ -dependent inactivation of  $\text{K}^{+}$ -currents or via a reduction in the inactivation of  $\text{Na}^{+}$ -currents, events which may occur in DH neurones (Alkon *et al.*, 1986; Colbert and Johnston, 1998; De Riemer *et al.*, 1985; Madison *et al.*, 1986; Pedrosa-Ribeiro and Putney, 1996). A further mechanism underlying the sensitization of WDR PNs by PKC may—in analogy to PKG and PKA (Section 10.4.3)—be a decrease in the efficacy of ININ transmission effected via the phosphorylation of inhibitory GABAergic receptors (Leidenheimer *et al.*, 1992; Lin *et al.*, 1996a,b,c).

On the other hand, certain actions of PKC may decrease neuronal activity. Thus, a PKC-mediated phosphorylation of group I mGlu and  $\text{NK}_1$  receptors, thereby enhancing their desensitization, might counter excitatory actions at DH neurons (Gereau and Heinemann, 1998; Quartara and Maggi, 1997). Further, the induction of PKC by 5-HT<sub>2</sub> agonists leads to an increase in currents at inhibitory glycinergic receptors targeting WDR PNs. Via this mechanism, PKC may also reduce nociception (Xu *et al.*, 1996a). Finally, as mentioned above, increases in  $[\text{Ca}^{2+}]_i$  levels may enhance the activity of a compensatory ATPase-coupled pump for  $\text{Ca}^{2+}$ -extrusion and PKC appears to be involved in this effect (Montieh and Roufogalis, 1995; Young *et al.*, 1998).

Many isoforms and cellular pools of PKC have been identified (Casabona, 1997; Newton, 1997; Ramakers *et al.*, 1997) and, as implied by the preceding comments, they may play differential roles in the modulation of nociceptive transmission. Interestingly, a  $\text{Ca}^{2+}$ -independent isoform of PKC appears to be involved in the above-mentioned facilitation of glycine currents (Xu *et al.*, 1996a). This

is in contrast to the  $\text{Ca}^{2+}$ -dependent isoform of PKC which phosphorylates NMDA receptors—although its precise identity remains to be defined (Nagashima *et al.*, 1991). Recently, a PKC $\gamma$  isoform was detected in lamina II-localized ININs receiving input from C fibres expressing  $\text{P}_{2X3}$  receptors (Section 7.4.4). Transgenic mice lacking this PKC $\gamma$  isoform failed to develop alterations in nociception following PAF injury suggesting that it plays an important role in neuropathic pain (Malmberg *et al.*, 1997b). A characterization of the roles of various DH-localized pools and isoforms of PKC remains a challenging task for the future.

#### 10.4.3.2. Actions of cAMP and PKA

There is evidence that PKA plays a role in the sensitization of DH neurones. Increases in  $[\text{Ca}^{2+}]_i$  favour the activity of AC, and the positive coupling of CGRP, other neuropeptides and  $\text{A}_{2A}$  receptors to AC suggests that, via the induction of cAMP, they can induce PKA (Section 3.2). In addition, descending pathways may be involved in the activation of PKA: for example, dopamine D<sub>1</sub> receptors and several subtypes of serotonergic receptor (5-HT<sub>4</sub>, 5-HT<sub>6</sub> and 5-HT<sub>7</sub>) all generate cAMP via the stimulation of AC (Boess and Martin, 1994; Millan, 1997).

Consistent with a role of PKA in enhancing nociception and sensitization, selective inhibition of PKA attenuates the induction of mechanical allodynia by cutaneous capsaicin (Sluka and Willis, 1997). Further, the spinal administration of cAMP, stabilized cAMP analogues or the catalytic subunit of PKA potentiates the excitatory influence of EAAs upon DH neurones, and diminishes opioidergic mechanisms of antinociception (Cerne *et al.*, 1992; Malmberg *et al.*, 1997a).

Although the above observations would be consistent with an enhancement of NMDA receptor-mediated currents, it is unclear how this could be caused by cAMP/PKA. Indeed, the mechanistic bases of their facilitatory influence upon DH neurones is currently under exploration. However, the phosphorylation by PKA (in analogy to PKC) of inhibitory GABAergic receptors would lead to an increase in neuronal sensitivity (Robello *et al.*, 1993, 1997; Sluka and Willis, 1997; Zarri *et al.*, 1994). There is also evidence from studies in other tissues that PKA (together with a calmodulin-dependent K II) may enhance excitability by the phosphorylation of AMPA receptors, and the possible phosphorylation of certain VDCCs should also be considered (Ben-Ari *et al.*, 1992; Blackstone *et al.*, 1994; Barria *et al.*, 1997). PKA may also enhance the activity of COX 2 in certain cell types (Minghetti and Levi, 1998). Finally, via phosphorylation of the nuclear regulatory element, 'CREB' (Section 10.4.2.5), PKA, together with calmodulin, plays an important role in LTP and other longer-term plastic events potentiating neuronal function in cerebral structures and, likely, the DH (Ardenghi *et al.*, 1997; Carafoli *et al.*, 1997; Deisseroth *et al.*, 1998; Hughes and Dragunow, 1995; Yin and Tully, 1996).

#### 10.4.3.3. Actions of cGMP and PKG

A NO-triggered increase in cGMP levels in WDR neurones contributes to mechanisms underlying sensitization by the induction of PKG, which subsequently phosphorylates inhibitory GABAergic and glycinergic receptors (Leidenheimer, 1996; Lin *et al.*, 1996a,b,c, 1997; Meller *et al.*, 1992a,b,c; Robello *et al.*, 1996, 1997; Sluka and Willis, 1997). As indicated in Sections 10.4.3.1 and 10.4.3.2, the deactivation of these inhibitory receptors by their phosphorylation is a property shared with PKC and PKA. Indeed, it has been shown that PKG phosphorylates GABA<sub>A</sub> receptors in other tissues (cortex and cerebellum) at a consensus site shared with PKA (Leidenheimer, 1996; Robello *et al.*, 1996, 1997; Sluka and Willis, 1997; Zarri *et al.*, 1994). The inhibition of GABAergic transmission by PKG and other PKs exacerbates processes of sensitization triggered by nociceptive PAF input to WDR DH neurones. Further, a component of descending inhibition exerted via the recruitment of GABAergic ININs in the DH is compromised by PKG-mediated phosphorylation of GABAergic receptors (Lin *et al.*, 1997; Peng *et al.*, 1996). This leads to a shift in the overall pattern of descending modulation towards facilitation (Section 10.8). Two additional actions of PKG and cGMP which result in elevations of  $[Ca^{2+}]_i$  may also contribute to the excitation of DH neurones. Thus, PKG can modify the operation of VDCCs (Van Coppenolle *et al.*, 1997), while observations in DRG neurones suggest that cGMP can mobilize  $[Ca^{2+}]_i$  from ryanodine-sensitive intracellular stores, thereby further accentuating processes underlying sensitization (Crawford *et al.*, 1997).

In line with a putative role in enhancing nociception, levels of cGMP are increased in the DH under conditions of peripheral inflammation (Garry *et al.*, 1994b; Igwe and Ning, 1994). Further, the spinal administration of cGMP analogues elicits hyperalgesia (Garry *et al.*, 1994a) and potentiates the responsiveness of deep laminae WDR neurones to mechanical stimulation (Lin *et al.*, 1997). Contrariwise, blockade of the activity of cGMP prevents the sensitization of DH neurones by capsaicin (Lin *et al.*, 1997).

#### 10.4.3.4. Key roles of $[Ca^{2+}]_i$ and PKs in the sensitization of DH neurones: a summary

To summarize (see Fig. 5), increases in the levels of  $[Ca^{2+}]_i$ , and in the activity of PKC PKA, PKG—and, probably, calmodulin-dependent PKs—likely represent key, intracellular substrates underlying the rapid and sustained sensitization of WDR neurones. Nevertheless, their roles, together with those of other intracellular signalling systems, in the control of neuronal excitability in the DH and the induction of painful states require considerable further clarification. In this respect, it is unlikely that mechanisms of sensitization are restricted to WDR PNs in deeper laminae. The significance of alterations in the levels of  $[Ca^{2+}]_i$  and the induction of various PKs in other classes of neurones, in particular ININs and superficial NS neurones, would be of importance to establish.

### 10.5. A $\beta$ Fibre-Mediated Sensitization of DH Neurones in Inflammatory States

Inasmuch as A $\beta$  and C fibre input excites a common population of WDR neurones in the deep DH, the possibility that activation of A $\beta$  receptors can likewise elicit processes of sensitization must be considered. However, A $\beta$  fibre stimulation is *not* normally perceived as noxious (Sections 3.1.1 and 4.6.2) (Fig. 2) and, under *normal* circumstances, the following arguments indicate that activation of A $\beta$  fibres is unlikely to sensitize DH neurones.

1. The stimulation of A $\beta$  fibres activates AMPA channels of comparatively low  $Ca^{2+}$ —yet high  $Na^+$ —permeability and possessing very rapid, transient kinetics (Dickenson, 1997; Fletcher and Lodge, 1996; Furuyama *et al.*, 1993; Pellegrini-Giampietro *et al.*, 1997; Tomiyama *et al.*, 1996) (Section 3.2.3). As such, even though the depolarization elicited by engagement of AMPA receptors activates VDCCs, there is no sustained or marked increase in  $[Ca^{2+}]_i$  levels in DH neurones and any minor increases in  $[Ca^{2+}]_i$  may be confined to a discrete region of the cytosol (Berninger and Poo, 1996; Kharazia and Weinberg, 1997; Lerea *et al.*, 1997; Morris, 1997; Ottersen and Landsend, 1997; Sakai *et al.*, 1997; Simpson *et al.*, 1995). Further, in the absence of a pronounced increase in  $[Ca^{2+}]_i$ , levels the activation (phosphorylation) of AMPA receptors by calmodulin-dependent PK II and PKA does not occur (Sections 3.2.3 and 10.3.2.1).
2. Upon the *selective* activation of A $\beta$  fibres, C fibre-coupled NMDA and NK<sub>1/2</sub> receptors are quiescent. Thus, there is no subsequent increase in  $Ca^{2+}$ -influx,  $[Ca^{2+}]_i$  levels or the activity of PKs. [In this respect, the differential localization of AMPA and NMDA receptors in specific populations of ININ in the superficial DH should also be pointed out (Coggeshall and Carlton, 1997).]
3. Since A $\beta$  fibres excite ININs, their cumulative mono- and *poly*-synaptic impact upon WDR neurones is less pronounced than that of C fibres which excite WDR neurons both directly and indirectly via EXINs (Fig. 2). Thus, A $\beta$  fibre stimulation generally elicits only rapid EPSPs and localized, minor increases in neuronal  $[Ca^{2+}]_i$ , which do not, under normal conditions, lead to neuronal sensitization.

Nevertheless, the  $Ca^{2+}$ -permeability and density of DH-localized AMPA receptors is enhanced by PAF injury, and NMDA receptor activation may, at least in certain neurones, activate AMPA receptors via a calmodulin-dependent PK II (Section 10.3.2.1). Indeed, Herrero *et al.* (1995) recently suggested that stimulation of A $\beta$  fibres *can* elicit wind-up under conditions of inflammation. In a further study, Ma and Woolf (1996b) also raised the possibility that A $\beta$  fibre stimulation may, likewise under conditions of inflammation, acquire the capacity to provoke central sensitization. This phenomenon, termed 'progressive tactile hypersensitivity' refers to a *slowly*-developing (hours), A $\beta$  fibre-mediated allodynia to non-noxious mechanical

stimulation. Notably, as compared to *rapid* (minutes) C fibre-mediated mechanisms of wind-up, this time-scale is similar to that seen for the appearance of inflammatory allodynia in man following tissue injury. Indeed, these findings raise the possibility of temporally-different patterns of hypersensitivity involving both C and A $\beta$  PAFs under conditions of inflammation.

The roles of ionic and soluble transduction mechanisms in A $\beta$  fibre-mediated sensitization of DH neurones remain to be further explored (Ma and Woolf, 1997). However, apart from AMPA receptors, a possible implication of SP and NK<sub>1</sub> receptors would be of particular interest in the light of

1. the recently-described phenotypic switch whereby inflammation leads to the synthesis of SP in A $\beta$  fibres (Neumann *et al.*, 1996) (Section 8.2.5);
2. the upregulation of NK<sub>1</sub> receptors in the DH seen following peripheral inflammation and PAF injury (Abbadie *et al.*, 1996; Goff *et al.*, 1998); and
3. the migration, following PAF injury, of A $\beta$  fibres from deeper laminae receiving principally innocuous, sensory input into more superficial laminae containing NS and WDR neurones and receiving nociceptive information from C fibres (Woolf *et al.*, 1992) (Section 11.3.2) (Fig. 2).

Indeed, NK<sub>1</sub> receptor antagonists can prevent the emergence of progressive, mechanical hypersensitivity under conditions of inflammation (Ma and Woolf, 1997). This observation is consistent with a role of SP released from A $\beta$  fibres in its mediation. However, a C fibre-mediated induction of sensitization in DH neurones may be a pre-condition for A $\beta$  fibre-mediated processes of sensitization to occur. Thus, it cannot be excluded that the reduction by NK<sub>1</sub> antagonists of tactile hypersensitivity reflects the blockade of C fibre-coupled NK<sub>1</sub> receptors involved in the induction and maintenance of neuronal sensitization in the DH (Section 9.1.3). Moreover, as discussed in Section 9.2.3. Cervero and Laird (1996b) suggested that A $\beta$  fibre-mediated allodynia may reflect an *indirect* ININ-mediated engagement of C fibre terminals in the DH. This mechanism would also be consistent with a blockade of tactile hypersensitivity by NK<sub>1</sub> receptor antagonists.

## 10.6. Reduction in the Functional Activity of ININs

### 10.6.1. Inhibition of ININ Activity Mimics and Enhances Sensitization in the DH

In Section 10.7, evidence was presented that an induction of PKA, PKC and/or PKG in deep laminae WDR PNs contributes to their sensitization by phosphorylating inhibitory GABAergic and/or glycinergic receptors. Such mechanisms are likely triggered both by the prolonged stimulation of nociceptors upon inflammatory tissue damage and, although direct evidence is lacking, by PAF injury. The attenuation of ININ tone at WDR neurones via such *intrinsic* intracellular mechanisms enhances their excitability, and contributes to processes

underlying sensitization, hyperalgesia and allodynia (Lin *et al.*, 1996a,c, 1997; Sluka and Willis, 1997).

The possibility that other mechanisms may more directly lead to a reduction in the activity of GABAergic and glycinergic ININs in the DH has attracted much attention, in particular as concerns the effects of PAF injury. This interest is underpinned by observations that pharmacological interruption of glycinergic and GABAergic transmission in the DH produces a long-lasting increase in the responsiveness of DH neurones to low intensity, A $\beta$  fibre stimulation which resemble hyperexcitability-based, allodynic states (Sivilotti and Woolf, 1994). A loss of GABAergic tone in the DH following PAF injury may also facilitate the ability of A $\beta$  fibre input to sensitize DH neurones (Section 10.5). Further, behavioural evidence that a loss of functional ININ activity alters nociceptive processing in the DH is provided by studies of the spinal administration of strychnine and bicuculline, which block glycinergic and GABA<sub>B</sub> receptors, respectively. The resultant touch-evoked allodynia and increased flexor withdrawal is comparable to that seen upon induction of central sensitization by nerve damage: further, this allodynia-like response to mechanical A $\beta$  fibre input is similarly prevented by NMDA and AMPA antagonists (Hao *et al.*, 1992; Sorkin and Puig, 1996; Wall and Bennett, 1994; Woolf and Doubell, 1994; Xu *et al.*, 1993a; Yaksh, 1989). Strychnine and bicuculline also potentiate the hyperalgesia/allodynia associated with nerve injury, actions likewise prevented by NMDA receptor antagonists (Milne *et al.*, 1996; Satoh and Omote, 1996; Seltzer *et al.*, 1991; Yamamoto and Yaksh, 1993). Conversely, the GABA<sub>A</sub> and GABA<sub>B</sub> agonists, baclofen and muscimol, respectively, antagonize the allodynia provoked by PAF injury (Hwang and Yaksh, 1997).

As described in Section 13.2, similar changes in nociception due to a loss of GABAergic ININ activity have been reported following focal, spinal cord ischaemia (Hao *et al.*, 1992). Further, the spinal administration of 5-HT<sub>1A</sub> receptor agonists elicits a behavioural state mimicking mechanical allodynia, apparently via (the hyperpolarization of) GABAergic (or other types) of ININ in the DH. The induction of such an allodynia-like state by 5-HT<sub>1A</sub> agonists is prevented both by GABAergic agonists, which restore ININ activity, as well as by antagonists at NMDA receptors (Millan *et al.*, 1996; Yang *et al.*, 1998). AMPA receptor antagonists are also effective, presumably via blockade of actions mediated by A $\beta$  fibres transmitting normally non-noxious, mechanical input (Millan *et al.*, 1996). Interestingly, further, spinal administration of nociceptin, the heptadecapeptide ligand of a recently-cloned 'opioid receptor homologue', elicits allodynia via inhibition of glycinergic ININs (Hara *et al.*, 1997; Meunier, 1997).

Pharmacological blockade of activity at inhibitory GABAergic and (glycinergic) receptors elicits rhythmic, burst-like firing in neurones in the VH and other tissues (Forti *et al.*, 1997). Burst activity increases the efficacy of synaptic transmission and enhances transmitter release, thereby improving synaptic signalling and information

transfer (Lejeune *et al.*, 1997; Lisman, 1997; Woolf and King, 1989). Further, burst-like activity mediated by NMDA receptors has been specifically implicated in LTP, a process of synaptic strengthening underlying hippocampal memory consolidation, and which is analogous to mechanisms involved in the sensitization of DH neurones. Notably, both activation of NMDA receptors and inhibition of GABAergic receptors appears necessary for optimal generation of LTP (Huerta and Lisman, 1995) (Section 10.2.1).

A reduction in ININ tone in the DH may, then, together with an increase in C fibre input, synergistically:

1. increase the spontaneous activity and excitability of WDR PNs;
2. perturb and extend their RFs; and
3. trigger synchronized and oscillating circuits reflecting a generalized increase in neuronal excitability, and resulting in a disruption of nociceptive processing in extensive regions of the DH (Biella *et al.*, 1997; Bracci *et al.*, 1996a,b; Brewer and Ray, 1995; Castro-Alamancos and Connors, 1997; Dubner, 1992; Eblen-Zajjur and Sandkühler, 1997; Forti *et al.*, 1997; Kaneko and Hammond, 1997; Khandwala *et al.*, 1997; Lin *et al.*, 1996a,b,c) (Section 9.1.4.2).

It is likely that similar phenomena contribute to the sensitization of nociceptive neurones at the thalamic and cortical level (Sections 12.3.2 and 13.3).

To summarize, an increase in the excitability of WDR PN neurones in the DH can be directly initiated or aggravated by a suppression in the activity of GABAergic and/or glycinergic ININs. In addition, ININs reduce release from the central terminals of nociceptive C fibres and mechanosensitive A $\beta$  fibres involved in mediating mechanical allodynia. The loss of this inhibitory influence upon PAF input into the DH further amplifies processes eliciting hyperexcitability in WDR PNs (Malcangio and Bowery, 1996b; Sorkin and Puig, 1996; Todd and Spike, 1993; Todd *et al.*, 1996).

#### 10.6.2. Mechanisms Underlying a Reduction of ININ Activity

##### 10.6.2.1. Evidence for a reduction in GABAergic ININ activity upon PAF injury

The above observations suggest that a (pharmacological) reduction in the activity of GABAergic or glycinergic ININs mimics and/or exacerbates central sensitization and the accompanying hyperalgesia/allodynia. The question arises, then, as to whether a *pathophysiological* loss of ININ tone in the DH may contribute to the *induction* of painful states.

As concerns PAF injury, there is evidence for a functional reduction in the GABAergic inhibition of DH-localized C fibre terminals (Bhisitkul *et al.*, 1990). Indeed, the slow depolarizing waves (DRPs) elicited in PAFs by ININs seem to be reduced in the first few weeks following nerve injury, suggestive that the functional influence of ININs upon central PAF terminals is reduced (Laird and Bennett, 1992; Wall and Devor, 1981)

(Section 9.1.4.2). These findings may be related to a decrease in the density of GABA<sub>B</sub> receptors documented in the DRG ipsilateral to PAF injury (Castro-Lopes *et al.*, 1995; Oyelese *et al.*, 1997; Towers *et al.*, 1997).

Much interest has been focused on the question of whether PAF injury precipitates a reduction in the number of GABAergic or other types of ININ in the DH (Castro-Lopes *et al.*, 1993; Dumoulin *et al.*, 1996; Gu *et al.*, 1997; Hammond, 1997; Kelly *et al.*, 1997; Oliveira *et al.*, 1997). Indeed, based upon the appearance of 'dark' neurones in the DH, it has been concluded that neurectomy can provoke the transynaptic degeneration of intrinsic ININs, primarily in laminae I and II (Ibuki *et al.*, 1997; Mao *et al.*, 1997; Nachemson and Bennett, 1993; Sugimoto *et al.*, 1989) (Fig. 2). This apparent loss is, further, potentiated by administration of strychnine or bicuculline, possibly due to disinhibition of reverberating, excitatory circuits (Bracci *et al.*, 1996a and b; Eblen-Zajjur and Sandkühler, 1997) (Sugimoto *et al.*, 1989) (Sections 10.6.1, 12.3.2 and 13.3). The supersensitivity displayed by mononeuropathic rats to the analgesic actions of baclofen (Abrams, 1996; Anghinah *et al.*, 1994; Smith *et al.*, 1994a) may also be taken as evidence for a degeneration—or reduced activity—of GABAergic neurones, since this would lead to supersensitive, postsynaptic GABAergic receptors in the DH. Indeed, PAF axotomy increases the density of GABA<sub>A</sub> receptors in the superficial DH (Castro-Lopes *et al.*, 1995). Further, in analogy to the burst firing which is induced in the DH by a suppression of ININ activity (Section 10.6.1), rhythmic discharges of DH neurones have been reported in the DH upon peripheral nerve damage, consistent with a loss of ININ control (Lombard and Larabi, 1983).

Pretreatment with NMDA receptor antagonists can prevent certain of the neurochemical and behavioural changes, such as DH sensitization and allodynia, which accompany PAF injury (Carlton *et al.*, 1997; Kim *et al.*, 1997b; Satoh and Omote, 1996; Smith *et al.*, 1994a; Woolf and Chong, 1993; Yoshimura and Nishi, 1995). Further, upon PAF injury, the activation of NMDA receptors by C fibres triggers the sensitization of WDR neurones in the DH (Section 10.3). On this basis, it has been contended that PAF injury elicits a transient but massive release of EAAs at NMDA receptors onto small, vulnerable ININs. This may lead to an excessive accumulation of [Ca<sup>2+</sup>]<sub>i</sub>, and the induction of NO and other mechanisms provoking their excitotoxic degeneration (Choi and Rothman, 1990; Gu *et al.*, 1997; Lerea, 1997; Mao *et al.*, 1997; Melino and Bernassola, 1997; Minghetti and Levi, 1998; Nishio and Watanabe, 1998). In certain studies, a modest decrease in gene expression for NMDA receptors has been detected in the DH following PAF injury (Coggeshall and Carlton, 1997; Hama *et al.*, 1995). This may reflect a loss of NMDA sites on degenerated ININs, although it cannot be discounted that a functional down-regulation of NMDA receptors by a transient enhancement in input from damaged PAFs is involved.

AMPA receptors have also been implicated in degenerative processes in CNS neurones (Pellegrini-Giampietro *et al.*, 1997) and other processes may be involved in the loss—or rescue—of DH-localized ININs following PAF injury. For example, it is possible that damage to PAFs leads to an atrophy of ININs by deprivation of neurotrophic factors normally delivered from their central terminals (Oliveira *et al.*, 1997) (Section 14.5.3). Interestingly, it was recently suggested that PGs (PGE<sub>2</sub>), despite their pronociceptive roles in the DH (Section 3.2.8.2), may play a role in *diminishing* (apoptotic) cell loss in the superficial DH following peripheral nerve injury, possibly via the activation of a mitogen-activated PK (Kawamura *et al.*, 1997a,b). Further, it has been shown that PGE<sub>2</sub> can *protect* neurones against NMDA receptor (and NO)-mediated toxicity (Akaike *et al.*, 1994). Evidently, then, the mechanisms involved in the putative loss—and protection—of DH-localized ININs following PAF injury require further elucidation.

#### 10.6.2.2. Temporal evolution of changes in ININ activity: lack of a decrease upon peripheral inflammation

Based on the above findings concerning PAF damage, Dubner and Ruda (1992) speculated that, under conditions of prolonged, inflammatory pain, small GABAergic ININs may degenerate due to an excessive, excitatory, NMDA receptor-mediated C fibre input (Mattson and Mark, 1996; Solum *et al.*, 1997; Zhang *et al.*, 1998a). Further, they proposed that GABAergic ININs inhibit the activity of dynorphinergic 'EXINs'. A disinhibition of the latter would compound sensitization by:

1. further exciting sensitized WDR PNs; and
2. enhancing release from terminals of C fibres targeting WDR neurones.

In line with this hypothesis, DYN gene expression is enhanced in the DH under conditions of PAF damage and peripheral inflammation (Draisci *et al.*, 1991; Hunter *et al.*, 1995; Kajander *et al.*, 1990; Millan, 1993; Ossipov *et al.*, 1997). Further, DYN has been shown to enhance C fibre reflexes and it may also enhance spinal cord levels of SP and EAAs, presumably derived from PAF terminals (Ossipov *et al.*, 1997; Suarez-Roca and Maixner, 1993). The intrathecal injection of DYN was, in addition, reported to elicit allodynia, while spinal administration of DYN and antibodies to DYN respectively inhibited and potentiated opioidergic analgesia following PAF injury. These actions of DYN are likely exercised via a facilitatory interaction at the modulatory glycine site of NMDA receptors (Brauneis *et al.*, 1996; Ho *et al.*, 1997; Jarvis *et al.*, 1997; Laughlin *et al.*, 1997; Ossipov *et al.*, 1997; Vanderah *et al.*, 1996b; Zhang *et al.*, 1997c). Despite the potential interest of this hypothesis, however, there remain several questions:

1. While exogenous administration of *high* concentrations of DYN may, indeed, exert excitatory and pronociceptive actions via an interaction with NMDA receptors, the princi-

pal, physiological  $\kappa$ -opioid receptor-mediated role of endogenous pools of DYN in the DH is *antinociceptive*. Further, an action of DYN at DH-localized  $\kappa$ -receptors *counters* rather than exacerbates inflammatory pain, while administration of DYN-specific antisera to neutralize the actions of DYN exerts little or *no* anti-allodynic actions against neuropathic pain (Hunter *et al.*, 1995; Mackawa *et al.*, 1995; Millan, 1990, 1993; Nichols *et al.*, 1997; Ossipov *et al.*, 1996, 1997; Schaible *et al.*, 1992; Riley *et al.*, 1996; Stiller *et al.*, 1993).

2. Acute and chronic noxious stimulation, including inflammation, actually *increases* the number of GABAergic ININs, and levels of GABA, in the DH at times when sensitization and hyperalgesia are *already* apparent: synthesis of the co-localized, antinociceptive neuropeptides, GAL and NPY, is increased in parallel (Castro-Lopes *et al.*, 1992, 1994; Hylden *et al.*, 1991; Ji *et al.*, 1994, 1995; Malcangio and Bowery, 1996b; Mantyh *et al.*, 1994; Nahin and Hylden, 1991).
3. Pharmacological blockade of activity at GABA<sub>B</sub> receptors *potentiates* inflammatory hyperalgesia (Malcangio and Bowery, 1994, 1996b).
4. The density of GABA<sub>B</sub> receptors in the DH is slightly reduced by inflammation and the actions of GABA<sub>B</sub> agonists are attenuated (Castro-Lopes *et al.*, 1995; Coggeshall and Carlton, 1998; Malcangio and Bowery, 1994, 1996b). This may reflect a down-regulation of GABA<sub>B</sub> receptors by an *increase* in the release of GABA.

The above observations suggest that an *enhancement* in GABAergic tone under inflammatory conditions may *counter* increases in nociception. Evidence that GABAergic ININ activity can be decreased by inflammatory pain is, thus, *lacking*.

Moreover, a recent study of PAF injury similarly observed an *increase* in DH levels of both glycine and GABA, and blockade of transmission at these sites potentiated thermal hyperalgesia (Satoh and Omote, 1996). These changes were preventable by NMDA antagonists in each case. Consequently, several further questions must also be raised which likewise concern a putative role of ININ loss following PAF damage:

1. In line with the above observations, bicuculline enhances the thermal hyperalgesia elicited by PAF injury, suggesting that GABAergic ININs are functionally active and that—like peripheral inflammation—they act to moderate nociception (Yamamoto and Yaksh, 1993).
2. Transynaptic 'degeneration' and other neurochemical changes seen in the DH, although predominantly ipsilateral, are also seen *bilaterally*—even where changes in nociception are unilateral (Ibuki *et al.*, 1997; Mao *et al.*, 1997; Satoh and Omote, 1996; Sugimoto *et al.*, 1990) (Section 9.1.4.2).
3. The long-term *recovery* of GABAergic profiles in the DH following their reduction by PAF injury—or damage to the DH itself—suggests that they do *not* actually degenerate, but rather

decrease their activity (Hao *et al.*, 1992; Ibuki *et al.*, 1997).

It cannot be entirely excluded that a compensatory increase in GABA synthesis in residual, surviving GABAergic ININs underlies the recovery of GABA levels. However, this seems unlikely and evidence that (intact) GABAergic neurones in superficial lamina *transiently* display a *reduction* in GABA synthesis following PAF damage was recently presented (Dumoulin *et al.*, 1996).

Thus, although a proportion of ININs may be eliminated following PAF injury by an NMDA receptor-mediated excitotoxic C fibre input, it is *unlikely* that there is a generalized degeneration of ININs in the DH (Mattson and Mark, 1996). In addition, there is *no* evidence for a reduction in the activity of GABAergic ININs in the DH under conditions of peripheral inflammation. An alternative interpretation of these findings, which does *not* evoke NMDA receptor-mediated excitotoxic damage, is that the activity of ININs is tonically enhanced by PAF input. Thus, a sustained increase in PAF input under conditions of peripheral inflammation enhances GABAergic activity in the DH. Further, as concerns PAF injury, following an initial, intense discharge, and prior to the development of ectopic activity (Section 8.2.2), damaged PAFs may traverse a period of quiescence whereby their stimulatory input onto ININs is reduced. This would lead to a transient and reversible reduction in the activity of GABAergic ININs. The reduction in GABAergic activity subsequently recovers by compensatory mechanisms and in parallel with the restoration of input from damaged PAFs due to their ectopic firing and other mechanisms discussed in Section 8.2. In some cases, a lack of recovery of PAF input may be associated with a more prolonged reduction of ININ activity (Castro-Lopes *et al.*, 1993; Kelly *et al.*, 1973).

#### 10.6.3. Alterations in ININ Activity upon PAF Injury: A Summary

To summarize, an (at least) transient, functional reduction of tonic GABAergic and glycinergic ININ activity can mimic and accentuate processes of DH sensitization, thereby contributing to the hyperalgesia and allodynia elicited by PAF injury. It is unclear which mechanisms might provoke such a change in ININ activity. The destruction of a subpopulation of ININs in the DH may be attributable to NMDA receptor-mediated, excitotoxic mechanisms. In this case, a compensatory acceleration of synthesis in surviving populations of ININs would account for the recovery of normal levels of GABA. On the other hand, the *loss* of a facilitatory PAF input onto ININs provides an alternative explanation for a temporary reduction in ININ tone in the DH upon following PAF injury. Further, this possibility is consistent with the *induction* of GABAergic activity in the DH induced by an increase in PAF input under conditions of peripheral inflammation. An assessment of the relative merits of these theories for the loss of ININ tone in the DH upon PAF damage will require further ex-

perimental analysis. Irrespective of the underlying mechanisms, there is a consensus that a reduction in ININ tone in the DH has highly undesirable consequences for nociceptive processing and pain. Moreover, as discussed in Sections 12.3.2 and 13.3, there is evidence that a suppression of ININ activity in the thalamus and other cerebral structures involved in the processing of nociceptive information, may also play an important role in the induction of painful states.

As a final comment, GABA plays a neurotrophic role in the developing CNS. In this light, it might be speculated that the consequences of an alteration in GABAergic activity in the DH following PAF injury may not be limited to the modulation of nociception. Rather, GABA may be involved in the modulation of trophic processes including, perhaps, the reorganization of input from injured PAFs (Dumoulin *et al.*, 1996) (Section 11.2).

#### 10.7. Reduction of Stimulatory A $\beta$ Fibre Input to ININs upon PAF Injury

In accordance with traditional formulations of the 'gate' theory of nociceptive processing, it has been suggested that stimulation of A $\beta$  fibres provides a substrate for the analgesic effects of non-noxious manipulations, such as rubbing the site of cutaneous tissue injury. Since A $\beta$  fibres do not directly inhibit PNs, their actions could be mediated via the activation of ININs, which subsequently interact with C fibre terminals (Wall and Devor, 1981) or PNs themselves (Sections 4.6 and 9.1.4) (Fig. 2). Indeed, there is evidence for a reduction of ININ-mediated actions at fine calibre PAF terminals following PAF injury (Sections 9.1.4 and 10.6.2.1). Thus, the reduction of a A $\beta$  fibre-mediated stimulation of ININs upon PAF injury might disinhibit and further sensitize nocisponsive neurones in the DH. There are several possible mechanisms via which an attenuation of A $\beta$  input to ININs might take place.

1. There is some evidence that low threshold mechanoreceptors show an altered (decrease) in their responsiveness following tissue injury (Na *et al.*, 1993; Treede *et al.*, 1992b; Wahren *et al.*, 1989).
2. A component of A $\beta$  fibre-mediated input to the DH may, at least temporarily, be directly incapacitated by lesions to PAFs (Laird and Bennett, 1992; Wall and Devor, 1981).
3. A reduction in the facilitatory A $\beta$  input at ININs in deeper laminae would occur upon the re-orientation of A $\beta$  fibres into superficial DH laminae (Section 11.2).

A loss of excitatory A $\beta$  input would provide a putative mechanism for a—possibly *rapid*—loss of ININ tone in the DH following PAF injury (Section 10.6). Nevertheless, under normal conditions, evidence that A $\beta$  fibres exert a major, inhibitory role upon PNs via stimulation of ININs is equivocal. Further, under conditions of secondary hyperalgesia and neuropathic pain (Sections 9.1.3 and 11.2), *direct, excitatory* actions of A $\beta$  fibres at WDR neurones in deep DH laminae—and, following rewiring, at NS neurones in superficial laminae—are of key

importance in mediating mechanical allodynia. These actions of A $\beta$  fibres *facilitate* rather than inhibit nociception and, overall, likely outweigh the functional effects of any reduction in excitatory input onto ININs (Sections 9.1.2 and 10.5).

## 10.8. Modulatory Role of Descending Pathways

### 10.8.1. A Decrease in Descending Inhibition and an Increase in Descending Facilitation

As indicated in Sections 6.4 and 9.1.4.2, exposure to noxious stimuli may, via a supraspinal loop, modify the activity of pathways descending from cerebral centres to the DH. Indeed, under conditions of inflammation, a transient or sustained role of descending, inhibitory pathways in dampening the activity of sensitized PNs in the DH has been proposed (Basbaum and Fields, 1984; Cervero and Laird, 1996a,b; Le Bars, 1988; Lin *et al.*, 1997; Millan, 1986, 1990, 1993, 1995, 1997; Owens *et al.*, 1992; Ren and Dubner, 1996; Sandkühler, 1996; Schaible and Grubb, 1993; Stanfa *et al.*, 1994; Traub, 1997; Zhang *et al.*, 1997f). These descending mechanisms operate via direct inhibition of PNs, suppression of release from PAF terminals and the engagement of ININs (Section 5.1).

Contrariwise, under certain conditions, a *decrease* in descending inhibition might, either directly or indirectly, contribute to an increase in the excitability of DH-localized PNs. Although there is little evidence for such a reduction in the activity of descending pathways upon exposure to noxious stimulation, *intracellular* events triggered in WDR neurones by noxious stimulation can lead, via the activation of PKs, to a weakening of GABAergic and/or glycinergic tone (Section 10.4.2). Consequently, the component of descending inhibition which is mediated via activation of DH-localized ININs is compromised, and processes of sensitization amplified (Lin *et al.*, 1997). Further, spinal and supraspinal actions of morphine may act synergistically in exerting antinociceptive actions. It has been suggested that this interaction, which is expressed in the rostral ventromedial medulla, is perturbed under conditions of neuropathic pain, resulting in a reduced efficacy of morphine (Heinricher *et al.*, 1994; Ossipov *et al.*, 1997). Whether this loss of synergy reflects a reduction in descending inhibition, or the parallel activation of descending facilitation, is unclear. In any case, as described in Section 10.8.5., the rostral ventromedial medulla is a key site for the initiation of facilitatory networks running to the DH.

As discussed in the following paragraphs, an *enhancement* in the activity of descending, *facilitatory* mechanisms may contribute to an increase in nociception and the induction of sensitization.

### 10.8.2. Adrenergic Mechanisms

There is extensive evidence for a facilitatory influence of both acute and prolonged, noxious stimulation upon the activity of centrifugal, adrenergic pathways. Further, a tonic, antinociceptive role of NAD, exerted via inhibitory DH-localized  $\alpha_{2A}$ -ARs negatively coupled to AC, inhibits inflammatory nociception (Schaible *et al.*, 1991;

Stanfa *et al.*, 1994; Millan, 1997). However, there is some evidence that NAD mediates *pro*-nociceptive actions in the DH via activation of excitatory  $\alpha_1$ -ARs positively coupled to PLC and increases in  $[Ca^{2+}]_i$  (Jordan *et al.*, 1979; Jones, 1992; Millan, 1997). Thus, an increase in activity at PN-localized  $\alpha_1$ -ARs might be involved in mechanisms underlying sensitization.

### 10.8.3. Serotonergic Mechanisms

The activity of descending, serotonergic pathways in the DH is likewise modified under conditions of acute and prolonged nociceptive and neuropathic pain, and spinal 5-HT turnover is modified in chronic pain patients (Von Knorring, 1989; Weil-Fugazza, 1989; Wolfe *et al.*, 1997; Millan, 1995). Inasmuch as serotonergic mechanisms in the DH exert both antinociceptive and *pronociceptive* actions via different 5-HT receptor subtypes, it is conceivable that an increase in activity at the latter contributes to DH sensitization (Millan, 1995, 1997). Further, stimulation of serotonergic neurones projecting to the DH from brainstem raphe nuclei results in a biphasic excitatory and inhibitory influence upon DH neurones (Zhuo and Gebhart, 1997). In this regard, 5-HT<sub>2C</sub> and 5-HT<sub>2A</sub> receptors are positively coupled to PLC and their activation suppresses K<sup>+</sup>-currents (Boess and Martin, 1994; Millan, 1997). Further, 5-HT<sub>3</sub> receptors directly activate a cation-permeable ion channel which triggers the opening of VDCCs, and their engagement can also induce PLC and further increases in  $[Ca^{2+}]_i$  (Boess and Martin, 1994; Millan, 1995; Rondé and Nichols, 1997). Thus, 5-HT<sub>2A</sub>, 5-HT<sub>2C</sub> or 5-HT<sub>3</sub> receptors localized on PNs, EXINs or the terminals of PAF fibres may play a role in mediating pronociceptive actions of 5-HT and mechanisms of descending facilitation (Inoue *et al.*, 1997; Kjorsvik *et al.*, 1997; Millan, 1995, 1997; Saria *et al.*, 1990). On the other hand, 5-HT<sub>1A</sub> receptors which, like 5-HT<sub>3</sub> receptors, are enriched in the superficial DH, are negatively coupled to AC and their stimulation enhances and suppresses K<sup>+</sup>- and Ca<sup>2+</sup>-currents, respectively (Boess and Martin, 1994; Millan, 1995; Yang *et al.*, 1998). Thus, it has been proposed that inhibition of 5-HT<sub>1A</sub> receptors localized on ININs play a role in processes underlying DH sensitization and allodynia by the disinhibition of WDR PNs (Millan *et al.*, 1994, 1996; Millan, 1995, 1997) (Section 10.6.2). In this light, thus, the putative actions of 5-HT<sub>1A</sub>, 5-HT<sub>2A</sub>, 5-HT<sub>2C</sub> and 5-HT<sub>3</sub> antagonists in models of neuropathic pain would be of interest to evaluate.

Interestingly, there is evidence for plasticity in descending serotonergic pathways under conditions of noxious stimulation or nerve damage. Thus, in addition to changes in spinal levels of 5-HT, the sprouting of serotonergic neurones has been seen in the DH following peripheral capsaicin treatment or PAF injury. Notably, serotonergic terminals in deeper laminae extend into lamina II (Godefroy *et al.*, 1987; Marlier *et al.*, 1992; Polistina *et al.*, 1990; Wang *et al.*, 1991). These changes may

involve specific, intrinsic growth-promoting proteins, the significance of which in encouraging the regeneration of (injured) nerves is considered in Section 11.3 (Ching *et al.*, 1994). In addition, serotonergic neurones projecting to the DH bear TRK C receptors for NT 3, the potential role of which is considered in Section 14.5.3 (Arvidsson *et al.*, 1994).

The above observations suggest that a perturbation of serotonergic transmission in the DH may be involved in modulating (enhancing) nociception under conditions of nociceptive and neuropathic pain. In this context, it is of note that descending serotonergic pathways modulate the rostral transmission of normally-innocuous, tactile information via an influence upon PSDC neurones (Wu and Wessendorf, 1992) (Section 6). Whether this role can be related to the induction of mechanical allodynia, and whether 5-HT modulates transmission of nociceptive (visceral) information by PSDC pathways, would be of interest to evaluate.

#### 10.8.4. Dopaminergic Mechanisms

Dopaminergic networks in the DH are also involved in the modulation of nociception, and multiple dopaminergic receptors exert a contrasting influence upon nociception. Thus, D<sub>2</sub> and D<sub>1</sub> receptors, which are positively and negatively coupled to AC, mediate antinociceptive and pronociceptive actions respectively, presumably via direct actions at WDR neurones in the DH (Millan, 1997; Verma and Kulkarni, 1993). Correspondingly, an increase in activity at dopamine D<sub>1</sub> receptors, or a reduction in activity at dopaminergic D<sub>2</sub> receptors, might contribute to the sensitization of WDR neurones in the DH.

#### 10.8.5. Role of Cerebral Mechanisms in Triggering Descending Facilitation

A loss of cerebral GABAergic inhibitory tone may result in the disinhibition of descending, facilitatory pathways (Hammond, 1997; Monhemius *et al.*, 1997) and several—non-monoaminergic—mechanisms may play a role in engaging descending facilitatory pathways. Notably, neuropeptide FF and CCK, each of which counters antinociceptive mechanisms in the DH (Sections 3.2.6 and 4.5). Several studies have suggested that the rostro-medial region of the ventral medulla is a major centre for the initiation of mechanisms of descending facilitation and hyperalgesia. Indeed, the temporary interruption of neuronal transmission in this structure by local application of lidocaine attenuates the allodynia associated with nerve damage or inflammation (Almeida *et al.*, 1996; Morgan *et al.*, 1994; Wiertelak *et al.*, 1994a,b,c,d; Watkins *et al.*, 1994). Recent evidence suggests that the novel opioid peptide, nociceptin, may play a role in hyperalgesic mechanisms in this and other structures, such as the PAG (Heinricher *et al.*, 1997; Morgan *et al.*, 1997). Further, neurotensin is implicated in pronociceptive mechanisms in the rostro-medial ventral medulla, and a circuit invol-

ving medullary pools of neurotensin, and CCK in the DH, was suggested to mediate the hyperalgesia of the tail elicited by noxious, chemical stimulation of the paw (Herrero and Cervero, 1996; Skinner *et al.*, 1997; Smith *et al.*, 1997a; Urban *et al.*, 1996a,b; Urban and Gebhart, 1997; Zhuo and Gebhart, 1997). Whether the DH pool of CCK involved is derived from descending terminals, EXINS or PAFs is unclear. In any case, this observation supports the hypothesis that supraspinal mechanisms and descending facilitation are involved in the induction of referred pain (Section 9.1.4.2). A further supraspinal structure excited by ascending nociceptive input, the anterior pretectal area of the brainstem, may also, via descending facilitatory pathways, exert an excitatory influence upon NS neurones in the superficial DH. This region has likewise been implicated in the mediation of painful states due to PAF injury, as well as in the induction of referred pain (Rees and Roberts, 1993; Rees *et al.*, 1995b).

#### 10.8.6. Physiological Activation of Mechanisms of Descending Facilitation

The above findings suggest that a supraspinal loop engaging descending, facilitatory mechanisms may contribute to the induction of nociception and DH sensitization (Mansikka and Pertovaara, 1997a; Pertovaara *et al.*, 1996). Notably, such descending pronociceptive mechanisms may be elicited not only by exposure to noxious stimuli, but also by other stimuli such as vagal stimulation and/or 'illness' (Lovick, 1993; Urban *et al.*, 1996a,b; Watkins *et al.*, 1994; Wiertelak *et al.*, 1994a,b,c,d; Zhuo and Gebhart, 1992, 1997). Indeed, as concerns the response to 'illness', the release of IL-1 $\beta$  by macrophages has been suggested to activate vagal, sensory afferents running to the nucleus tractus solitarius. Therefrom, a descending facilitatory pathway is activated which elicits nociception by the recruitment of NO and NMDA receptors in the DH (Watkins *et al.*, 1994, 1995; Wiertelak *et al.*, 1994a,b,c,d). It was pointed out in Sections 10.4.2 and 10.8.1 that mechanisms of descending inhibition at WDR PNs may be defective in prolonged, painful states due to PAF- or CNS-injury. A parallel enhancement in mechanisms of descending facilitation implies a displacement in the overall influence of modulatory, descending pathways towards an *enhancement* of nociceptive transmission. This *disequilibrium* will amplify the excitation and sensitization of DH neurones transmitting nociceptive information to cerebral structures (Traub, 1997).



## 11. NEUROPATHIC PAIN: REORGANIZATION OF CENTRAL AND PERIPHERAL PROJECTIONS OF PAFS FOLLOWING INJURY

### 11.1. Peripheral-Central Interface in the DH

A distinctive mechanism involved in the induction of prolonged, neuropathic pain consists of—probably permanent—changes in the DH projection targets of PAFs following peripheral nerve injury. This reorganization of PAF input to the DH is a process which lies at the interface of ‘peripheral’ and ‘central’ mechanisms underlying chronic pain. Processes of atrophy and regeneration following destruction of PAFs may be attributed to a complex and interactive mesh of factors both intrinsic and extrinsic to damaged PAFs, full details of which are beyond the scope of this review (Deller and Frotscher, 1997; Fu and Gordon, 1997). Attention here is focused on the relationship of such events to alterations in nociception. In this light, the implication of two, specific molecules is of particular pertinence.

1. neurotrophins, in view of their crucial role as trophic factors for sensory nerves, and of the modulatory influence of NGF upon nociception via actions at the peripheral terminals of small calibre C fibres (Sections 7.6 and 7.7);
2. the growth associated phosphoprotein (GAP) 43, which plays a key role in the growth and orientation of injured—and, probably, intact—small calibre C fibres (Section 11.3).

### 11.2. Central Degeneration and Regrowth of Injured PAFs: Abnormal Patterns of A $\beta$ Fibre Connectivity

The transection of peripheral nerves leads to marked degenerative/atrophic and regenerative changes in their central terminals. Following destruction of the peripheral branches of PAFs, a subpopulation of terminals in the DH may persist, while others die by processes resembling apoptosis. Still others may undergo degenerative (‘chromolytic’) changes followed by a switch to a regenerative, ‘growth mode’—although the latter processes does not necessarily depend on the former (Cameron *et al.*, 1997; Fu and Gordon, 1997; Lieberman, 1971; McMahon and Priestley, 1995). Most notably, as concerns nociceptive processing, A $\beta$  fibres sprout—within a dorsoventral plane—to inappropriate targets within the superficial DH (Ambron and Walters, 1996; Cameron *et al.*, 1997). That is, following axotomy of A $\beta$  fibres distal to the DRG, their central projections in laminae III and IV begin to penetrate superficial laminae (in particular lamina, II<sub>0</sub>). Therein, they may potentially interact, either synaptically or via volume transmission, with NS (and WDR) neurones which they would not otherwise access (Woolf *et al.*, 1992) (Fig. 2). This reorientation of A $\beta$  fibres into superficial laminae is compounded by a phenotypic switch whereby they begin to synthesize the pronociceptive and excit-

atory transmitters, SP and VIP—in addition to EAAs (Section 8.2.5). Further, there is an upregulation of NK<sub>1</sub> receptors and an increased Ca<sup>2+</sup>-permeability of AMPA receptors in superficial DH (Abbadie *et al.*, 1996; Coggeshall and Carlton, 1998; Goff *et al.*, 1998). Thus, an aberrant pattern of A $\beta$  input to nocisponsive neurones in the superficial DH provides a substrate for the mediation of mechanical allodynia and hyperalgesia (Doubell *et al.*, 1997; Lekan *et al.*, 1996, 1997; Woolf and Doubell, 1994; Woolf *et al.*, 1992) (Section 9.1.2).

In addition to the extra-territorial sprouting of damaged A $\beta$  fibres, there is some evidence that regenerating, damaged C fibres may expand into deeper DH laminae (Cameron *et al.*, 1992; Florence *et al.*, 1993; Lekan *et al.*, 1997; LaMotte *et al.*, 1989; McMahon and Kett-White, 1991). Should C fibres infiltrating deeper laminae contact (or volume activate) WDR and NS neurones, they would also contribute to patterns of abnormal signalling and hyperalgesic states.

PAF sprouting following injury is, in general, far more marked in immature than in adult animals (Fitzgerald *et al.*, 1994; McMahon and Priestley, 1995; Shortland and Fitzgerald, 1994; Wilson and Kitchener, 1996). This difference provides several, important insights into processes potentially promoting the regeneration of damaged nerves (Fawcett, 1992; Schwab, 1990).

1. Immature nerves developmentally express high levels of several ‘growth-associated-factors’ which are less prominent in uninjured, adult, peripheral neurones. These include GAP 43, which, as described in Section 11.3, plays an important role in the regeneration of damaged (and intact) C fibres, and cytoskeletal proteins such as tubulin, which support GAP 43-coordinated growth cones (Benowitz and Routtenberg, 1997; Coggins and Zwiers, 1991; Fournier and McKerracher, 1997; Meiri and Burdick, 1991; Strittmatter *et al.*, 1995).
2. There is a lesser degree of myelination and a generally more permissive environment for nerve growth in the immature DH (Kolodkin, 1996; Nieto, 1996).
3. Immature neurones are more dependent upon peripheral stores of neurotrophins: the loss of this peripheral source of neurotrophins upon nerve section leads, thus, to a greater degree of central degeneration in the immature DH and to the liberation of a greater number of potential synaptic sites for regenerating axons (Wilson and Kitchener, 1996).

Despite these differences, as indicated above, the reorientation of PAFs to inappropriate targets in the DH *also* occurs following peripheral nerve lesions in mature subjects.

To summarize, following transection of PAFs, axonal transport is reduced, the DRG loses access to neurotrophins and other essential, trophic factors (Gold *et al.*, 1991; Rich *et al.*, 1987; Wong and Oblinger, 1991), PAF phenotype is modified (Section 8.2.5), intraneuronal structural changes occur due to an altered expression of cytoskeletal proteins, and, ultimately, DH terminals of PAFs

display morphological alterations in their structure and 'transganglionic' atrophy. An important consequence of these events is a decrease in the density of functional synaptic contacts and vesicles in the DH, resulting in the appearance of so-called 'vacant' synapses potentially accessible to other neurones, such as migrating A $\beta$  fibres. (Mechanisms triggering the migration of A $\beta$  fibres into superficial laminae are discussed in detail in Section 11.3.3).

Although, *sub-total*, peripheral nerve damage (as compared to complete transection) does *not*, at least, initially, incur the degeneration of central DH terminals, this can occur in the absence of successful *peripheral* regeneration (Aguayo, 1985; Castro-Lopes *et al.*, 1990; Hachisuka *et al.*, 1989; Kitchener *et al.*, 1994; Knyihar-Csillik and Török, 1989; Knyihar-Csillik *et al.*, 1987, 1989, 1990, 1992; Snow and Wilson, 1991). Indeed, the regeneration and re-establishment of the *peripheral* targets of injured PAFs encourages, and may be a pre-condition for, restoration of their central re-growth (Ambron and Walters, 1996; Chong *et al.*, 1996; McMahon and Kett-White, 1991; Winter *et al.*, 1992).

### 11.3. The Role of GAP 43 and other Factors in the Central and Peripheral Regeneration of Injured PAFs

#### 11.3.1. The Induction of GAP 43 in Injured C Fibres: Short-Term and Long-Term Role in Neuronal Sensitization

GAP 43 is a calmodulin-binding phosphoprotein activated (phosphorylated) by PKC and deactivated (dephosphorylated) by calcineurin, which fulfils a crucial role in controlling the growth and connectivity of axons (Aigner and Caroni, 1995; Benowitz and Routtenberg, 1997; Li *et al.*, 1995; Ramakers *et al.*, 1997). It is found almost exclusively in their pre-synaptic terminals, wherein it is closely-attached to the terminal membrane. GAP 43 is virtually undetectable in large diameter mature PAFs, and modestly-expressed in their mature, small calibre counterparts (Benowitz and Routtenberg, 1997; Leslie *et al.*, 1995). It is a principal component of the growth cones of developing neurones, sprouting, intact neurones and injured, regenerating C fibres (Benowitz and Routtenberg, 1997; Buffo *et al.*, 1997). The precise signals triggering GAP 43 activation upon nerve injury and other conditions remain to be defined. However, a PKC-mediated—and calmodulin-repressible—phosphorylation of GAP 43 at residue Ser<sup>41</sup> transforms cells into a growth mode (Benowitz and Routtenberg, 1997; Ghosh and Greenberg, 1995; Gu and Spitzer, 1995; Sjaastad and Nelson, 1997). The actions of GAP 43 may involve a modification of its interaction with the cytoskeleton, the activation of specific G proteins and/or the induction of various, nuclear transcription factors (Hens *et al.*, 1993; Namgung *et al.*, 1997; Ramakers *et al.*, 1997; Verkade *et al.*, 1997). An activation of various Ca<sup>2+</sup>-dependent and -independent isoforms of PKC has been observed in injured nerves. Of these, a PKC $\beta$  isoform is likely

implicated in the activation of GAP 43, although additional isoforms, acting via GAP 43 and/or other mechanisms, may also be involved in neuronal regeneration (Benowitz and Routtenberg, 1997; Kawano *et al.*, 1997; Okajima *et al.*, 1995).

In the light of this role of PKC in the activation of GAP 43, it is of interest to recall the positive coupling to PKC of several, pronociceptive, inflammatory mediators at C fibre terminals, including SP, BK, 5-HT and PGE<sub>2</sub>. Further, GAP 43 is up-regulated in C fibre terminals upon prolonged peripheral inflammation (Leslie *et al.*, 1995). Nevertheless, in addition to PKC, other permissive and/or obligatory factors are likely involved in the regulation of GAP 43 activity in PAFs (and other neurones) inasmuch as their *transient* excitation is *not* sufficient for sustained GAP 43 activation and the induction of neuronal growth (Dekker *et al.*, 1989; Namgung *et al.*, 1997). In this regard, one potentially important, intracellular regulator element should be mentioned: the IEG, c-jun. As discussed in Section 8.2.6.3, c-jun plays a role in modulating patterns of gene transcription following its induction in damaged PAFs (Herdegen *et al.*, 1997). The GAP-43 gene possesses a highly-conserved, c-jun-sensitive, regulatory element which modulates its transcription. Further, levels of c-jun are increased and co-expressed with GAP 43 in a subset of neurones following their injury (Schaden *et al.*, 1994). Thus, c-jun may be involved in the induction of GAP 43 expression following PAF damage. In this regard, moreover, c-jun (and PKC) may intervene in the induction of GAP 43 by NGF (Kaplan and Stephens, 1994; Leslie *et al.*, 1995) (Section 11.3.4.2).

There is evidence that GAP 43, once phosphorylated by PKC, may also modulate transmitter release. This suggests that, at central and/or peripheral terminals of regenerating neurones, in addition to its long-term role in the modification and re-establishment of synaptic connectivity, GAP 43 might *rapidly* modulate nociception via alterations in the release of SP or other pronociceptive substances (Dekker *et al.*, 1989; Hens *et al.*, 1993; Ramakers *et al.*, 1997). In the DH, this might occur upon NMDA receptor-mediated activation of intrinsic neurones to release a retrograde factor which then enhances PKC activity in PAF terminals: for example, arachidonic acid metabolites, PGs or EAAs acting at PLC-coupled, group I mGlu receptors (Sánchez-Prieto *et al.*, 1996). Further, in contrast to a lack of effect of *transient* depolarization, presynaptic pools of GAP 43 are induced/phosphorylated in parallel with the expression of LTP in the hippocampus (Benowitz and Routtenberg, 1997; Namgung *et al.*, 1997) (Section 10.2.1). This observation is consistent with a broader role of GAP 43 in adaptive processes underlying prolonged and rapid alterations in synaptic transmission. Further, it provides an interesting parallel to the rapid and long-term actions of neurotrophins in modulating synaptic transmission (Section 14.4).

In conclusion, an exploration of the role of GAP 43 in DH-localized PAF terminals in the sustained and rapid enhancement of neuronal sensitization and nociception upon prolonged tissue inflammation, or PAF injury, would be of interest. Such a

potential role of GAP 43 in supraspinal structures might also be envisaged.

### 11.3.2. *The Role of GAP 43 and Other Intrinsic Factors in the Central Regeneration of Damaged PAFs*

GAP 43 is present in a minority of PAFs under normal conditions but it reappears in virtually all damaged, small calibre C fibres following their injury (Chong *et al.*, 1992; Leslie *et al.*, 1995; Namgung *et al.*, 1997; Schreyer and Skene, 1991; Sommerville *et al.*, 1991; Tetzlaff *et al.*, 1991; Van der Zee *et al.*, 1989) and plays a role in the regeneration of their peripheral and central terminals, to both of which it is transported. Anatomical and ultrastructural studies have, indeed, shown that GAP 43 is concentrated in growth cone-like structures of C fibre terminals in the DH following their peripheral injury: further, its appearance coincides with the onset of their regenerative, central regrowth (Cameron *et al.*, 1997; Chong *et al.*, 1994; Coggeshall *et al.*, 1991; Doubell and Woolf, 1997; Knyihar-Csillik *et al.*, 1992; Schreyer and Skene, 1991; Woolf *et al.*, 1990).

It might reasonably be assumed that GAP 43 is also present in the terminals of A $\beta$  fibres which infiltrate Lamina II following their migration from deeper laminae (Koerber, 1996; McMahon and Kett-White, 1991; Shortland and Woolf, 1993; Wilson and Kitchener, 1996; Woolf *et al.*, 1992). However, a recent study has, surprisingly, indicated the contrary (Doubell and Woolf, 1997). This observation suggests that GAP 43 may *not* be critical for the sprouting of the central terminals of A $\beta$  fibres. Other classes of growth-associated protein may, thus, be involved (Doubell and Woolf, 1997). In this context, it is of note that several other substances contained in PAF terminals and potentially involved in axonal orientation and growth appear in the DH territories of injured nerves following their lesioning. These include soybean agglutinin, the presence of which is associated with sensory neurone growth; the carbohydrate-binding lectin, R2-14.5, which promotes neuronal regrowth and the neuronal adhesion molecule RL-29, which regulates mRNA expression in PAFs (Barondes *et al.*, 1994; Cameron *et al.*, 1997; Fields and Itoh-Kouichi, 1996; Fu and Gordon, 1997) (Section 11.3.4.4). In addition, the induction of mRNA encoding the cytoskeletal protein, tubulin, suggests that this offers physical support for the regeneration and orientation of the growth cones of injured neurones (Challacombe *et al.*, 1996; Fournier and McKerracher, 1997). The roles of GAP 43, cytoskeletal proteins and other factors in synaptic remodelling and axonal regeneration following damage to PAFs is the subject of intensive investigation (Fu and Gordon, 1997).

### 11.3.3. *Mechanisms Underlying A $\beta$ Fibre Migration into Foreign DH Laminae*

The mechanisms underlying the reorientation of A $\beta$  fibres into alien territories remain unclear. However, it is likely that several, interrelated and interactive processes are involved.

1. Synaptic sites in superficial laminae (II<sub>0</sub>) are vacated by the degeneration and/or withdrawal of damaged C fibres (Castro-Lopes *et al.*, 1990; Deller and Frotscher, 1997; Knyihar-Csillik *et al.*, 1987) (Section 11.2). The argument that a loss of 'competing' C fibres in lamina II permits expansion of A $\beta$  fibres away from their normal sites of termination is supported by developmental studies showing that:

1. A $\beta$  fibres *do* initially run to superficial lamina but they are eventually displaced by incoming C fibres; and
2. prevention of C fibre innervation by capsaicin treatment allows A $\beta$  fibres to maintain their presence in superficial laminae (Cameron *et al.*, 1997; Fitzgerald *et al.*, 1994; Shortland *et al.*, 1990). Further, NGF can *prevent* the sprouting of A $\beta$  fibres into lamina II following PAF lesions, possibly since it acts as a trophic factor for C fibres, thereby preventing their withdrawal from superficial lamina (Bennett *et al.*, 1996a). However, as discussed in Section 11.3.4.2, the role of NGF as a trophic factor for the central regrowth of injured C fibres is unclear (Zhou *et al.*, 1996b; Gallo *et al.*, 1997; Song *et al.*, 1997).

2. Lamina II-localized C fibre terminals, or non-neuronal glial and microglial cells in their vicinity, may release substances attracting A $\beta$  fibres and encouraging their growth (Doubell *et al.*, 1997; Goodman *et al.*, 1996; Song *et al.*, 1997). For example, an increase in the release of C fibre-localized neuropeptides possessing trophic properties, such as NPY or GAL, could be involved (Hökfelt *et al.*, 1994; Xu and Wiesenfeld-Hallin, 1997). However, for several reasons, a more specific and attractive candidate would be BDNF.

1. Unlike NGF, BDNF is a trophic factor for A $\beta$  fibres (Lexin and Barde, 1996; Mannion *et al.*, 1996).
2. BDNF can induce the expression of molecules encouraging axonal regrowth, such as tubulin and GAP 43, and it encourages branching in some peripheral neurones (Fournier *et al.*, 1997; Kobayashi *et al.*, 1997a);
3. following damage to PAFs, BDNF is induced in (TRK A-bearing) injured C fibres, wherein it is transported to their spinal terminals (Barakat-Walter, 1996; Cho *et al.*, 1997b,c; Funakoshi *et al.*, 1993; Michael *et al.*, 1997a; Vergé *et al.*, 1995b; Zhou and Rush, 1996);
4. BDNF levels are concentrated in lamina II of the DH (Cho *et al.*, 1997b,c; Conner *et al.*, 1997; Ernfors *et al.*, 1990; Furukawa *et al.*, 1997); and
5. in a cAMP-dependent manner, BDNF modifies the turning behaviour of the growth cones of spinal neurones (Song *et al.*, 1997).

Although the density of TRK B receptors is decreased in the *peripheral* branches of damaged PAFs, this is probably not the case for their central terminals (Fu and Gordon, 1997). Thus, the release of BDNF by the central terminals of damaged C

fibres in laminae II may—in analogy to the orienting response of TRK A receptor-bearing C fibres to NGF (Gallo *et al.*, 1997; Song *et al.*, 1997)—attract TRK B receptor-bearing A $\beta$  fibres into lamina II<sub>0</sub>. However, additional factors may be involved inasmuch as it is difficult to explain the *dorsoventral* orientation of A $\beta$  infiltration of lamina II by a mechanism *exclusively* implicating BDNF (Doubell and Woolf, 1997).

3. In superficial laminae vacated by degenerated C fibre terminals, there may be a relative absence of molecules inhibitory to growth cones, such as myelin, sulphated proteoglycans and other proteins synthesized by astrocytes and oligodendrocytes: thus, the extracellular matrix is relatively favourable to neuronal growth (Fazeli and Walsh, 1996; Fawcett, 1992; Fu and Gordon, 1997; Golding *et al.*, 1997; Kolodkin, 1996; Nieto, 1996; Schwab, 1990, 1996).
4. A modulation in the expression, or Ca<sup>2+</sup>/CAMP-dependent actions, of 'attractant and repellant' molecules involved in central axonal guidance and target recognition, such as netrins and semaphorins, may be involved (Kobayashi *et al.*, 1997a,b; Kolodkin, 1996; Ming *et al.*, 1997; Olson, 1997; Tanelian *et al.*, 1997; Tessier-Lavigne and Goodman, 1996). For example, during development, semaphorin III, which acts via a recently-cloned neuropilin receptor (Kitzuka *et al.*, 1997; Kolodkin *et al.*, 1997), induces growth cone collapse in sensory, small calibre C and A $\delta$  PAFs in the VH (Tanelian *et al.*, 1997). If PAF damage results in a reduced expression of repellant factors for A $\beta$  fibres in the superficial VH, their infiltration of lamina II would no longer be discouraged (Messersmith *et al.*, 1995; Püschel, 1996; Püschel *et al.*, 1996; Wright *et al.*, 1995; Tanelian *et al.*, 1997). On the other hand, a repellant factor expressed upon PAF injury in deeper laminae may drive A $\beta$  fibres out of this region. Contrariwise, an increase and decrease in the expression of a chemoattractant for A $\beta$  fibres in superficial and deep lamina, respectively, would also facilitate migration of A $\beta$  fibres in lamina II.

Mechanisms analogous to those outlined above are probably involved in the reorientation of C fibres into deeper laminae following their peripheral injury (Section 11.2). The nature of multiple mechanisms underlying patterns of regeneration and reorganization of PAF terminals in the DH following destruction of their peripheral branches will provide fertile territory for further investigation (Fazeli and Walsh, 1996; Fields and Itoh-Kouichi, 1996; Kikuchi *et al.*, 1997; Kolodkin, 1996; Kobayashi *et al.*, 1997a; Naciff *et al.*, 1996; Nieto, 1996; Taniguchi *et al.*, 1997; Tessier-Lavigne and Goodman, 1996).

#### 11.3.4. Peripheral Regeneration of Damaged PAFs

##### 11.3.4.1. The importance of Schwann cells

Regeneration of the peripheral branches of damaged PAFs is probably imperative for the regrowth of their *central* branches and the restitution

of a normal phenotype. Peripheral regeneration involves the re-access of damaged PAFs to neurotrophins and many other nutrient factors (Aigner and Caroni, 1995; Berninger and Poo, 1996; Benowitz and Routtenberg, 1987; Deller and Frotscher, 1997; Fu and Gordon, 1997; Terenghi *et al.*, 1997; Vergé *et al.*, 1995a; Wells *et al.*, 1994).

For the successful peripheral regeneration of damaged (myelinated) neurones, Wallerian degeneration is probably a prerequisite. That is, the removal of myelin and other factors inhibiting nerve regeneration. This process is effected primarily by macrophages which, together with damaged PAFs themselves, release mitogens triggering the proliferation of Schwann cells (Brown *et al.*, 1997; Fields and Itoh-Kouichi, 1996; Fu and Gordon, 1997; Matsuoka *et al.*, 1997). In parallel to the switch of injured neurones from a 'transmission' to a 'growth' mode, Schwann cells switch from a '*sheath*' to a '*support*' mode for PAFs. Thus, in addition to the elaboration of myelin for larger calibre neurones, they play a more general role in supporting the growth of injured PAF.

1. Schwann cells become a rich source of the neurotrophins, NGF, BDNF and GDNF as well as the cytokine, LIF, and other molecules permitting the regeneration of damaged PAFs (Bunge, 1993).
2. They secrete cellular adhesion molecules (CAMs), such as N-cadherin and ninjurin, extracellular matrix molecules, such as laminin and fibronectin, and other elements providing an environment conducive to the growth of damaged axons (Section 11.3.4.4).
3. Peripheral nerves likely regenerate through columns of basal laminae (endoneurial tubes or 'Bands of Bungner') filled with Schwann cells which have proliferated following axonal loss. Schwann cells also provide, thus, the physical support necessary for the regrowth of injured neurones (Fu and Gordon, 1997; Martini, 1994; Venstrom and Reichardt, 1993; Xu *et al.*, 1995c).
4. Schwann cells may contribute to the distribution and clustering of axonal Na<sup>+</sup>- and K<sup>+</sup>-channels in myelinated axons, thereby allowing for optimal neuronal conduction properties (Kaplan *et al.*, 1997; Joe and Angelides, 1992; Rasband *et al.*, 1998).

One particularly interesting mode of reciprocal interaction between regenerating PAFs and surrounding Schwann cells has recently been brought to light by Livesey *et al.* (1997). Damage to PAFs results in a massive induction of the cytokine, LIF, in Schwann cells (Jonakait, 1993). As outlined in Section 8.2.6.2, LIF can modify the phenotype of certain, injured PAFs. In addition, it prompts the expression and secretion of the protein Reg-2 in injured PAFs which, together with other substances, acts as a potent mitogen for Schwann cells (Livesey *et al.*, 1997; Matsuoka *et al.*, 1997). Thus, via injured PAFs, Schwann cells actually promote their own proliferation thereby creating a physical and chemical environment favourable to PAF regeneration (*vide supra*). In line with these findings, LIF has been shown to rescue damaged PAFs from de-

generation (Cheema *et al.*, 1994). Interestingly, LIF may also play a role, together with NGF, in promoting the sprouting of sympathetic neurones into the PAF following PAF injury (Thompson and Majithia, 1997) (Section 8.2.4.2).

#### 11.3.4.2. NGF and processes of regeneration in GAP 43-Positive C fibres

Following lesions of C fibres, a reduced provision of NGF to their DRG results in an alteration of their phenotype (Section 8.2.6). Correspondingly an eventual reaccess to NGF may play a role both in the restitution of a normal phenotype and in mechanisms underlying their regeneration. As discussed above (Section 11.3.4.1), Schwann cells constitute a rich source of NGF, and exogenous NGF administration was reported to reduce the transganglionic degeneration of C fibre terminals in the DH provoked by axotomy (Fitzgerald *et al.*, 1985; McMahon and Bennett, 1997). Further, studies performed both *in vivo* and on cultured sensory neurones suggest that, via an action at TRK A receptors, NGF can increase the stability of GAP 43 and enhance growth in intact C fibres (Benowitz and Routtenberg, 1997; Leslie *et al.*, 1995; Mohiuddin *et al.*, 1995) (Section 11.3.1). The 'spreading' response elicited in developing, sensory neurones by NGF is also a GAP 43-dependent process (Aigner and Caroni, 1995). A more general role of NGF in encouraging PAF regrowth may also be derived from its promotion of the proliferation and migration of non-neuronal cells, thereby providing an environment conducive to regrowth and improving the irrigation of damaged PAFs. Further, there has been recent interest in the possibility that low affinity p<sup>75NTR</sup> receptors for NGF on Schwann cells are involved in 'constitutive' apoptosis, although it is still controversial as to whether their occupation by NGF suppresses or activates such processes (Bredesen and Rabizadeh, 1997; Dechant and Barde, 1997; Fu and Gordon, 1997).

Notwithstanding these observations, several phenotype changes in damaged PAFs are mediated *independently* of NGF (Section 8.2.6) and NGF is *not* likely to be an absolute (or sufficient) requirement for *initiating* the regeneration of damaged PAFs (Diamond *et al.*, 1987, 1992a). Notably, NGF was found *not* to modify GAP 43 expression following nerve transection (Vergé *et al.*, 1990). Further, in view of the initial loss of TRK A receptors and the *reduction* in access to NGF upon transection of PAFs, NGF is unlikely to be essential for *triggering* either GAP 43 expression or nerve regeneration *per se*. Indeed, there is even evidence to suggest that, under certain conditions, NGF may *retard* the regrowth of some damaged neurones, perhaps by mechanisms involving the induction of NO (Diamond *et al.*, 1987, 1992a,b; Gold and Spencer, 1993; Melino and Bernassola, 1997; Gold *et al.*, 1991, 1993). Thus, the significance of NGF for regenerative processes in damaged, adult C fibres remains unclear.

#### 11.3.4.3. Roles of GDNF and other trophic factors

As mentioned in Section 11.3.2, a substantial majority of small calibre PAFs display GAP 43 expression. Evidently, they cannot all be TRK A-positive, NGF-dependent cells. Indeed, a further population of fine calibre, nociceptive PAFs, characterized by the expression of P<sub>2X3</sub> receptor on their peripheral terminals, does *not* possess TRK A receptors (Sections 3.2.1. and 8.2.5). Rather, following an early developmental switch, these neurones become dependent on, and regulated by, GDNF. GDNF acts via a receptorial complex consisting of a GFR $\alpha$ -1 (GDNFR $\alpha$ ) binding site (of which multiple forms may exist), together with a further 'Ret' TRK protein product (Jing *et al.*, 1997; Kotzbauer *et al.*, 1996; Leclerc *et al.*, 1997; Liebl *et al.*, 1997; Molliver *et al.*, 1997). GDNF can prevent the degeneration of this population of PAFs following their injury. Thus, GDNF likely fulfils an important role in the protection, rescue and subsequent regeneration of certain classes of C fibre following their peripheral damage (Leclerc *et al.*, 1997; Matheson *et al.*, 1997; Naveilhan *et al.*, 1997). Studies of motoneurones suggest that mRNA encoding Ret and GFR $\alpha$ -1 is induced by nerve lesions, and GDNF may even be synthesized by injured motoneurones themselves, although such findings remain to be documented for sensory nerves (Naveilhan *et al.*, 1997).

As concerns those neurotrophins which act predominantly on *large* calibre PAFs (BDNF, NT 4/5 and NT 3), their roles remain comparatively obscure. Nevertheless, studies of central axons and motoneurones indicate that BDNF can improve their regenerative capacity and enhance the expression of growth-supporting molecules such as GAP 43 and tubulin (Fournier *et al.*, 1997; Kobayashi *et al.*, 1997b), raising the possibility that such actions may be exerted at injured, large calibre PAFs. Further, BDNF may fulfil a protective (autocrine) role in protecting sensory neurones in the DRG from degeneration (Acheson *et al.*, 1995). NT 3 (together with NGF) induces GAP 43 synthesis and neurite extension in cultured, sensory neurones and, *in vivo*, it encourages the regeneration of injured (NPY-containing), large calibre PAFs—as well as sympathetic neurones (Mohiuddin *et al.*, 1995; Molliver *et al.*, 1997; Sawai *et al.*, 1996; Sterne *et al.*, 1997; Tafreschi *et al.*, 1998) (Section 8.2.4.2). Further, TRK C receptors for NT 3 are up-regulated following damage to PAFs (Funakoshi *et al.*, 1993).

#### 11.3.4.4. Cellular adhesion and extracellular matrix molecules

Apart from growth factors, many other classes of molecule are involved in triggering and coordinating the regrowth of damaged (and intact) PAFs (Deller and Frotscher, 1997; Fu and Gordon, 1997; Smith *et al.*, 1993). In this regard, CAMs have attracted particular attention (Fields and Itoh-Kouichi, 1996; Fu and Gordon, 1997). As mentioned above, CAMs are released by Schwann cells and certain other cell types, and they play a generalized role in axonal regrowth and navigation by permitting the adhesion of axons to other axons, to Schwann cells and to

basement membranes, etc. Further, several CAMs are transiently induced in Schwann cells following PAF injury and, once PAF regrowth is achieved and axonal contact re-established, Schwann cell phenotype reverts to normal and their induction is terminated (Bunge, 1993; Fazeli and Walsh, 1996; Kolodkin, 1996). That is, the expression of CAMs may be 'axon damage-dependent'. One example of such a potentially-important CAM is provided by the recently-identified 'ninin', which is induced in Schwann cells (and DRG neurones) upon nerve injury and which promotes axonal growth (Araki and Milbrandt, 1996). Interestingly, CAMs are also transiently induced in the DH upon PAF transection (Bonfanti *et al.*, 1996) suggesting that they may also play a role in central processes of regrowth. CAMs also play an important role in facilitating the infiltration of injured nerves—and the adhesion to damaged PAFs—of monocyte-derived macrophages. These cells are key participants in the phagocytosis of the myelin of injured PAFs (Wallerian degeneration), a process which anticipates regenerative processes of injured PAFs (Brown *et al.*, 1997) (Section 11.3.4.1).

In addition to their structural roles, extracellular matrix molecules such as fibronectin and, in particular, laminin, may fulfil a more direct role in permitting the regeneration and navigation of injured PAFs following Wallerian degeneration (Cowen and Gavazzi, 1998; Diamond and Springer, 1994; Luckenbill-Edds, 1997). Certain actions of laminin appear, interestingly, to reflect a modulation of  $\text{Ca}^{2+}$  influx and  $[\text{Ca}^{2+}]_i$  levels in growth cones (Agius and Cochard, 1998; Kuhn *et al.*, 1998). Indeed, via interactions with GAP 43, calmodulin and various kinases, and in response to laminin and multiple types of stimuli, alterations in the levels of  $[\text{Ca}^{2+}]_i$  play an important and diverse role in controlling the morphology and behaviour of the growth cones of regenerating injured PAFs (Ghosh and Greenberg, 1995; Gu and Spitzer, 1995; Komuro and Rakic, 1996; Sjaastad and Nelson, 1997) (Sections 8.2.2.5 and 11.3.1).

#### 11.3.4.5. NO and neuropeptides

NO justifies brief mention inasmuch as its synthesis in PAFs is enhanced by their injury (Vergé *et al.*, 1992b; Xu and Wiesenfeld-Hallin, 1997), and since it plays an important role both centrally and peripherally in the modulation of nociception (Sections 3.2.8.3 and 7.5.2.5). Schwann cells provide an important source of NO which, by improving local blood flow and other actions, may indirectly improve the immediate environment for PAF regeneration. However, NO participates in processes underlying (apoptotic) cell death and, by virtue of its complex interactions with PAFs, Schwann cells and other tissues types, as well as with molecules such as NGF, NO likely exerts both beneficial and deleterious effects as concerns PAF recovery (Melino and Bernassola, 1997; Minghetti and Levi, 1998; Nishio and Watanabe, 1998; Zochodne *et al.*, 1997; Yonehara *et al.*, 1997).

As discussed in Section 8.2.5, the gene expression of many neuropeptides, such as VIP, PACAP, GAL

and NPY, is modified in damaged PAFs—as well as in sympathetic fibres (Jonakait, 1993). These neuropeptides exert a diversity of peripheral trophic actions which likely play an important role in creating an environment favourable for PAF regeneration (Hökfelt *et al.*, 1994) (Section 3.2.6).

#### 11.3.4.6. The interactive nature of regenerative mechanisms

To summarize, following transection of PAFs, peripheral nerve regeneration is probably indispensable for the subsequent regrowth and connectivity of their atrophied, central branches. Ultimately, both peripheral and central processes of regeneration play a key role in determining those changes in nociception which ensue upon PAF damage. Their further characterization should, thus, provide important insights into the mechanisms underlying neuropathic pain and its potential management. In this regard, many novel molecules, both intrinsic and extrinsic to injured PAFs, likely await discovery (Ambron and Walters, 1996; Camborieu *et al.*, 1998; Fu and Gordon, 1997; Kotzbauer *et al.*, 1996; Kolodkin, 1996; Nieto, 1996; Reinhardt *et al.*, 1994). Notably, recent evidence suggests that cooperative and convergent, mechanisms triggered by a multiplicity of factors, including neurotrophins, GAP 43, cytokines, CAMs, extracellular matrix molecules and neuropeptides may be of importance in determining the regeneration and functional activity of damaged PAFs (Diversé-Pierluissi *et al.*, 1997; Rozenburt, 1985; Yao *et al.*, 1997).

Notwithstanding the diversity of above-discussed mechanisms encouraging the peripheral regeneration of damaged PAFs, they do not generally regain their original configuration in (cutaneous) tissue. Rather, an alteration of their topography is associated with a reorganization of the RFs of DH neurones which become large and diffuse. These expanded RFs eventually coalesce into smaller, contiguous units and this process of central compensation may reflect a role of spinal NMDA receptors in strengthening synaptic input from specific areas of reinnervated tissue (Lewin *et al.*, 1994a). Further, such a retuning of DH synapses has been implicated in the reconstruction of cortical, somatosensory maps following peripheral nerve damage (Kaas, 1991). These findings further underpin the key role of NMDA receptors in the plastic response of the DH to PAF injury (Section 10.3).

### 11.4. Reorganization of PAF Input to the DH Following Injury: Overview of Functional Consequences for Nociceptive Transmission

The arrival of foreign, large calibre A $\beta$  fibres in laminae II following PAF injury (Section 11.2) may have profound functional consequences inasmuch as this organizational change is compounded by the transformation of their phenotype to a SP-synthesizing mode (Marchand *et al.*, 1994; Neumann *et al.*, 1996) (Section 8.2.5). Since damaged A $\beta$  fibres continue to produce EAAs, they now possess two key elements underlying the induction of sensitization in DH neurones (Section 10.3.2.1). Stimulation of A $\beta$

fibres will therefore, strengthen synaptic signalling and encourage response amplification at sensitized NS (and WDR) neurones bearing NMDA, AMPA, mGlu<sub>1</sub> and (up-regulated) NK<sub>1</sub> receptors in superficial DH laminae (Section 11.2). Further, the stimulation (or spontaneous ectopic firing) of A $\beta$  fibres will be misinterpreted as noxious. This abnormal pattern of signalling by A $\beta$  fibres likely contributes to both hyperalgesia and, most importantly, mechanical allodynia following PAF damage (Woolf and Doubell, 1994; Ma and Woolf, 1996b). Indeed, Molander *et al.* (1992) have shown that stimulation of A $\beta$  fibres can elicit c-fos expression in the DH following sciatic nerve damage, an effect normally seen only for C fibres. Other factors may also intervene in the enhancement of nociceptive transmission by errant A $\beta$  fibres. Thus, their re-routing to superficial laminae may allow them to 'escape' presynaptic inhibitory controls from ININs and descending pathways (Laird and Bennett, 1992; Wall, 1995). Further, following their re-orientation from deeper to superficial laminae, A $\beta$  fibres themselves will no longer be able to stimulate ININs, thereby contributing to a loss of inhibitory ININ tone and aggravating WDR neuronal sensitization in deep DH laminae (Section 10.7) (Fig. 2). In addition, there is limited evidence that regenerating, damaged C fibres may expand into deeper DH laminae in which case, they may also contribute to patterns of abnormal signalling and hyperalgesic states (Section 11.2).

### 11.5. Peripheral and Central Sprouting of Intact PAFs

#### 11.5.1. Sprouting of Intact Collaterals into Denervated, Peripheral Tissue: A Role for NGF

As mentioned in Section 11.3.4.2, the regeneration of *damaged*, sensory C fibres may *not* imperatively depend upon the availability of NGF (Diamond *et al.*, 1987, 1992b). However, developmentally, NGF augments the density of peripheral, thermosensitive nociceptors (Lewin and Mendell, 1994) and, under certain conditions, NGF plays a role in the reinnervation of denervated skin by adjacent, *intact*, cutaneous C fibres (Goodness *et al.*, 1997). This process can be reversibly interrupted by administration of antibodies against NGF (Mearow and Kril, 1995; Ro *et al.*, 1996). Indeed, there is an increase in levels of mRNA encoding NGF in denervated skin together with an induction of mRNA encoding TRK A and p75<sup>NTR</sup> receptors—as well as GAP 43—in the peripheral branches of sprouting neurones (Leslie *et al.*, 1995; Mearow *et al.*, 1994; Mearow and Kril, 1995). An elevation in the density of TRK A receptors on non-neuronal cells in the skin has also been documented (Terenghi *et al.*, 1997). These observations collectively suggest that the collateral, *peripheral* sprouting of *intact* C fibres, in *contrast* to the regeneration of their damaged neighbours—and in analogy to sympathetic neurone sprouting—is markedly NGF-dependent (Davis *et al.*, 1997a; Diamond *et al.*, 1987, 1992a,b; Kawaja *et al.*, 1997; Miller *et al.*, 1994).

An important question arises as to whether the sprouting of intact C fibres may be involved in changes in nociception. As concerns areas of denervated skin, there are indications from studies of sciatic ligation and the subsequent sprouting of adjacent, saphenous nerves that collaterals from the latter play a role in the accompanying hyperalgesia and allodynia. However, their contribution appears to be time- and response-dependent and may depend upon a continuing, sensitizing input to the DH from the damaged sciatic nerve itself (Ro and Jacobs, 1993; Sotgiu *et al.*, 1996; Tal and Bennett, 1994). A related question concerns the 'extra-territorial' hyperalgesia and allodynia evoked from the adjacent area of skin innervated by the intact saphenous nerve itself (Tal and Bennett, 1994). Since saphenous and sciatic nerves are subserved by largely *separate* spinal ganglia, mechanisms of inter-nerve communication cannot be involved (Section 8.2.3) and it appears that capsaicin-sensitive fibres of the saphenous nerve mediate this increased nociception from their *own* territory (Mansikka and Pertovaara, 1997b; Sotgiu and Biella, 1997; Tal and Bennett, 1994). While the underlying mechanisms remain unclear, there is no evidence for supersensitivity of saphenous PAFs *per se*. It is, thus, possible that widespread, intersegmental mechanisms of disinhibition and sensitization in the DH (Sections 9.1.4.2, 10.3 and 10.6) are triggered via damage to the sciatic nerve. This may lead to either:

1. secondary alterations in the activity of saphenous nerve via antidromic mechanisms described in Section 9.1.4.2;
2. an increase in the responsiveness of WDR neurones in the DH receiving nociceptive input from the saphenous nerve (Mansikka and Pertovaara, 1997b; Sang *et al.*, 1996; Sotgiu and Biella, 1997).

These observations may, thus, provide a special case of the phenomenon of 'referred' pain discussed in Section 9.1.4, and they likewise implicate central processes of sensitization in the DH.

As indicated in Section 11.5.2, it is possible that changes in nociception (allodynia) from the region bordering the sciatic nerve-denervated area involve the collateral, *central* sprouting of saphenous A $\beta$  afferents in the L4 segment of the DH (Doubell *et al.*, 1997).

Interestingly, Leslie *et al.* (1995) reported that the increase in NGF levels evoked by inflammation upregulates GAP 43 in the peripheral terminals of C fibres. This observation correlates well with a role of NGF/GAP 43 in the collateral sprouting of *intact* nerves into denervated skin (Section 11.5) and raises the possibility of a reorganization of the C fibre innervation of inflamed tissue.

#### 11.5.2. Collateral Sprouting of Intact PAFs to the DH

The reorganization of synaptic architecture in the DH following peripheral axotomy appears *primarily* to reflect central re-innervation by *damaged* axons (those with regenerating peripheral branches). The collateral sprouting ('reactive synaptogenesis') of intact PAFs has long been considered rare (Chong *et al.*, 1994; Coggeshall, 1994; Doubell *et al.*, 1997;

Knyihar-Csillik and Török, 1989; Knyihar-Csillik *et al.*, 1990; McMahon and Kett-White, 1991; Pubols and Bowen, 1988). This contention is largely based on early studies in which the peripheral regeneration of surgically-destroyed nerves was artificially prevented. Under these conditions, the virtual disappearance of PAF markers, such as fluoride-resistant acid phosphatase, was indefinitely maintained (Devor and Claman, 1980). In line with these findings, other studies indicated that the loss of DH pools of SP following peripheral nerve injury was permanent, likewise indicating a lack of collateral sprouting, at least of C fibres (Shehab and Atkinson, 1986a,b; Barbut *et al.*, 1981). Further, the 'priming' or 'conditioning' of PAFs by injury to their peripheral branches is, generally, necessary for the triggering of their sprouting into the DH territory of an adjacent nerve (McMahon and Kett-White, 1991; Pubols and Bowen, 1988).

Other studies have, nevertheless, raised the possibility that a subpopulation of *non-injured* nerves may sprout into DH regions vacated following injury to an *neighbouring* nerve (Coggeshall, 1994; Doubell *et al.*, 1997).

1. Neurotoxic (intraneural pronase) lesions of PAFs initiated the collateral sprouting of *undamaged*, adjacent nerves to regions outside their normal, somatotropic DH territories in certain—though not all—studies (LaMotte *et al.*, 1989; LaMotte and Kapadia, 1993).
2. Capsaicin-induced destruction of C fibres in the sciatic nerve elicits the (non-collateral) sprouting of A $\beta$  fibres into lamina II regions vacated by degenerating C fibres (Mannion *et al.*, 1996).

This observation suggests that 'priming' of A $\beta$  fibres may *not* be imperative for their central sprouting. Indeed, Doubell *et al.* (1997) recently showed that, following injury to the sciatic nerve, a subpopulation of saphenous, myelinated A $\beta$  fibres sprouts, in a dorsoventral plane, into the lateral part of lamina II which is normally occupied by sciatic terminals. Assuming that these A $\beta$  fibres contact those NS cells in lamina II which are normally targetted by C fibres input, this may contribute to the hypersensitivity/allodynia seen at the border of denervated skin (Section 11.5.1).

Genuine collateral sprouting of intact PAFs into DH territories of adjacent nerves appears, therefore, to be limited and uncommon. Nevertheless, these observations indicate that *intact*, myelinated PAFs *do* have the capacity to sprout following damage to C fibres or adjacent nerves. The induction of intracellular factors required for PAF sprouting may *not*, thus, be critically dependent upon their damage. Indeed, the nature of those intrinsic and extrinsic mechanisms which permit the central sprouting of *intact* as compared to injured PAFs would be of interest to delineate. The sprouting of descending serotonergic neurones following PAF damage (Marlier *et al.*, 1992) (Section 10.8.3) further indicates that injury to neurones themselves may *not* be critical for the initiation of processes underlying their regrowth. Whether intact C fibres sprout collaterally in the DH remains to be determined.

## 11.6. Surgical and Chemical Destruction of PAF Input into the DH

### 11.6.1. Surgical Interruption of PAF Input to the DH via Lesions Proximal to the DRG

There are several important differences between the effects of distal, peripheral nerve axotomy and those of PAF transection *proximal* to the DRG (that is, on the DH side). Thus, transection of PAFs proximal to the DRG leads neither to degeneration of cells bodies in the DRG, nor to growth of their peripheral branches. Moreover, sectioned, central terminals immediately disappear and the regenerating central processes of their DRG cells generally do *not* re-gain access to the DH. This likely reflects a variety of external and internal factors including a relative lack of GAP 43, which is necessary for *sustained, long axon growth* (Chong *et al.*, 1994; Ramakers *et al.*, 1997). Further, the barrier of glial cells in the dorsal re-entry zone of the DH physically prevents access of PAFs to the DH. Indeed, in contrast to neurotrophin- and CAM-rich Schwann cells (the peripheral environment of regenerating PAFs) (Section 11.3.4.1), DH-localized oligodendrocytes and astrocytes are hostile to axonal re-entry and re-growth due to their expression and display of molecules inhibitory to growth cones (Golding *et al.*, 1997; Kolodkin, 1996; Kozlova *et al.*, 1995; Lekan *et al.*, 1997; Olson, 1997; Schwab, 1990, 1996; Stensaas *et al.*, 1987; Tessler *et al.*, 1988; Weiss *et al.*, 1996). Under these conditions of complete and rapid loss of PAF input to the DH, then, the contribution of structural changes to pain *differ* from those provoked by *peripheral* nerve lesions.

Observations of PAF markers, such as CGRP and fluoride-resistant acid phosphatase, indicate that, under these conditions, the collateral sprouting of *intact*, unmyelinated PAFs and myelinated A $\beta$  fibres into deafferented, superficial DH regions does occur (Lekan *et al.*, 1997; LaMotte *et al.*, 1989; McMahon and Kett-White, 1991; McNeill *et al.*, 1990; McNeill and Hulsebosch, 1987). Correspondingly, a reappearance of lost synapses has been documented (Chung *et al.*, 1989). Thus, the occurrence of spontaneous pain and the continued (or even increased) responsiveness of DH neurones to high intensity, sensory input *despite* the loss of original PAF input may be explained by several mechanisms:

1. sensitization of DH neurones triggered by the transient and intense activation of PAFs upon their injury;
2. a reduction in ININ tone reflecting the loss of facilitatory PAF input and their partial excitotoxic degeneration: this leads to chronically-disinhibited, spontaneously-active and hyperexcited neuronal circuits in the DH;
3. supraspinal mechanisms of sensitization and an enhancement of descending facilitation; and
4. a novel source of sensory PAF input to denervated DH neurones from collaterally sprouted intact nerves.

The mechanisms underlying the collateral sprouting of intact neurones under these conditions remain to be examined (Fu and Gordon, 1997; Jansc  and



Lawson, 1990; Kapadia and LaMotte, 1987; LaMotte *et al.*, 1982). As concerns the increased sensitivity of DH neurones, it is possible that an elevation in the DH density of NK<sub>1</sub> and CGRP receptors is involved (Coggeshall and Carlton, 1997). Further, an increase in the density and Ca<sup>2+</sup>-permeability of AMPA receptors in the DH may also be implicated in the enhanced sensitivity of DH neurones (Section 10.3.2.1).

#### 11.6.2. Chemical Destruction of Small Calibre C Fibres by Capsaicin

As discussed in Section 9.1, the acute, cutaneous application of capsaicin sensitizes nociceptive neurones in the DH and provokes a A $\beta$  fibre-mediated mechanical allodynia in a manner similar to that seen for painful states due to inflammation of PAF injury.

The *permanent* elimination of small calibre C fibres by developmental treatment with capsaicin leads to a variety of neuroplastic changes, including an increase in the spontaneous activity and RF size of DH neurones. These effects can be inhibited by antagonists at NMDA receptors indicating their involvement in mediating DH sensitization under these conditions (Chiang *et al.*, 1997). The destruction of C fibres by capsaicin results in a pronounced decrease in thermal sensibility and a loss of peripheral NI. Further, the administration of capsaicin markedly depletes TRK A and vanilloid receptors and reduces SP and CGRP levels in nociceptive, small calibre PAFs in parallel with an induction of GAL, VIP and NO synthase (Farkas-Szallasi *et al.*, 1995; Kashiba *et al.*, 1997; Xu *et al.*, 1997c; Vizzard *et al.*, 1995). These changes resemble those seen upon peripheral nerve damage (Höckfelt *et al.*, 1994) (Section 8.2.5). An induction of GAP 43 synthesis has also been observed, as well as a (NGF-reversible) reduction in axonal flow, effects likewise common to peripheral nerve damage (Kashiba *et al.*, 1997; Taylor *et al.*, 1985) (Sections 8.2.5 and 11.3.2). Further, NGF can protect against and restore the changes in neuropeptide content and function provoked by capsaicin treatment (Donnerer *et al.*, 1996). The marked and sustained disappearance of C fibre terminals in the DH following capsaicin treatment suggests that they do not recover. However, in analogy to the surgical destruction of PAFs, the capsaicin-induced lesioning of C fibres may be a sufficient stimulus to trigger A $\beta$  fibre sprouting into lamina II (Mannion *et al.*, 1996) (Section 11.2).

Notwithstanding these similarities to peripheral nerve injury, there are several distinctive differences between capsaicin treatment and surgical damage to PAFs. For example, capsaicin administration does not modify the levels of somatostatin, which is contained in a population of small calibre PAFs differing to those expressing VIP, GAL or CGRP (Farkas-Szallasi *et al.*, 1995, 1996; Höckfelt *et al.*, 1994; Kashiba *et al.*, 1996, 1997). Additional comparisons of the functional and neurochemical consequences of selective, neurotoxic destruction of C fibres, as compared to surgical axotomy of peripheral nerves (containing all classes of PAF) should

yield novel insights into mechanisms controlling PAF phenotype, regrowth and the modulation of nociception.

## 12. NOCICEPTIVE AND NEUROPATHIC PAIN: PROCESSES OCCURRING IN SUPRASPINAL CENTRES

### 12.1. Sensitization of Neurones in the S I and Thalamus

Central adaptive responses to nociceptive and neuropathic pain, involving alterations in neuronal responsiveness together with a reorganization of patterns of synaptic connectivity, are not restricted to the DH. They may likewise occur in supraspinal centres (Besson *et al.*, 1995; Castro-Alamancos, 1997; Darian-Smith and Gilbert, 1995; Faggin *et al.*, 1997; Guilbaud and Benoist, 1995; Guilbaud *et al.*, 1994; Pettit and Schwark, 1996; Sherman and Guillery, 1996; Zhang and Rowe, 1997). As yet, data are limited but there is evidence that such changes occur both at the cortical level as well as in several thalamic nuclei, including the 'ventrobasal complex' (VPL/VPM), the nucleus centrolateralis of the intralaminar thalamus and several components of the medial thalamus—although no data appear, as yet, to be available for posterior thalamic nuclei (Guilbaud *et al.*, 1994; Ralston *et al.*, 1995). For example, the induction of acute hind-limb inflammation by carrageenin increases the responsiveness of S I and thalamic neurones to stimulation of the inflamed joint in parallel with an increased responsiveness of DH neurones and of joint nociceptors. These changes evolve in synchrony with the development of hyperalgesia and can be reversed by administration of anti-inflammatory agents into the treated joint (Guilbaud *et al.*, 1986, 1994; Hoheisel and Mense, 1989; Mense, 1993). Alterations in peripheral sensitivity are, thus, reproduced in supraspinal centres responsible for the sensation of pain and, in line with such an onward transmission of changes in sensitivity, it has been shown that an increased excitability of thalamic neurones is accompanied by a potentiation in responses at the cortical level (Lee and Ebner, 1992). Further, the existence of bi-directional circuits interconnecting the thalamus and cortex allows for the reciprocal modulation of their activity (Eaton and Salt, 1995; Gil and Amitai, 1996a,b; Nothias *et al.*, 1988).

### 12.2. Adaptive Changes in Higher Centres

#### 12.2.1. Distinctive Changes in Supraspinal Structures

The above-mentioned findings might be considered to imply a 'domino-like' phenomenon whereby peripheral increases in sensitivity are progressively transferred to higher levels of processing in a comparatively unmodulated fashion. However, the sequential, supraspinal transfer of nociception should *not* be regarded as a purely passive process inasmuch as several studies have provided evidence that supraspinal changes in nociceptive processing, in particular in the S I, may occur *differentially* to those in downstream structures (Dong and Chudler,

1995; Guilbaud *et al.*, 1994; Guilbaud and Benoist, 1995; Sherman *et al.*, 1997a).

#### 12.2.2. Adaptive Changes at the Cortical Level (S I)

Further evidence for changes in higher centres has been obtained in studies of the long-term effects of arthritic inflammation of the joint, and of peripheral nerve damage (Guilbaud *et al.*, 1994; Schaible and Grubb, 1993; Schaible and Schmidt, 1988). Thus, in a neuropathic model of sciatic ligation (2 weeks following injury), the responsiveness of thalamic and S I neurones to mechanical and cold thermal stimuli of the paw was amplified (cf allodynia) and the S I displayed a reorganization of somatic input. Moreover, there was an increased participation from the saphenous nerve—though this change may have been secondary to an abnormal position or gait of the paw rather than reflecting the peripheral or central sprouting of saphenous nerves (Guilbaud *et al.*, 1990, 1992; Guilbaud and Benoist, 1995) (Section 11.5.1).

There is evidence that the *superimposition* of distinctive, adaptive changes at higher levels can either accentuate, or attenuate, changes in neuronal responsivity. Notably, one class of S I neurone has been described in the primate for which the adaptive (sensitized) response to sustained noxious thermal stimulation is *less* marked than in either the thalamus or DH, indicating the involvement of counter-adaptive processes (Kenshalo *et al.*, 1979, 1980; Kenshalo and Isensee, 1983; Dong and Chudler, 1995). Instructive results were also acquired in a model of chronic (3 weeks) arthritic inflammation of a single hind-paw. In contrast to normal rats, mild mechanical stimulation of the joints and contiguous skin activated neurones in both thalamic and S I neurones (Dostrovsky and Guilbaud, 1990; Lamour *et al.*, 1983; Guilbaud *et al.*, 1994; Schaible and Grubb, 1993). Further, in the studies of Lamour *et al.* (1983) several excitatory changes detected in the thalamus, including paroxysmal discharges, responsiveness to brushing of the skin, and after-discharges exceeding the duration of stimulation were *not* detected in S I of the cortex. These observations also suggest the overlay of additional processes at the S I cortical level *moderating* the intensity and extent of sensitization. In support of the contention that cortical adaptivity does *not* merely mimic antecedent changes in the thalamus, there was a striking displacement of the laminar, topographic organization of the responsiveness of NS and WDR cortical neurones. Whereas these were normally encountered in the infragranular layer, they became apparent in lamina V which otherwise contains NON-N neurones (Lamour *et al.*, 1983). Further, many S I neurones developed bilateral RFs as compared to the contralateral RFs seen in normal animals. Corticospinal neurones have also been shown to display functional and structural changes upon PAF damage (Tseng, 1996) and a functional reorganisation of the cortex has been documented following injury to PAFs mediating other modes of sensory input (Darian-Smith and Gilbert, 1995; Pons *et al.*, 1991; Zhang and Rowe, 1997).

The above findings strongly suggest that nociceptive input may initiate distinctive patterns of *cortical* adaptation, possibly involving novel patterns of synaptic strength or connectivity, in analogy to the marked influence of other modes of sensory input upon cortical function (Darian-Smith and Gilbert, 1995; Pons *et al.*, 1991; see Zhang and Rowe, 1997, Section 14). Further, they suggest that the further elaboration of adaptive changes at the cortical level can lead to a *reduction* in alterations in sensitivity as compared to the DH and thalamus (Hsu and Shyu, 1997). Nevertheless, a recent discussion of comparative changes in the thalamus and S I in response to noxious stimulation (Guilbaud and Benoist, 1995) has pointed out that some changes may be *more* pronounced in the S I than in the thalamus, suggesting a further *amplification* of increases in sensitivity. Indeed, the involvement of EAAs and NMDA receptors in the transfer of nociceptive information via thalamocortical and intracortical networks provides a mechanistic basis for processes of rapid sensitization and more prolonged forms of synaptic plasticity at the cortical level (Section 12.3.3).

To summarize, the question of comparative changes in neuronal responsiveness at the cortical and thalamic as compared to spinal level requires further examination. Nevertheless, it is evident that the S I, thalamus and other higher centres do *not* merely behave as passive recipients and relayers of information from the DH. Rather, they are themselves involved in the further integration of adaptive, neuronal changes in acute and chronic painful states due to either inflammation or peripheral nerve damage (Sherman and Guillery, 1996).

#### 12.2.3. Adaptive Changes at the Thalamic Level

In this light, there is also evidence for distinctive, adaptive changes at the level of the thalamus in response to alterations of sensory input (Faggini *et al.*, 1997; Guilbaud *et al.*, 1989b; Nicolelis *et al.*, 1993; Sherman *et al.*, 1997a,b). For example, as discussed in Sections 9.2.1 and 13.4, a disruption of the interaction between thermosensory and cold channels in thalamic posterior nuclei may contribute to cold allodynia (Craig *et al.*, 1996). Indeed, such forms of 'thalamic' pain may reflect organizational (possibly structural) and adaptive changes triggered by damage to the thalamus itself, to the STT, to other ascending pathways or to PAFs (Ralston *et al.*, 1995) (Section 13). In support of the argument that changes in thalamic function triggered at the level of PAFs are expressed in a more complex fashion than can be accounted for by simple extrapolation of alterations in the activity of DH neurones, Nicolelis *et al.* (1993) showed that the anaesthetic block of tactile, mechanical information can immediately elicit distinctive, spatiotemporal alterations in the RFs and responsiveness of thalamic neurones. Further, Sherman *et al.* (1997a,a) have reported alterations in the response properties and RFs of thalamic neurones upon blockade of glycinergic ININ activity in the DH, supporting a role of thalamic (and cortical) changes in the mediation of allodynia. More persistent, and perhaps irreversible, alterations in thalamic

function may ensue upon prolonged alterations in peripheral nociceptive input. In view of the existence of somatovisceral convergence at the thalamic level, such changes may be pertinent not only to pain resulting from damage to the thalamus itself and from PAF injury, but also to the phenomenon of referred pain (Apkarian *et al.*, 1995) (Section 9.1.4.2).

#### 12.2.4. Other Structures

To summarize, distinctive patterns of adaptive changes in the response to acute and prolonged nociceptive and neuropathic pain occur in both the thalamic and S I. Further, adaptive processes in the cortex do *not* simply reproduce adaptive changes in subcortical structures (Faggin *et al.*, 1997). The occurrence of such distinctive, supraspinal changes is consistent with a role of EAAs/NMDA receptors as transmitters/receptors in ascending projections to the thalamus, in thalamocortical projections and in intracortical pathways, as well as with a modulatory influence of GABAergic mechanisms upon thalamic and cortical sensory processing (Gil and Amitai, 1996b) (Sections 6.1.1, 12.3 and 14). Nevertheless, the underlying mechanisms require further elucidation. Further, an extension of such observations to other tissues would be of interest, in particular to those corresponding to the *affective* axis of nociceptive processing and sensation—the VPI/VMpo of the thalamus and the S II, anterior cingulate and insular cortices. Along these lines, Matsumoto *et al.* (1996) recently reported increases in spontaneous activity and responsiveness to mechanical stimulation in PBN neurones following chronic inflammation. This suggests that adaptive changes do, indeed, occur in supraspinal structures other than the thalamus.

### 12.3. Roles of Neurotransmitters in Adaptive Changes in Higher Centres

#### 12.3.1. GABA and EAAs

Many neurotransmitters involved in the cerebral processing of nociceptive information, and in the above-described patterns of adaptive changes in supraspinal centres, likely remain to be identified. However, based on observations in the DH (Sections 10.3 and 10.6), it is not unreasonable to suspect an involvement of GABA and NMDA receptors.

#### 12.3.2. GABAergic Mechanisms

The importance of GABAergic ININs in suppressing neuronal excitability (Zhang *et al.*, 1997d) and in negatively controlling nociceptive output from both thalamic relay and cortical neurones should be underlined (Kao and Coulter, 1997; Kapur *et al.*, 1997; Kim *et al.*, 1997a; Paré *et al.*, 1991; Roberts *et al.*, 1992; Oliveras and Montagne-Clavel, 1994; Alloway *et al.*, 1989) (Section 6.2.3.). Indeed, as described in Section 13.3., the interruption of GABAergic transmission in the cortex or thalamus can provoke pain and expand RFs (Dykes *et al.*, 1984; Hicks *et al.*, 1986), while antagonism of local GABAergic receptors increases the RF size of neurones in the gracile nucleus (Berkley, 1997). Further,

a reduction in the inhibitory control of thalamic input to the cortex by cortical ININs may trigger synchronized, widely-dispersed, excited, seizure-like circuits (Contreras *et al.*, 1997).

In analogy to processes occurring in the DH (Section 10.6), thus, a disruption of GABAergic transmission in the thalamus or other cerebral structures may *disinhibit* the transfer and modulation of nociceptive information and contribute to painful states. A degeneration of GABAergic ININs might, in theory, be provoked by an excessive, excitotoxic release of EAAs from an overactive STT, other sources of nociceptive input or corticothalamic pathways (Ralston *et al.*, 1995). Alternatively, one might argue that, in an opposite fashion, a *loss* of an excitatory input from the STT onto thalamic GABAergic ININs following peripheral nerve damage may result in a *temporary* and reversible diminution in their activity (Section 10.6.2). As yet, no concrete data are available in this regard (Ralston *et al.*, 1995).

Indeed, it remains to be determined whether events in peripheral nerves can transiently or permanently disable the activity of GABAergic—or other classes of—ININ in the thalamus and/or cortex. Nevertheless, thalamocortical pathways involved in the synchronization of neocortical activity, as well as intrinsic cortical and thalamic networks themselves, may be involved in the generation of burst-like activity following breakdown of GABAergic inhibition. It might be speculated, then, that, in analogy to the DH (Sections 9.1.4.2 and 10.6), neuronal disinhibition provoked by the discrete or generalized loss of supraspinal GABAergic tone may set off reverberatory firing patterns in cerebral nociceptive circuits (Ben-Ari *et al.*, 1997; Bramham *et al.*, 1996; Berzaghi *et al.*, 1995; Castro-Alamancos and Connors, 1996; Crick and Koch, 1998; Forti *et al.*, 1997; Witte *et al.*, 1997; Zhuo *et al.*, 1997b—though see Liu *et al.*, 1991) (Section 13.3).

#### 12.3.3. EAAs, NMDA and MGlu Receptors

Both NMDA and group I MGlu receptors are involved in the induction and maintenance of processes of sensitization in the DH (Section 10.3). Further, via the induction of LTP and other processes, NMDA—and, under certain conditions, group I mGlu-receptors play a key role in modulating synaptic plasticity in the hippocampus and other cerebral structures (Bliss and Collingridge, 1993; Bortolotto *et al.*, 1994; Huber *et al.*, 1998; Martin and Morris, 1997; McEachern and Shaw, 1996; Vickery *et al.*, 1997) (Section 10.2.1). These observations suggest that NMDA and, possibly, group I mGlu receptors may mediate adaptive events in the thalamus and other higher centres underlying prolonged, painful states. In line with this contention, NMDA (and group I mGlu) receptors fulfil a crucial role in the excitation of thalamic neurones: by

1. direct nociceptive input from the STT and other ascending pathways;
2. corticothalamic circuits; and
3. nociceptive input received via other regions involved in the integration of nociceptive information, such as the PAG (Dougherty *et al.*, 1996;

Eaton and Salt, 1995, 1996; Kao and Coulter, 1997; Salt and Eaton, 1995; Vaccarino *et al.*, 1997).

In addition, NMDA receptors play a major role in thalamocortical transmission of sensory information (Isaac *et al.*, 1997), and the stimulation of thalamocortical afferents can evoke a NMDA-receptor dependent form of LTP in the cortex (Castro-Alamancos, 1997; Castro-Alamancos and Connors, 1996) (Section 6.2.3).

The above observations are consistent with the notion that NMDA receptors play a key role in sensitizing neurones in the thalamus, cortex and other supraspinal structures under conditions of excessive or prolonged nociceptive stimulation (Conti and Hicks, 1996; Salt *et al.*, 1995; Ralston *et al.*, 1995). Indeed, there is direct evidence that NMDA receptors in the thalamus are involved in the development and maintenance of inflammatory hyperalgesia, possibly via mechanisms involving the induction of NO, c-fos or nuclear transcription factors (Bester *et al.*, 1997; Do *et al.*, 1994; Kolhekar *et al.*, 1997; Lin *et al.*, 1997c; Redburn and Leah, 1997). Indeed, NO may itself modulate responses to sensory input and EAAs in the thalamus (Shaw and Salt, 1997).

Administration of COX inhibitors to the PAG elicits antinociception, an action reflecting the activation of descending pathways to the DH (Vanegas *et al.*, 1997) (Section 5). Further, activation of NMDA receptors can increase the cerebral production of PGs via the activation of COX 2 (Miettinen *et al.*, 1997) (Section 3.2.8.4). This mechanism is triggered in cortical neurones by 'spreading depression', a process implicated in the induction of migraine blockade (Sections 4.7 and 7.9). These findings suggest a possible interplay between cerebral populations of NMDA receptor and PGs in processes underlying painful states, an issue requiring further evaluation.

#### 12.3.4. Other Potential Mediators

As proposed in Section 14, the neurotrophin, BDNF, which displays reciprocal interactions with NMDA and GABAergic receptors, is an attractive candidate for a modulatory role in nociceptive transmission in the cortex and/or other supraspinal regions (Berninger and Poo, 1996; Gwag *et al.*, 1993; Li *et al.*, 1994; Marty *et al.*, 1997). Interestingly, there is recent evidence that GAP 43, an intrinsic component of neuronal terminals involved in axonal growth and regeneration (Section 11.3.2), may be able to induce LTP (Namgung *et al.*, 1997). This suggests that it may play a more rapid and multifarious role in remodelling central synaptic transmission than has hitherto been assumed.

As discussed in Section 4.8, a possible role of cytokines, such as IL-1 $\beta$  and TNF $\alpha$ , in the modulation of sensory processing in the cortex and other higher tissues must be evoked. For example, TNF $\alpha$  can enhance EAA-mediated ion currents and IL-6 modulates the response to sensory input of neurones in the S I region of the cortex (Grassi *et al.*, 1994; Oka *et al.*, 1995; Shin *et al.*, 1997). It is also likely

that neuropeptides are involved in adaptive processes in higher centres.

Data concerning plastic changes at higher levels, and the neurotransmitters and other factors involved in their mediation, clearly remain fragmentary and require considerable clarification.

### 13. PAIN DUE TO CNS DAMAGE: CENTRAL PAIN

#### 13.1. The Pathological Origins of Central Pain

Central pain—the pain provoked by damage to (or a dysfunction of) the CNS itself—displays a diversity of pathologies. For example, stroke-induced ischaemic damage, multiple sclerosis, malignant disease and Parkinson's disease (Boivie, 1994; Boivie and Östeberg, 1995; Bowsher, 1996; Chulder and Dong, 1995). Onset of pain following injury may be immediate or delayed (months). Although there may be a 'hypoalgesia' to some stimulus modalities, spontaneous pain and abnormal sensations of temperature are characteristic, in particular cold allodynia. A dysfunction of the posterior region of the thalamus (VMpo nuclei) may play a crucial role in this regard (Sections 9.2.4 and 13.4). 'Thalamic' pain is *not*, nevertheless, synonymous with 'central' pain which, as implied by its multiple origins, does not invariably involve damage to the thalamus itself. For example, damage to the STT can result in deficits in nociceptive and thermosensory sensation, as well as pain (Casey *et al.*, 1996a). Pain resulting from damage to the STT (which provides nociceptive input to the thalamus) might be considered as analogous to the pain caused by damage to PAFs (which transmit nociceptive information to the DH). Indeed, several potential mechanisms underlying central pain resemble those spinal events involved in the induction of pain due to peripheral nerve injury. Notably, in analogy to the reduction in GABAergic tone in the DH upon PAF injury (Section 10.6), a dysfunction of thalamic or cortical GABAergic inhibitory mechanisms, thereby disinhibiting local and remote nociceptive circuits, may be involved in the induction of central pain.

#### 13.2. A Model of Pain Due to Spinal Damage: Loss of GABAergic Inhibition in the DH

A photochemically-induced, ischaemic lesion of the spinal cord elicits a mechanical allodynia resembling that associated with peripheral nerve injury (Hao *et al.*, 1992, 1996a,b; Zhang *et al.*, 1994a). Following this manipulation, WDR neurones in the DH display a prolonged and enhanced response to electrical or innocuous, mechanical stimulation, whereas their response to thermal stimuli is normal. This suggests that a perturbation of A $\beta$  fibre input and/or processing underlies the mechanical allodynia which can, further, be attenuated by AMPA antagonists. The GABA<sub>B</sub> agonist, baclofen, also reverses both allodynia and the abnormal responsiveness of WDR neurones, suggesting that their enhanced excitability and the accompanying allodynia reflect a loss of GABAergic inhibition in the DH. In line with

this hypothesis, ischaemia has been shown to decrease both GABA levels in the spinal cord, and the number of GABAergic cells in laminae I and II (Zhang *et al.*, 1994a; Martiniak *et al.*, 1991). Interestingly, NMDA antagonists, such as dizolcine, prevent these behavioural changes. Although this finding might be taken as evidence that an excitotoxic action of EAAs is involved in the damage of GABAergic ININs, the underlying mechanisms remain unclear. Further, the loss of GABAergic neurones is *transient* and they recover in parallel with the disappearance of allodynia, suggesting that they do *not* irreversibly degenerate (Hao *et al.*, 1996a; Zhang *et al.*, 1994a) (Section 10.6).

In a small population of lesioned animals, a more chronic mechanical allodynia develops. This is irreversible to baclofen but naloxone-reversibly inhibited by the CCK<sub>B</sub> antagonist, CI 988, which also enhances morphine antinociception. This provides a further parallel to peripheral nerve damage in suggesting that an upregulation of the activity of CCK-containing neurones in the DH—or PAF terminals—interferes with an endogenous, opioidergic tone inhibiting pain and allodynia (Xu *et al.*, 1994; Section 3.2.6). The inhibition of this mechanical allodynia by A<sub>1</sub> agonists provides a further parallel to models of PAF injury (Section 3.2.8.2) (Sjölund *et al.*, 1998).

### 13.3. Reduced GABAergic Transmission in the Thalamus and Cortex: Burst Firing and Reverberatory Circuits

Disinhibitory mechanisms involving a loss of GABAergic tone may play a more general role in the induction of central, painful states. Indeed, the GABA<sub>A</sub> antagonist, picrotoxin, elicits pain-like behaviour upon local introduction both into the trigeminal nucleus (the cerebral homologue of the DH) and the 'ventrobasal complex' of the thalamus, wherein GABAergic mechanisms modulate the output of thalamocortical pathways running to the S I (McCormick, 1992; Roberts *et al.*, 1992; Sakai *et al.*, 1979; Oliveras and Montagne-Clavel, 1994; Tasker, 1990) (Section 12.3.2). The GABA<sub>B</sub> antagonist, bicuculline, also alters RFs and neuronal responsiveness upon application into the thalamus (Hicks *et al.*, 1986). Further, a lesion-induced, neuronal loss (presumably of ININs) in the thalamus has been shown to modify sensory responsiveness therein (Kayser *et al.*, 1985).

These findings suggest that a dysregulation of GABAergic mechanisms in the thalamus may contribute to chronic pain states. Indeed, vascular lesions of the thalamus might result in a preferential loss of GABAergic ININs inasmuch as small ININs are particularly vulnerable to ischaemic damage triggered by activation of NMDA receptors coupled to increases in [Ca<sup>2+</sup>]<sub>i</sub>, NO and other mechanisms (Choi and Rothman, 1990; Lin *et al.*, 1997; Marcoux, 1994; Mattson and Mark, 1996; Solum *et al.*, 1997). In addition to damage to the thalamus itself, disruption of afferent input to the thalamus from the STT can elicit 'thalamic' pain (Boivie *et al.*, 1989; Bowsher, 1996). Thus, extrapolating from the hypothesized degeneration of GABAergic ININs

in the DH by the excitotoxic actions of EAAs released from injured PAFs (Section 10.6), one might speculate that a liberation of EAAs from intensely-activated, damaged STT fibres might similarly lead to a loss of GABAergic ININs in the thalamus. This possibility remains to be directly examined. An alternative hypothesis is that the STT physiologically *stimulates* GABAergic ININs. A loss of STT input following its damage might thus, result in a diminished GABAergic tone in the thalamus permitting the escape of nociceptive information transmitted by *other* pathways under GABAergic control (Section 12.3). In line with this possibility, the density of GABAergic dendrites is reduced in the thalamus following damage to the ML pathway (Ralston *et al.*, 1995).

Ralston *et al.* (1995) have generated a specific hypothesis concerning GABAergic ININs which may account for the pain arising from vascular damage to the thalamus or from lesions of the STT. They suggest that GABAergic modulation of sensory input in the thalamus is more pronounced for *innocuous*, mechanical input originating in the PSDC and accessing the thalamus via the ML than for nociceptive input derived from the STT. Lesions of the STT, by liberating synaptic targets, encourage sprouting of ML neurones into vacant sites. As a consequence, they escape GABAergic control and attain nocisponsive neurones which they would not normally target. This hypothesis clearly resembles the sprouting of A $\beta$  fibres into lamina II of the DH following PAF injury (Section 11.2). In addition, it is conceivable that ML fibres mediating nociceptive information from the viscera may be involved in such organizational changes and contribute to spontaneous pain and hyperalgesia (Section 6.1).

Neurones in S I and S II are also under GABAergic control (Alloway *et al.*, 1989) and application of picrotoxin to these regions provokes a pain-like behaviour which is accompanied by epileptic, electroencephalographic activity (Forti *et al.*, 1997; Oliveras and Montagne-Clavel, 1996). In analogy, iontophoretic application of GABAergic antagonists to nocisponsive, cortical neurones increases their RF size and provokes burst firing—this pattern of discharge being critical for persistent, epileptic-like, excitability changes (Alloway *et al.*, 1989; Forti *et al.*, 1997; Dykes *et al.*, 1984). The cortex also provides a reciprocal pathway to the thalamus, via the VMpo, which is likely subject to GABAergic inhibition. Thus, in analogy to the DH, a loss of GABAergic tone might set up a network of self-sustaining, excitatory and synchronized bursting circuits both intrinsic to and inter-connecting the thalamus and cortex and dispersing both ipsi- and contralaterally (Benardo, 1997; Ben-Ari *et al.*, 1997; Bramham *et al.*, 1996; Crick and Koch, 1998; Lytton *et al.*, 1997; Parker *et al.*, 1998; Plenz and Kitai, 1996; Steriade, 1998; Zhou *et al.*, 1997b; Zhang *et al.*, 1997d). Such changes would be analogous to epileptic seizures caused by a loss of ININ tone, and rhythmic, neuronal circuits triggered by ischaemic damage to the CNS (Berzaghi *et al.*, 1995; Castro-Alamancos and Connors, 1997; Forti *et al.*, 1997; Witte *et al.*, 1997—though see Liu *et al.*, 1991). These findings are of pertinence to clinical

observations of bursting-like patterns in the thalamus of patients with central pain (Lenz *et al.*, 1989). In this light, further, the utility of anti-epileptic and anti-convulsant agents, such as carbamazepine, felbamate, gabapentin and valproate, in the treatment of central and other neuropathic pain syndromes is of relevance. Although their mechanisms of action are unclear, they may suppress excitation in bursting populations of intrinsic neurones and thalamocortical/corticothalamic networks via their  $\text{Ca}^{2+}$ -/ $\text{Na}^{+}$ -channel blocking properties, strengthening of GABAergic tone and/or a reduction in GLU release (Fields *et al.*, 1997; Gee *et al.*, 1996; Hunter *et al.*, 1997b; Shimoyama *et al.*, 1997; Stanfa *et al.*, 1997; Tasker, 1990; Boivie *et al.*, 1989; Todorovic and Lingle, 1998).

Burst firing and the synchronous and cooperative activity of neural circuits may fulfil a *physiological* role in facilitating information transfer and response patterns in the cortex and other structures (Chergui *et al.*, 1997; Lisman, 1997; Lumer *et al.*, 1997). However, under *pathological* conditions, due to a loss of ININs, this may lead to excessively-active, sensitized circuits contributing to chronic pain (Chergui *et al.*, 1997; Crick and Koch, 1998; Lisman, 1997; Lumer *et al.*, 1997) (Sections 9.1.4.2 and 12.3.2).

#### 13.4. Disinhibition of Thalamocortical Pathways by Thalamic Damage: Cold Allodynia

One frequent complication of stroke-induced thalamic damage is cold allodynia. There is evidence that the cold allodynia associated with secondary hyperalgesia and PAF damage reflects activation of cold-sensitive C rather than A $\beta$  fibres (Sections 3.1.1 and 9.2.4). Such C fibres are also involved in mediating the cold allodynia due to vascular lesions of the thalamus. Information concerning cutaneous, cold stimuli originating in lamina I NS neurones is transmitted to the thalamus via the dorsal STT which targets the MDvc of the medial thalamus, which itself projects to the anterior cingulate cortex (Sections 6.2.2 and 6.3) (Dostrovsky and Craig, 1996; Craig *et al.*, 1996; Castro-Alamancos, 1997; Hsu and Shyu, 1997). On the other hand, thermosensory information pertaining to cold is mediated by A $\delta$  fibres running via the ventral STT to the VMpo of the posterolateral thalamus, and thence to the insular cortex. Craig *et al.* (1996) have shown that a conduction block of A $\delta$  fibres transmitting cold stimuli can elicit a cold allodynia mediated via cold-sensitive C fibres. Further, the syndrome of cold allodynia due to thalamic damage is invariably associated with vascular lesions of the thalamus incorporating the VMpo but *not* the medial thalamus. Craig *et al.* (1996) have postulated that a disinhibition of this latter channel is involved. Thus, under normal circumstances, A $\delta$  fibre-mediated thermosensory input to the VMpo *inhibits* activation of the medial thalamus by C fibre-mediated cold input. However, this modulatory influence is eliminated by lesion-induced damage to the VMpo. This possibility is supported by an acute, clinical model of cold allodynia in which a specific activation of the anterior cingulate cortex is seen

(Craig *et al.*, 1996). Interestingly, as pointed out in Section 6.2.2, the VMpo forms part of an inhibitory corticothalamic feedback loop, the dysregulation of which by damage to the VMpo, might also contribute to persistent cold allodynia (Nothias *et al.*, 1988).

Whether a comparable disruption of thalamic integration between thermosensory and pain signalling underlies cold allodynia due to events at the level of peripheral nerves would be of interest to determine. Although no pertinent data are, as yet, available, it is conceivable that the overactivation of the thalamo-cingulate pathway in cold allodynia involves the disabling of GABAergic or other types of ININ interconnecting the VMpo and the medial thalamus. In this light, it is of note that the novel anticonvulsants, lamotrigine, felbamate and gabapentin, inhibit cold allodynia in rodents. Their effects likely involve an (indirect) potentiation of GABAergic transmission, although other actions, such as an inhibition of GLU release and blockade of  $\text{Ca}^{2+}$ -channels may also be involved (Section 8.2.2).

#### 13.5. Mechanisms Involved in the Response of the Thalamus and other CNS Tissues to Injury

As for peripheral nerve injury (Section 11), important insights into processes underlying central pain will likely be gained by an improved understanding of mechanisms underlying both neuronal damage and neuronal *recovery*. A brief consideration of certain of the factors involved in the response to thalamic injury is, thus, justified (Aguayo, 1985; Ambron and Walters, 1996; Marty *et al.*, 1994; Minghetti and Levi, 1998; Olson, 1997; Schwab, 1996). Indeed, there is preliminary evidence that GAP 43, neurotrophins, other growth factors, cytokines, NO and PGs all play a significant role in the response of cerebral tissue to injury, in analogy to their important functions in the periphery upon PAF damage (Deller and Frotscher, 1997; Ebadi *et al.*, 1997; Fu and Gordon, 1997; Lin *et al.*, 1997; Minghetti and Levi, 1998; Olson, 1997) (Sections 8 and 11).

Lesions of the thalamus induce the expression of GAP 43, the activation of which encourages neuronal growth, coordinates the reorganization of synaptic connectivity and enhances the capacity of neurones to respond to trophic factors such as NGF (Benowitz and Routtenberg, 1997). Indeed, as concerns regenerative changes following thalamic injury, the induction of GAP 43 by individual neurones is proportional to their ability to regenerate their axons. Further, the targetted over-expression of GAP 43 can elicit sprouting following lesions to the CNS, and GAP 43 can also modify the efficacy of transmission at synapses displaying LTP and other plastic changes (Buffo *et al.*, 1997; Fawcett, 1992; Namgung *et al.*, 1997; Vaudano *et al.*, 1995).

Following thalamic damage, NGF is produced both in intrinsic glial and microglial cells, as well as in mast cells and macrophages which migrate into injured tissue from leaky vessels (Deller and Frotscher, 1997; Ebadi *et al.*, 1997; Fu and Gordon, 1997). One interesting, potential mechanism for the induction of NGF in microglial cells involves a role

of A<sub>2A</sub> receptors activated by adenosine released (as ATP) from degenerating neurones (Heese *et al.*, 1997). A putative role of thalamic, neuronal pools of BDNF should also be borne in mind as concerns both structural changes and the modulation of synaptic transmission (Section 14). Indeed, BDNF expression is enhanced by neuronal damage, while knock-out mice lacking TRK B receptors show both an *increased* vulnerability to neuronal CNS lesions and a lower regenerative capacity of neuronal tissue (Alcántara *et al.*, 1997). As a further example, GDNF can attenuate CNS damage due to ischaemia by a reduction in the synthesis of NO (Wang *et al.*, 1997f). The role of these and other neurotrophins in modulating neuronal phenotype/regeneration and nociception following CNS injury remains to be explored in detail.

Inflammatory responses in the CNS, involving gliosis and the above-mentioned infiltration of damaged tissue by immune-competent cells, occur following injury (Köller *et al.*, 1997; Ridet *et al.*, 1997; Rothwell, 1997). Correspondingly, cytokines such as TNF $\alpha$  and IL-1 $\beta$  are generated both by invading macrophages as well as by resident glial and microglial cells, and may reciprocally modify their activity (Arvin *et al.*, 1996; Ebadi *et al.*, 1997; Shen *et al.*, 1997; von Zahn *et al.*, 1997) (Section 4.8). These cytokines likely fulfil a diversity of interactive roles associated with tissue repair and damage (Merrill and Benveniste, 1996). Further, as discussed in Section 4.8, ILs, TNF $\alpha$  and other cytokines may exert a complex modulation of nociception via an influence upon synaptic transmission, including NMDA receptor-mediated processes of sensitization (Grassi *et al.*, 1994; Heyser *et al.*, 1997).

Cytokines can induce glial and microglial expression of NO synthase and COX 2 synthase to yield NO and PGs, respectively (Section 4.8). This of significance since the generation of (neuronal and non-neuronal pools of) NO and PGs in the DH by C fibre input enhances nociception by mechanisms described in Section 3.2.8, while a role for NO in the sensitization of nocisponsive neurones in the thalamus has also been proposed (Do *et al.*, 1994; Kolhekar *et al.*, 1997). Further, although NO may exert certain neuroprotective actions in the CNS, excessive levels of NO can provoke and aggravate tissue damage, and NO may also indirectly modify the response to tissue damage via its influence upon the cerebral microvasculature (Iadecola *et al.*, 1996; Ladiwala *et al.*, 1998; Merrill and Benveniste, 1996; Minghetti and Levi, 1998; Nogawa *et al.*, 1997; Salvemini *et al.*, 1995; Thippeswamy and Morris, 1997). There is some evidence that the induction of COX 2 expression is associated with degenerative processes. However, it has been suggested that PGs generally play an *opposite* role to NO in exerting primarily *neuroprotective* actions, for example in countering the excitotoxic effects of overstimulation of NMDA receptors (Kawamura *et al.*, 1997a,b; Minghetti and Levi, 1998).

Indeed, via the production of NO and an excessive accumulation of [Ca<sup>2+</sup>]<sub>i</sub>, NMDA receptors are strongly implicated in processes of cell degeneration provoked by ischaemic tissue damage (Choi and Rothman, 1990; Lerea, 1997; Liu *et al.*, 1994c; Lin

*et al.*, 1997). On the other hand, there is evidence that they may play a more constructive role in the control of neuronal growth and migration via actions controlling [Ca<sup>2+</sup>]<sub>i</sub> levels in the growth cones of sprouting neurones (Sjaastad and Nelson, 1997; Ghosh and Greenberg, 1995; Komuro and Rakic, 1993). Further, the proliferation, differentiation and synthetic activity of glial cells may be modified by glutamatergic mechanisms (Steinhäuser and Gallo, 1996).

Finally, tissue acidosis provoked by ischaemia may also modify the activity of many receptor types, both facilitatory and inhibitory to nociceptive transmission (King *et al.*, 1997a) (Section 7.4.5.4). Of particular note are GABA<sub>A</sub> receptors, the activity of which is either potentiated or inhibited dependent upon their subunit composition (Krishek *et al.*, 1996).

Thus, following damage to the thalamus and other CNS regions, degenerative and regenerative events—and the resultant changes in nociception—likely involve a multitude of factors, many of which resemble those encountered following PAF injury, and many of which may directly modulate nociceptive processing (Section 11). However, these processes require considerable further characterization.

## 14. CENTRAL ACTIONS OF NEUROTROPHINS AND THEIR RELEVANCE TO NOCICEPTIVE PROCESSING

### 14.1. A Role for Neurotrophins in the Modulation of Nociception in the CNS?

In Sections 10 and 13, several mechanisms emerged as of particular importance in determining those alterations in nociceptive processing and transmission which underlie the induction of painful states. These include:

1. amplification of responsiveness at sensitized neurones in the DH, thalamus and cortex;
2. a key role of NMDA receptors both in sensitization processes and in the transfer of nociceptive information from PAFs to the DH, and therefrom to higher centres;
3. a widespread inhibitory influence of GABAergic ININs upon nociceptive transmission in the DH and supraspinal structures; and
4. a pronounced influence of neurotrophins, such as NGF, upon the activity, phenotype and growth status of PAFs.

In this section, these themes are drawn together within a hypothetical framework which proposes that *central* actions of neurotrophins, in particular BDNF, may play an important role, in interaction with glutaminergic (NMDA) and GABAergic mechanisms, in strengthening or otherwise modulating transmission at synapses involved in the transfer and integration of nociceptive information at supraspinal and spinal loci.

#### 14.2. Neuronal Sources of Neurotrophins: Physiological Modulation

Neurotrophins are generated in discrete populations of *neurones* localized in several structures involved in nociceptive processing, and including the S I cortex, the thalamus, the striatum and the DH. Further, neuronal pools of neurotrophins are generated both constitutively as a function of 'basal', neuronal activity as well as in response to appropriate-excitatory-stimuli (Conner *et al.*, 1997; Lo, 1995; Lu *et al.*, 1991; Marty *et al.*, 1997; Thoenen, 1995; Zhou and Rush, 1996). A detailed discussion of the diverse roles of neurotrophins, in particular the widely-distributed BDNF, in the transient and long-term sculpting of synaptic architecture and modulation of synaptic transmission is beyond the scope of the present review (Thoenen, 1995; Marty *et al.*, 1997; Lewin and Barde, 1996; Berninger and Poo, 1996; Lo, 1995; Patterson and Nawa, 1993; Schmidt-Kastner *et al.*, 1996). Nevertheless, the following points support a role of neuronal pools of neurotrophins in the modulation of nociception in the CNS.

#### 14.3. Induction and Release of Neuronal Pools of Neurotrophins: NMDA Receptor-Mediated Stimulation

Neurotrophins are released from neurones by an unconventional mechanism which requires an increase in  $[Ca^{2+}]_i$  levels, yet which is dependent on extracellular  $Na^+$  rather than  $Ca^{2+}$  (Blöchl and Thoenen, 1995). A rise in cAMP levels may also trigger the release of NGF (Thoenen, 1995). Increases in neuronal excitability are associated with an enhanced secretion of neurotrophins. In this regard, it is of particular significance that glutamergic mechanisms, involving the activation of NMDA receptors and in increase in  $[Ca^{2+}]_i$ , induce the release and synthesis of neurotrophins (Castrén *et al.*, 1993a; Goodman *et al.*, 1996; Gwag *et al.*, 1993; Zafra *et al.*, 1991; Thoenen, 1995; Lu *et al.*, 1991). Although the decrease in cAMP levels provoked by group II and III mGlu receptors suggests that they may suppress neurotrophin production, the activation of group I mGlu receptors, which are positively coupled to PLC and increases in  $[Ca^{2+}]_i$ , may accelerate neurotrophin synthesis and release.

To date, a systematic evaluation of the potential influence of nociceptive stimulation upon the activity of CNS pools of neurotrophins has not been undertaken. Nevertheless, the generation and secretion of neuronal pools of BDNF is facilitated under the following conditions, each of which is of relevance to the induction of painful states:

1. ischaemia, provoked by stroke-induced vascular damage to the thalamus, induces BDNF gene expression, and NMDA antagonists can prevent this effect (Hughes *et al.*, 1993);
2. cortical spreading depression, a process implicated in the triggering of migraine attacks (Sections 4.7 and 7.9), also enhances BDNF synthesis (Kokaia *et al.*, 1993; Lindvall *et al.*, 1992; Moskowitz, 1992); and

3. epileptiform activity in the cortex and hippocampus, which mimics the excited, oscillating neuronal circuits and burst firing triggered by a loss of ININ tone, also elicits BDNF synthesis (Elmér *et al.*, 1998) (Sections 10.6.2 and 13.3).

Interestingly, in contrast to NMDA receptors, and consistent with their *inhibitory* influence on neuronal activity, activation of GABAergic receptors *downregulates* neurotrophin production (Zafra *et al.*, 1991; Thoenen, 1995).

In correspondence with the above findings, LTP in the hippocampus and memory formation, which is sustained and suppressed by NMDA- and GABA-dependent processes, respectively, is associated with an induction of neurotrophins, notably BDNF (Bliss and Collingridge, 1993; Castrén *et al.*, 1993b; Collingridge and Singer, 1990; Gordon *et al.*, 1997a; Ma *et al.*, 1998; Patterson *et al.*, 1992; Wilson and Tonegawa, 1997). These observations concerning LTP are of particular importance since hippocampal LTP is analogous to NMDA receptor-mediated processes of wind-up implicated in processes of neuronal sensitization in the DH, thalamus and S I (Section 10.2.1). Further, with respect to the role of supraspinal mechanisms in mediating referred pain (Section 9.1.4), unilateral induction of LTP results, via intrahemispheric connections, in a bilateral induction of mRNA encoding neurotrophins and TRK A receptors (Bramham *et al.*, 1996).

The above findings indicate, thus, that neurotrophin levels are elevated by events (including activation of NMDA receptors) which enhance synaptic transmission and which trigger processes underlying synaptic plasticity. In addition, as outlined below, by a positive feedback (retrograde) mechanism, the release of neurotrophins initiates processes further reinforcing synaptic signalling.

#### 14.4. Actions of Neurotrophins: Modulation of Synaptic Transmission

##### 14.4.1. Anterograde Transport of BDNF

Recent studies (Altar *et al.*, 1997; Conner *et al.*, 1997; Smith *et al.*, 1997c; Von Bartheld *et al.*, 1996), have shown that BDNF is *anterogradely* transported to nerve terminals. This raises the possibility that *anterograde* release of BDNF may mediate rapid, postsynaptic actions involved in the modulation of LTP and memory formation (Section 10.2.1). Indeed, many hippocampal neurones express both BDNF and TRK B receptors raising the possibility of retrograde and anterograde mechanisms of actions (Smith *et al.*, 1997c). Similar findings also suggest an *anterograde* release of BDNF from PAF terminals in the DH (Canossa *et al.*, 1997; Cho *et al.*, 1997a,b; Michael *et al.*, 1997a; Zhou and Rush, 1996) (Section 14.5.3). Thus, at specific (glutamergic) synapses, it is conceivable that BDNF is released both *pre* and *postsynaptically*, and that it exerts actions at both *pre* and *postsynaptic* sites.

##### 14.4.2. Modulation of Glutamergic Transmission: Presynaptic and Postsynaptic Actions

Neurotrophins exert a marked influence upon gene expression and synaptic transmission. Such



actions are *not* restricted to delayed alterations in synaptic morphology and connectivity. Rather, neurotrophins also elicit rapid, TRK-mediated effects via multiple intracellular transduction mechanisms (Berninger and Poo, 1996). These actions of neurotrophins are expressed both *presynaptically* in a retrograde fashion at those synapses which provoke their release, as well as *postsynaptically*.

As concerns *postsynaptic* actions, a phosphorylation of ion channels and transmitter receptors is likely involved in the potentiation of postsynaptic ion currents (Holm *et al.*, 1997; Kaplan and Stephens, 1994; Levine *et al.*, 1995; Berninger and Poo, 1996; Swope *et al.*, 1992)—although other types of alteration in neuronal activity may also occur. Most pertinently, NMDA receptor-mediated currents are potentiated by their neurotrophin-mediated (phosphorylation). For example, BDNF rapidly phosphorylates postsynaptic NMDA receptors in the hippocampus (which are involved in LTP) by an intracellular mechanism involving increases in  $[Ca^{2+}]_i$ , and, probably, the activation of PLC or other PKs (Blanquet and Lamour, 1997; Sakai *et al.*, 1997; Suen *et al.*, 1997; Wang and Salter, 1994). In a recent study of hippocampal neurones, a further postsynaptic mechanism for the potentiation of NMDA receptor-mediated activity by BDNF was proposed. Jarvis *et al.* (1997) suggested that BDNF enhances NMDA receptor-mediated currents (and reduces their desensitization) by acting at the allosteric, facilitatory glycine<sub>B</sub> site, stimulation of which is obligatory for full activation of the ion channel coupled to NMDA receptors. The source of BDNF mediating this action is likely presynaptic terminals, from which BDNF can be anterogradely released (Section 14.4.1). However, a feedback action of BDNF following its release from postsynaptic neurones themselves is also a possibility.

More extensive data concerning *presynaptic* actions of neurotrophins have shown that they increase synaptic currents via an increase in the release of transmitters, including GLU (Berninger and Poo, 1996; Knipper *et al.*, 1994). These presynaptic actions reflect a rapid increase in  $[Ca^{2+}]_i$  levels. This rise is dependent upon extracellular  $Ca^{2+}$  and possibly involves L-type VDCCs which are susceptible to phosphorylation following induction of PKs via TRK receptors (Berninger *et al.*, 1993; Kaplan and Stephens, 1994; Sakai *et al.*, 1997; Sherwood *et al.*, 1997; Wildering *et al.*, 1995). These presynaptic actions imply, then, a retrograde role of neurotrophins to increase activity at those excitatory synapses which provoke their own release: that is, a positive feedback mechanism. This is reminiscent of the positive feedback action of GLU at presynaptic NMDA receptors on the central terminals of PAFs in the DH (Section 3.2.4). On the other hand, BDNF released in an anterograde fashion may also mediate actions at presynaptic terminals.

BDNF, NT 3 and NT-4/5 all potentiate transmission at hippocampal CA 1 synapses in a manner resembling LTP and involving the recruitment of glutamatergic mechanisms (Kang and Schuman, 1995; Messaoudi, 1998; Thoenen, 1995). In line with a physiological role of BDNF in this regard,

LTP and memory formation is accompanied by an increase in BDNF levels in hippocampus (Section 14.3). Further, LTP (and memory retention) is impaired upon antagonism of TRK B receptors by fusion products and by administration of antisense probes neutralizing BDNF. Similar findings have been obtained in BDNF knock-out mice in which adenovirus-mediated substitution of the BDNF gene results in a restoration of LTP (Figurov *et al.*, 1996; Korte *et al.*, 1995; Lu and Figurov, 1997; Ma *et al.*, 1998; Thoenen, 1995; Patterson *et al.*, 1996). Interestingly, BDNF has also been shown to block LTD in the cortex (Akaneya *et al.*, 1996).

Very recently, a novel aspect of the positive feedback actions of neurotrophins was revealed with the demonstration that BDNF can induce its own release from hippocampal neurones (Canossa *et al.*, 1997; Furokawa *et al.*, 1997).

#### 14.4.3. Modulation of GABAergic Transmission

In addition to the above-described, facilitatory influence of BDNF upon NMDA-mediated transmission, neurotrophins may also interact with GABAergic mechanisms. GABAergic ININs target hippocampal pyramidal neurones containing BDNF and displaying LTP. BDNF postsynaptically decreases GABAergic currents in these neurones by an IP<sub>3</sub>-mediated mobilization of  $[Ca^{2+}]_i$  which presumably leads to the phosphorylation of GABA<sub>A</sub> receptors (Section 10.4.3). Thereby, the induction of hippocampal LTP is facilitated (Jiang *et al.*, 1997; Tanaka *et al.*, 1997b). Further, NT 3 decreases GABAergic transmission in the hippocampus and potentiates both synaptic transmission and processes of LTP (Kim *et al.*, 1994), although it is not known whether this action is expressed pre- or post-synaptically. In fact, information concerning the modulation of GABAergic transmission by neurotrophins is limited, and they do *not* decrease GABAergic transmission in all structures examined to date (Section 14.5.1). Thus, a putative modulation by neurotrophins of synaptic events underlying nociception should *not* necessarily be assumed to reflect inhibition of GABAergic transmission.

#### 14.4.4. Overview of Short- and Long-Term Actions of BDNF

It may be concluded from the above paragraphs that BDNF and/or other neurotrophins rapidly modify neuronal excitability and processes of activity-dependent plasticity via mechanisms involving the potentiation of actions mediated by NMDA receptors and, possibly, a modulation of GABAergic transmission (Marty *et al.*, 1997; Rutherford *et al.*, 1997). Most significantly, via both presynaptic (retrograde) and postsynaptic actions, neurotrophins *increase* transmission at glutamatergic (NMDA receptor-coupled) synapses involved in plastic, long-term changes increasing neuronal sensitivity. Such rapid actions may be succeeded by persistent changes in synaptic efficacy due to phenotypic alterations in synaptic architecture and in patterns of synaptic connectivity, in particular under conditions of damage to nervous tissue and/or prolonged excitatory stimulation (Thoenen,

1995). As concerns longer-term changes in neuronal morphology and phenotype, via the modulation of  $[Ca^{2+}]_i$ , PKs and various nuclear regulatory elements involved in plastic synaptic events, neurotrophins may modify the CNS gene expression of many substances involved in the modulation of nociception, including NO and various neuropeptides (Berninger and Poo, 1996; Carmignoto *et al.*, 1997; Finkbeiner *et al.*, 1997; Holm *et al.*, 1997; Jones *et al.*, 1994; Liu *et al.*, 1997a; Planas *et al.*, 1997).

#### 14.4.5. Summary

To summarize, BDNF and other neurotrophins are released from neurones by excitatory stimuli, including the activation of NMDA receptors. BDNF plays an important role, by both pre- and postsynaptic mechanisms, in the strengthening of synaptic transmission via a reinforcement in NMDA receptor-mediated activity. Further, at certain, through not all, neurones, an inhibition of GABAergic activity is apparent. These actions are associated with a facilitation of NMDA-dependent and GABA-suppressible mechanisms of LTP in the hippocampus, a NMDA receptor-mediated and GABA receptor-inhibited process of synaptic amplification analogous to mechanisms of neuronal sensitization underlying painful states (Section 10.2.1). In addition, the recent demonstration of anterograde BDNF transport in neurones suggests that it may also mediate actions via 'conventional' synaptic release onto postsynaptic targets. It is not unreasonable, then, to hypothesize that BDNF and other neurotrophins may be involved in modulating synaptic events underlying the sensitization of spinal and supraspinal neurones involved in the transmission of nociceptive information.

### 14.5. Sites at Which Neurotrophins May Modulate Nociceptive Processing

#### 14.5.1. The S I of the Cortex

One locus where neurotrophins may modulate synaptic processes involved in nociceptive processing is the S I cortex, which possesses both a rich population of TRK B receptors and a high concentration of BDNF (Yan *et al.*, 1997; Zhou *et al.*, 1993). Indeed, thalamocortical afferents transmitting sensory information to the cortex exert their actions via EAAs/NMDA receptors (Section 6.3.1). Further, NMDA receptors play a major role in neuronal plasticity in the cortex and their activation modifies the expression of BDNF therein (Section 14.3). Thus, BDNF may, via pre and postsynaptic actions described in Section 14.4, reinforce NMDA receptor-mediated transmission of nociceptive information in the cortex (Armstrong-James *et al.*, 1993; Castrén *et al.*, 1992, 1993a; Conti and Hicks, 1996; Gordon *et al.*, 1997a; Li *et al.*, 1994; Marty *et al.*, 1997; Thoenen, 1995; Zafra *et al.*, 1991). On the other hand, BDNF modifies synaptic plasticity and connectivity in the S I cortex via a *facilitatory* (retrograde?) influence upon the activity of TRK B-bearing GABAergic ININs which, like thalamocortical afferents, target pyramidal neurones secreting BDNF (Jones *et al.*, 1994; Marty *et al.*, 1997;

Rocamora *et al.*, 1996; Rutherford *et al.*, 1997; Thoenen, 1995). Such actions upon GABAergic ININs may include alterations in their patterns of connectivity as well as changes in the levels of GABA and of other co-expressed transmitters, such as NPY (Marty *et al.*, 1997). Two modes of sensory input have been examined in detail as regards the influence of BDNF upon plastic events in the cortex.

1. Mechanical stimulation (deflection) of whiskers in mice leads to a specific up-regulation of BDNF in topographically-organized structures of the S I termed 'barrel columns'. Particularly pronounced effects are seen in layer IV which receives the most intense input from thalamocortical afferents originating in the ventrobasal complex (Chmielowska *et al.*, 1989; Rocamora *et al.*, 1996). In contrast, the opposite manipulation of sensory deprivation causes a *reduction* in cortical BDNF expression. This may lead to a *reduction* in GABAergic activity resulting in enlarged RFs and increases in spontaneous neuronal activity (Marty *et al.*, 1997). Such effects are reminiscent of changes triggered in the DH upon PAF damage due to a loss of GABAergic inhibitory transmission (Section 10.6).
2. The thalamus (lateral geniculate nucleus) is the major source of sensory input to the visual cortex. Like nociceptive input to the cortex, thalamocortical afferents transmitting visual information employ EAAs. Temporary, developmental deprivation of visual input leads to marked alterations in the RFs of neurones in the visual cortex and a to (reversible) reduction in the levels of BDNF and GABAergic transmission (Castrén *et al.*, 1992). It has been suggested that the down-regulation of BDNF may intervene in this diminution of GABAergic ININ activity (Marty *et al.*, 1997; Rocamora *et al.*, 1996).

To summarize, nociceptive (and other forms of sensory) input to the cortex mediated via thalamocortical pathways utilizing NMDA receptors may trigger the induction of BDNF which further reinforces excitation by both postsynaptic and (feedback, retrograde) presynaptic actions. Depending upon stimulus duration and other factors, this may lead to both rapid and persistent functional and phenotypic/morphological mechanisms underlying sensitization and increases in synaptic efficacy. However, in analogy to the parallel activation of PNs and ININs in the DH by C fibre input, BDNF may temper these actions via an enhancement of GABAergic tone. As described in Section 12.2, under diverse conditions, the increase in neuronal excitability provoked by nociceptive input may be either less or more marked in cortical than in thalamic regions. This raises the possibility that the precise balance between excitatory and inhibitory mechanisms involving NMDA receptors, neurotrophins and GABAergic ININs may be involved in such differences. On the other hand, a loss of excitatory, sensory (nociceptive) input to the cortex following damage to PAFs, the STT or thalamus may lead to a down-regulation in cortical activity of BDNF, a reduction in GABAergic tone and neuronal disinhibition (Cabelli *et al.*, 1995; Gordon *et*

*al.*, 1997a; Marty *et al.*, 1997; Rocamora *et al.*, 1996; Thoenen, 1995).

Similar events involving reciprocal interactions of BDNF and glutamatergic/NMDA and GABAergic transmission likely occur in other cortical regions receiving *nociceptive* input from the thalamus and other structures. The precise nature and time-course of such interactions, and their global influence upon nociceptive transmission and processing, remains to be established.

#### 14.5.2. The Thalamus and Other Cerebral Structures

The thalamus contains a high density of TRK B receptors and a substantial population of BDNF-positive neurones (Furukawa *et al.*, 1997; Thoenen, 1995; Yan *et al.*, 1997; Zhou *et al.*, 1993). Thalamic levels of BDNF are elevated both by selective activation of NMDA receptors and by generalized increases in the electrical activity of the thalamus (Castrén *et al.*, 1992; Schmidt-Kastner *et al.*, 1996). Further, ischaemic CNS damage can induce BDNF gene expression and, as discussed in Section 13.5, neurotrophins play a role in neuronal regeneration of the thalamus following its injury. Thus, vascular accidents underlying stroke-induced thalamic pain likely also induce an expression of neurotrophins in the thalamus. Both NMDA receptors and GABAergic mechanisms are involved in the induction of pain due to thalamic damage (Section 13). An interaction of BDNF with these mechanisms may, therefore, play a role in the modulation of painful states due either to damage to the thalamus itself, or to input from ascending nociceptive channels.

The striatum, amygdala and lateral hypothalamus, additional sites of termination of ascending nociceptive input, also possess TRK B receptors and neurones synthesizing BDNF. Thus, they also represent further potential sites at which neurotrophins may modify synaptic events involved in the processing of nociceptive information (Castrén *et al.*, 1993b; Furukawa *et al.*, 1997; Schmidt-Kastner *et al.*, 1996; Yan *et al.*, 1997). The midbrain is also rich in BDNF-immunoreactivity (Furukawa *et al.*, 1997). Although the underlying mechanisms are obscure, administration of BDNF or NT 3 into the midbrain elicits antinociception in parallel with an alteration in cerebral and spinal levels of 5-HT,  $\beta$ -endorphin, SP and NPY (Siuciak *et al.*, 1994, 1995).

#### 14.5.3. The DH of the Spinal Cord

The most intriguing, potential site of action of BDNF and other neurotrophins in the modulation of nociception is the DH. Although data are limited, recent studies support this possibility.

Both the DH and the (homologous) trigeminal nucleus possess a substantial population of TRK B receptors (Michael *et al.*, 1997b; Zhou *et al.*, 1993). As concerns potential sources of BDNF acting at these sites, there is little evidence for BDNF in intrinsic neurones in the DH or in the terminals of descending pathways. Thus, the most likely source of BDNF for the DH is PAFs (Acheson *et al.*, 1995; Zhou and Rush, 1996). Indeed, there is compelling evidence for anterograde transport of BDNF to

nerve terminals in the CNS and this process has been demonstrated to occur in PAFs, probably small calibre C fibres, projecting to the DH (Conner *et al.*, 1997; Zhou and Rush, 1996; Cho *et al.*, 1997a,b). Further, it has recently been demonstrated that axon terminals intensely labelling for BDNF are present in superficial DH laminae I and II—and to a lesser extent—in deeper laminae IV/V and lamina X (Conner *et al.*, 1997; Cho *et al.*, 1997a,b). That is, the principal laminae targetted by nocisponsive C fibres and transmitting nociceptive information to higher centres (Section 4.1). PAF damage has been shown to enhance BDNF levels in the DRG (Ernfors *et al.*, 1990) and peripheral tissue inflammation elicits a parallel increase in DRG and DH staining for BDNF (Cho *et al.*, 1997a,b). This induction of BDNF expression by noxious stimulation or PAF injury is consistent with its occurrence in nocisponsive, small calibre neurones, and can be prevented by antibodies to NGF (Cho *et al.*, 1997b,c; Michael *et al.*, 1997a). Those observations reinforce the argument that an anterograde transport of BDNF in C fibres is the primary source of BDNF in the DH and indicate that this process is accelerated by noxious, peripheral manipulation.

There is evidence from other tissues for the neuronal storage and secretion of BDNF (Fawcett, 1992; Fawcett *et al.*, 1997) (Section 14.2). Thus, it is likely that BDNF is released from C fibre terminals in the DH to exert *acute*, functional actions at intrinsic DH neurones. In this respect, one potential target of BDNF is the terminals of A $\beta$  fibres which bear TRK B receptors. This would potentially implicate BDNF in the modulation of mechanical allodynia. Further, as discussed in Section 11.3.3, following PAF injury, BDNF release from C fibre terminals may attract A $\beta$  fibres into Laminae II. It is also possible that BDNF acts directly on intrinsic DH neurones bearing TRK B receptors. In this respect, a potential interaction of BDNF with NMDA receptor-bearing PNs, EXINs or GABAergic ININs targetted by C fibres would be of special interest. Consistent with a putative role of BDNF in the enhancement of nociception, it was recently shown to increase the expression of both c-fos and NO synthase in DH neurones (Bennett *et al.*, 1996b). Further, BDNF reduces GABA<sub>A</sub> receptor-mediated conductances in injured PAFs, suggesting that it may facilitate nociceptive input from their terminals into the DH (Oyelese *et al.*, 1997). Thus, a potential, pronociceptive role of C fibre-derived pools of BDNF in the DH should provide fertile territory for future exploration. Further, an interesting possibility is that the central release of C fibre-localized pools of BDNF in the DH may be modulated by NMDA receptors on their terminals (Liu *et al.*, 1997b) (Section 3.2.4).

Comparatively little is known concerning potential actions of NGF at TRK A receptors in the spinal cord. Potential sources of NGF comprise both glial cells and intrinsic neurones. Anterograde delivery of NGF from PAFs to the DH has not, to date, been demonstrated (Anand *et al.*, 1995). In fact, evidence for TRK A receptors on intrinsic DH-localized neurones is limited, although they may be present both in superficial laminae (a principal tar-

get of nociceptive PAF input) as well as in lamina X (indicating a potential role in the integration of visceral sensory input and autonomic outflow) (Michael *et al.*, 1997b; Molliver *et al.*, 1995). On the other hand, fibres showing dual labelling for TRK A receptors and CGRP have been visualized in superficial DH laminae and the dorsal columns. This suggests a possible modulation by DH pools of NGF of the activity of the central terminals of nociceptive C fibres. However, superfusion of the spinal cord with NGF has been reported *not* to modify the release of SP therein (Averill *et al.*, 1995; Malcangio *et al.*, 1997a,b; Michael *et al.*, 1997a; Molliver *et al.*, 1995).

Administration of NT 3 into the midbrain elicits antinociception via a mechanism involving serotonergic transmission (Siuciak *et al.*, 1995). In this light, it is of interest that TRK 3 receptors have been detected in descending serotonergic fibres in the spinal cord (Arvidsson *et al.*, 1994). Further, binding sites for NT 3 have been visualized throughout the spinal cord, including superficial laminae (Zhou and Rush, 1994). The origins of putative DH pools of NT 3 remain, however, unclear. The demonstration that large, myelinated, mechanosensitive PAFs retrogradely transport NT 3 from the peripheral terminals to their DRG raises the possibility of its subsequent anterograde delivery to the DH, though this remains to be demonstrated (Di Stefano *et al.*, 1992). Malcangio *et al.* (1997b) showed that both the systemic and spinal administration of NT 3 reduced the enhancement of DH SP release elicited by electrical stimulation of the DRG, an action apparently mediated by activation of opioidergic ININs. The authors tentatively related this observation to the ability of peripherally-administered NT 3 to attenuate sensory deficits associated with a chemically-induced large fibre neuropathy (Helgren *et al.*, 1997). However, the systemic administration of NT 3 has been documented to elicit a transient hyperalgesia (Malcangio *et al.*, 1997b). Thus, the potential role of NT 3 in the DH and elsewhere in the modulation of nociception remains to be clarified.

#### 14.6. Summary

An examination of the potential role of BDNF and other neurotrophins in modulating rapid and prolonged synaptic events underlying neuronal sensitization and nociception would appear to be of considerable interest, in particular with regard to the DH and cortex. Although the above discussion focused on neuronal pools of neurotrophins, the production of neurotrophins by glial cells and immunocomponent cells provides a further potential source via which synaptic events might be modulated, for example following CNS injury. In this light, one final aspect should be noted. BDNF and other neurotrophins exert a marked modulatory influence upon processes of neuronal death elicited by ischaemic damage and the activation of excitotoxic NMDA receptors, effects in which NO may be involved (Samdani *et al.*, 1997) (Section 13.5). It was pointed out in Section 13.3 that a loss of vulnerable GABAergic ININs upon ischaemic damage to the CNS may be involved in the induction of central

pain. Thus, the possibility that neurotrophins may indirectly modify nociception via long-term, trophic actions at GABAergic and other cell types following tissue injury, should also be considered.

In conclusion, it is reasonable to hypothesize a role of BDNF—and, perhaps, other neurotrophins—in the modulation of plastic, synaptic events involved in the transfer and modulation of nociceptive information in the CNS. Such actions may be mediated both rapidly, via modification of transmitter release and receptor function, and more slowly and persistent, via a reshaping of synaptic morphology and patterns of neuronal connectivity. The actions of BDNF and other neurotrophins are likely expressed in interaction with glutamatergic neurones/NMDA receptors and GABAergic transmission. That is, excitatory and inhibitory systems playing crucial roles in the transmission and processing of nociception in DH the thalamus and the cortex. Although the DH and cortex are the most promising targets for an exploration of such potential mechanisms, the thalamus and other supraspinal regions also justify investigation. However, in particular as concerns interactions with GABAergic mechanisms, only direct study will allow for a characterization of the precise influence of neurotrophins upon nociceptive processing at various levels of the neuroaxis.

## 15. GENERAL DISCUSSION AND CONCLUSIONS: A SUMMARY OF KEY ISSUES

### 15.1. The Complexity of Mechanisms Involved in the Induction of Pain

The foregoing discussion exemplifies the extraordinary complexity and diversity of mechanisms involved in the induction of pain. Over the last decade, enormous advances have been made in our understanding of these processes and several, global aspects deserve brief emphasis.

1. A knowledge of:
  1. the intracellular transduction mechanisms activated by specific receptor types; and
  2. the localization of these receptors at the cellular level,
 provides a powerful basis for a rational prediction of their role in the modulation of nociceptive transmission. For example, the detection of excitatory P<sub>2x3</sub> receptors coupled to cation-permeable channels on peripheral, nociceptive C fibres terminals leads inevitably to the prediction that they fulfil a pronociceptive role at this locus.
2. Over recent years, the roles of many mediators in the response to, and the induction of, pain have emerged to be more diverse than previously realized. This increasing complexity reflects several factors: in particular the proliferation of receptorial and intracellular transduction mechanisms mediating the actions of specific transmitters, such as 5-HT, NPY and ATP. Further, the identification of previously-unsuspected loci of

action is also of significance: for example, actions of PGs in the DH, of EAAs (and opioids) in the periphery and of SP in the limbic system. Temporal aspects are also of importance as concerns adaptive events, in particular neuronal sensitization, underlying prolonged pain. Mechanisms which instantaneously modify neuronal activity via alterations in ionic flux, such as the activation of NMDA receptors or L-type VDCCs, have been shown to express *long-term actions*: thus, they sequentially induce increases in  $[Ca^{2+}]_i$  levels and activate specific PKs, nuclear transcription factors, IEGs and gene expression. Such intracellular cascades lead to sustained changes in neuronal phenotype and synaptic plasticity. Contrariwise, neurotrophins, such as BDNF and NGF, and intracellular growth-associated factors, such as GAP 43, may, in addition to their long-term modification of synaptic morphology, exert a *rapid* influence upon synaptic transmission via interactions with  $[Ca^{2+}]_i$ , various PKs and other intracellular and extracellular signals.

3. Considerably more work is needed at the *cerebral* level for an improved understanding of supraspinal mechanisms involved in the induction of pain, in particular its *emotional-cognitive* aspects. Initial analyses at the cellular level of supraspinal mechanisms triggered by peripheral inflammation or PAF injury have suggested several striking similarities to events occurring in the DH. Notably, as concerns the involvement of NMDA receptor-mediated processes of synaptic plasticity and the importance of inhibitory GABAergic transmission. Nevertheless, adaptive events occurring in supraspinal centres are distinctive and do *not* simply duplicate changes seen at the spinal level.
4. Experimental models of PAF injury have proven of decisive importance in furthering our understanding of processes underlying neuropathic pain and the regenerative capacity of damaged neurones (Bennett and Xie, 1988; Coyle, 1996; Kim and Chung, 1992). Such models have revealed certain important differences between nociceptive pain (due to nociceptor stimulation) and neuropathic pain (due to PAF damage) as concerns their induction and maintenance. For example, in terms of the phenotype changes provoked in small calibre C fibres, the (transient) reduction in the activity of DH-localized ININs elicited by PAF injury, abnormal patterns of ectopic firing in damaged PAFs and the reorientation of injured A $\beta$  fibres from deep into superficial laminae of the DH. Correspondingly, certain strategies for the relief of inflammatory as compared to neuropathic pain may well *differ*.
5. Perhaps more surprisingly, many *similarities* exist between painful states elicited by the stimulation as compared to the injury of PAFs. For example, the key role of large calibre, A $\beta$  fibres in mediating mechanical allodynia. Further, the emergence of nociceptive and neuropathic pain, in each case, critically depends upon the development of *central* processes of *sensitisation* in the DH and supraspinal structures. Indeed, in some respects,

the similarities between the pain provoked by PAF injury as compared to tissue inflammation are more striking than the differences. Consequently, it may be possible to elaborate strategies for the relief of both nociceptive and neuropathic pain based on countering such *common* processes as central sensitization, peripheral C fibre drive maintaining certain sensitized states and A $\beta$  fibre mediated mechanical allodynia. In this regard, it may be desirable to reduce *both* the initial PAF volley which triggers central sensitization *and* the subsequent C fibre, barrage drive underlying its persistence. This issue is currently undergoing clinical evaluation employing protocols of pre-emptive as compared to *post-hoc* administration of opioids, NMDA antagonists, Na<sup>+</sup>-channel blockers and other classes of analgesic agent (Andersen *et al.*, 1996; Dahl *et al.*, 1993; Gordon *et al.*, 1997b; Katz *et al.*, 1996; Smith *et al.*, 1994b; Rice, 1995a; Woolf and Chong, 1993).

6. A fundamental process underlying the induction of prolonged, painful states is sensitization peripheral nocisponsive terminals, and localized CNS neurones involved in the transmission of nociceptive information to successively higher centres. Sensitization is elicited by sustained and repetitive rather than phasic stimulation and, within a temporal framework, one might conceive of essentially three phases of neuronal activation (Tables 2, 5 and 6).
  1. The phasic engagement of a discrete population of DH neurones, mediated by AMPA receptors, and involving a spatially restricted influence upon  $[Ca^{2+}]_i$  concentrations and other intracellular signals, leading to a brief discharge of APs and the activation of 'discriminative-sensory' channels. This process corresponds to the adaptive, warning role of acute, localized and transient exposure to (cutaneous) noxious stimulation.
  2. More prolonged activation of a more extensive population of DH neurones by processes of temporal and spatial summation, with a greater recruitment of NMDA/mGlu/NK<sub>1</sub> receptors and VDCCs etc, leading to more pronounced and widely-distributed increases in  $[Ca^{2+}]_i$  levels and the activation of PKs, triggering alterations in ion channel/receptor function by phosphorylation and the activation of nuclear transcription factors, IEG and gene expression. However, these processes remain largely reversible (maintained by peripheral input) and morphological alterations in synaptic architecture and neuronal connectivity do not occur. This corresponds to subchronic, painful states which decline in parallel with the resolution of the inflammation/tissue injury by which they are provoked.
  3. Particularly in the case of injury to PAFs (or the CNS), long-term and abnormal patterns (spatially and temporally) or peripheral input, with a loss of ININ control leading to the aggravation and propagation of self-perpetuating sensitized states, accompanied by perma-

ment alterations in neuronal organization. This corresponds to chronic, maladaptive (generally neuropathic) painful states.

7. One major consequence of the neuronal excitation provoked by a loss of inhibitory transmission due to PAF or CNS injury is, then, the induction of widespread, generalized and reverberating, overexcited circuits. These may incorporate extensive regions of the DH and supraspinal structures, including oscillating ipsilateral and bilateral, intrathalamic, intracortical and thalamocorticothalamic networks. The induction of such states implies that the notion of anatomically-defined, precisely-localized 'pain centres' may be illusory. Imaging studies of the activation of cerebral regions in man have also indicated that a widespread 'neuromatrix' rather than individual loci are involved in the sensation of pain (Section 6). Thus, the discrete interference with activity in *specific* cerebral (or DH) regions may *not* necessarily be effective in interrupting hyperexcitability and affording pain relief.
8. This *lack* of discrete, circumscribed CNS regions underlying pain transmission and sensation is related to, and compounded, by the extensive *redundancy* of mechanisms transmitting nociceptive information, and the extensive pattern of reciprocal interactions amongst them. Thus, there exists a multiplicity (moving down from the cortex) of: cortical and subcortical structures integrating nociceptive information; ascending pathways for its transmission from the DH to supraspinal centres; pronociceptive neurotransmitters released from multiple classes of nociceptive onto DH neurones; inflammatory mediators acting at their peripheral terminals; mechanisms triggering abnormal patterns of firing in injured PAFs and cascades of intracellular signals initiated by peripheral and central mediators of pronociceptive actions (Table 4, Figs 3–5). Thus, selective inactivation of delimited regions of the CNS, or blockade of the actions of specific pronociceptive mechanisms, is *unlikely* to offer a *generalized* solution for the countering of processes underlying pain due to contrasting pathologies. Examples of manipulations manifesting limited efficacy are provided by lesions of specific cerebral nuclei, discrete elimination of the STT at the spinal level, sympathectomy, selective blockade of spinal NK<sub>1</sub> receptors or specific antagonism of peripheral B<sub>2</sub> receptors.
9. In the above light, it is also of significance that noxious stimulation both activates pronociceptive mechanisms *and* coactivates antinociceptive (or 'anti-pronociceptive') mechanisms counterbalancing their actions. For example: descending inhibition *and* facilitation; C fibre activation of WDR/NS PNs *and* GABAergic ININs in the DH; pronociceptive *and* antinociceptive transmitters in PAFs; and, at the molecular level, Ca<sup>2+</sup>- and PK-mediated processes of sensitization/desensitization and phosphorylation/dephosphorylation. Procedures for the supposedly discrete elimination of pronociceptive mechanisms must

take into account a potential long-term perturbation of intrinsic, *antinociceptive* mechanisms.

As summarized in the three preceding points, there is evidence for

1. diffuse cerebral 'neuromatrices' underlying pain sensation;
2. redundancy in channels for pain transmission channels; and
3. compensatory antinociceptive mechanisms activated by noxious stimulation.

These observations question whether discrete manipulations of specific components of pronociceptive mechanisms can offer a generalized strategy for pain relief. Nevertheless, analgesic strategies appropriate to the effective control of *specific* painful conditions remain a realistic proposition. For example, the vascular and/or neurogenic actions of 5-HT<sub>1B</sub> agonists on CBVs in the treatment of migraine or the use of (TTX-sensitive) Na<sup>+</sup>-channel antagonists for controlling ectopic activity of injured PAFs. Indeed, the recent discovery of many hitherto-unsuspected 'unconventional' mechanism underlying the induction of painful states should be emphasized. Notably: sympathetic mechanisms; immunocompetent and glial cells in the periphery and CNS; neurotrophins; cytokines; protons; Na<sup>+</sup>-channels; ATP; NO; vanilloids; and a multiplicity of neuropeptides. Correspondingly, the palette of potential targets and strategies for the development of novel analgesics is far richer than previously imagined. Thus, it is appropriate to conclude with a brief consideration of the implications of an improved understanding of mechanisms underlying pain for the discovery of novel, analgesic agents.

### 15.2. Mechanisms of Antinociception, Nociception and the Development of Novel Analgesics

In the seventies and eighties, considerable excitement was elicited by the discovery and cloning of endogenous opioid peptides and the characterization of descending, inhibitory monoaminergic pathways to the DH. Correspondingly, efforts were devoted to developing drugs which mimic or reinforce physiologically-engaged, 'endogenous' opioidergic monoaminergic or other mechanisms of antinociception (Basbaum and Fields, 1984; Fields and Basbaum, 1994; Millan, 1986, 1990, 1997). Unfortunately, for a variety of reasons, comparatively little progress in the development of improved analgesic agents has been achieved via this approach. For example, difficulties in dissociating the sedative/hypotensive actions of  $\alpha_2$ -AR agonists from their analgesic properties (Millan, 1998) and the—to date—failure to identify a key, DH-localized 5-HT receptor type mediating antinociception (Millan, 1995). Other factors, such as problems encountered in the cloning of opioid receptors and in the identification of endogenous ligands for  $\mu$ -opioid receptors—now resolved—may also be relevant (Mansour *et al.*, 1995; Zadina *et al.*, 1997).

The exponential growth of interest in mechanisms underlying the *induction* rather than the inhibition of pain may reflect, thus, a certain frustration with

strategies for the development of novel analgesics based upon the principle of reproducing endogenous mechanism of antinociception. Moreover, as indicated in Section 15.1, the availability of experimental models of PAF damage has provided a key impetus for studies of mechanisms underlying neuropathic pain, a condition which responds poorly to traditional analgesics such as opioids and anti-inflammatory agents. Also of key importance is, as mentioned above, an appreciation of the roles of many, novel mechanisms in the induction of nociception, including neurotrophins, cytokines,  $\text{Na}^+$ -channels, protons, DH mechanisms of sensitization,  $\text{A}\beta$  fibre-mediated mechanical allodynia, PAF phenotype changes in inflammatory and neuropathic pain, regenerative changes in damaged PAFs and sympathetic transmission.

An improved understanding of such mechanisms has contributed to a resurgence of optimism that it may be possible to prevent or interrupt mechanisms involved in the induction of pain. However, precisely which of this diversity of 'pronociceptive' mechanisms should most appropriately be manipulated remains to be elucidated. As suggested above (Section 15.1), in view of redundancy in nociceptive transmission and the existence of diffuse matrixes underlying pain sensation, any single mechanism may be insufficient. Indeed, it is worth reiterating that the distinctive quality of nociceptive pain relief afforded by  $\mu$ -opioids may reflect multiple actions at all *many* hierarchical levels: PAF terminals, the DH; the thalamus and other supraspinal relay centres; the cortex and limbic system and brainstem centres modulating descending inhibition. Via such complementary and diverse actions, morphine effectively modifies both the sensory *and* emotional-cognitive dimensions of pain.

### 15.3. Concluding Comments

In conclusion, there is a growing realisation that a characterization of the molecular bases of endogenous mechanisms *generating* rather than *inhibiting* nociception may provide more fertile territory for the discovery of novel strategies to alleviate pain. Instead of activating antinociceptive mechanisms or interfering with pronociceptive processes, it would obviously be desirable to terminate the pathological events, such as metastatic disease or arthritis, underlying chronic and clinical pain, thereby rendering analgesics superfluous. Unfortunately, this is not currently foreseeable and remains a task for the next century. Today, the development of novel, improved analgesics remains a major challenge to which an improved understanding of mechanisms underlying the induction of pain will hopefully make a major contribution.

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