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Descending control of pain

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Abstract

Upon receipt in the dorsal horn (DH) of the spinal cord, nociceptive (pain-signalling) information from the viscera, skin and other organs is subject to extensive processing by a diversity of mechanisms, certain of which enhance, and certain of which inhibit, its transfer to higher centres. In this regard, a network of descending pathways projecting from cerebral structures to the DH plays a complex and crucial role. Specific centrifugal pathways either suppress (descending inhibition) or potentiate (descending facilitation) passage of nociceptive messages to the brain. Engagement of descending inhibition by the opioid analgesic, morphine, fulfils an important role in its pain-relieving properties, while induction of analgesia by the adrenergic agonist, clonidine, reflects actions at α_2-adrenoceptors (α_2-ARs) in the DH normally recruited by descending pathways. However, opioids and adrenergic agents exploit but a tiny fraction of the vast panoply of mechanisms now known to be involved in the induction and/or expression of descending controls. For example, no drug interfering with descending facilitation is currently available for clinical use. The present review focuses on: (1) the organisation of descending pathways and their pathophysiological significance; (2) the role of individual transmitters and specific receptor types in the modulation and expression of mechanisms of descending inhibition and facilitation and (3) the advantages and limitations of established and innovative analgesic strategies which act by manipulation of descending controls. Knowledge of descending pathways has increased exponentially in recent years, so this is an opportune moment to survey their operation and therapeutic relevance to the improved management of pain.

Contents

Abbreviations: 5-HT, serotonin; α_2-AR, α_2-adrenoceptor; AC, adenylyl cyclase; ACh, acetylcholine; AMPA, α-amino-2,3-dihydro-5-methyl-3-oxo-4-isoxazolepropanoic acid; ATP, adenosine triphosphate; CB, cannabinoid; CCK, cholecystokinin; CGRP, calcitonin gene related peptide; DA, dopamine; DF, descending facilitation; DH, dorsal horn; DI, descending inhibition; DRG, dorsal root ganglion; DYN, dynorphin; ENK, enkephalin; β-EP, β-endorphin; EXIN, excitatory interneurone; GABA, γ-amino-butyric acid; GAL, galanin; 5-HT, serotonin; I, imidazoline; IML, intermediolateral cell column; IN, interneurone; ININ, inhibitory interneurone; i.c.v., intracerebroventricular; i.t., intrathecal; MC, melanocortin; MIA, morphine-induced antinociception; NA, noradrenaline; NMDA, *N*-methyl-D-aspartate; NO, nitric oxide; NPFF, neuropeptideFF; NPVF, neuropeptideVF; NRM, nucleus raphe magnus; NT, neurotensin; NST, nocistatin; NTS, nucleus tractus solitarius; OFQ, orphaninFQ; ORL, opioid-receptor-like; OT, oxytocin; PAG, periaqueductal grey; PAF, primary afferent fibre; PBN, parabrachial nucleus; PLC, phospholipase C; PN, projection neurone; POMC, pro-opiomelanocortin; PVN, paraventricular nucleus; RVM, rostroventromedial medulla; SP, substance P; SPA, stimulation-produced antinociception; VH, ventral horn; VP, vasopressin

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1. General introduction: scope and aims of review

Some 30-odd years ago, the concept was evoked that nociceptive information impinging upon the dorsal horn (DH) of the spinal cord from the skin, viscera and other tissues, is not automatically transferred to higher centres (Melzack and Wall, 1965). Rather, in accordance with now familiar "gate" terminology, processes integrated at the terminals of nocisponsive (pain-sensitive) primary afferent fibres (PAFs), and at the projection neurones (PNs) which they target, profoundly modify nociceptive (pain-signalling) messages prior to their dispatch to supraspinal centres.

At the time at which the "gate hypothesis" was forwarded, the astonishing diversity of mechanisms involved in the filtering and modulation of nociceptive transmission in the DH (and elsewhere) could hardly be suspected. Indeed, it is now clear that many classes of DH neurone, PAF themselves and, as discussed herein, fibres descending from the brain, exert a powerful modulatory influence upon the onward transfer of nociceptive information from the spinal cord to the brain. Moreover, it has become apparent that certain mechanisms enhance rather than impede the centripetal passage of nociceptive messages. In this respect, descending pathways are no exception and mechanisms of both "descending inhibition" (DI) and "descending facilitation" (DF) must be recognised. Intriguingly, there is no absolute, anatomical separation of substrates subserving these processes and the stimulation of a single supraspinal structure may-via contrasting mechanisms-simultaneously trigger both DI and DF. Further exemplifying the complexity and sophistication of descending controls, a single transmitter may, via divergent actions expressed through different receptor types, concomitantly promote and suppress nociceptive transmission in the DH.

The principle purpose of the present review is to discuss the remarkable diversity and therapeutic relevance of mechanisms underlying the modulation and expression of descending controls. Particular emphasis is afforded to the differential roles of individual neurotransmitters and receptor subtypes. Accordingly, the article is structured as follows.

First, Sections 2 and 3 provide a framework for discussion of the neurochemistry and pharmacology of descending controls in presenting several general principles concerning their neuronal organisation and operation.

Second, Section 4 focuses on the adaptive and pathophysiological significance of mechanisms of DI and DF, together with the influence of acute and long-term pain upon their activity.

Third, in the most extensive part of this article, Sections 5–11 discuss the roles of specific neurotransmitters in the modulation and mediation of descending controls. In this regard, particular attention is devoted to recent innovative studies of DF as compared to the more familiar role of DI. The present article does not, however, constitute an inventory of the multitude of transmitters and other mediators involved in the transmission and modulation of nociceptive processing in the DH and higher centres. Rather, the major criteria for inclusion are unequivocal evidence for: (1) their presence in descending pathways themselves; (2) a role of supraspinal pools in the direct modulation of mechanisms of DF or DI and/or (3) a role of segmental (DH) pools in the

expression of DI or DF. In view of the complex and diverse roles of individual transmitters, there is no obvious schema for their classification. However, in light of the enormous literature devoted to noradrenergic and serotonergic mechanisms of DI, and since α_2-adrenoceptor (AR) agonists are clinically-employed as analgesic agents, the initial part of this discussion focuses on monoamines (Sections 5–7). A detailed review of descending noradrenergic and serotonergic mechanisms for the spinal induction of antinociception has been published by the present writer (Millan, 1997). This article should be consulted for more extensive coverage of literature predating its appearance. Herein, novel insights gained subsequent to its appearance are accentuated, in particular as concerns the divergent roles of multiple classes of α-AR and serotonin (5-HT) receptor, and the significance of descending dopaminergic pathways. Other "conventional" transmitters are subdivided into three general groups-although differences are not invariably absolute: (1) those (like monoamines) which are almost exclusively contained in descending pathways (Section 8); (2) those (the majority) which are found both in descending pathways and, predominantly, in intrinsic DH neurones (Section 9) and (3) those contained both in descending pathways and, primarily, in the central terminals of PAFs (Section 10). Finally, an additional group of modulators (Section 11) is comprised by the cannabinoids and adenosine, both of which can be ubiquitously generated by neuronal and non-neuronal units, rather than synthesised by specific neuronal pathways. In principle, two other modulators, in each case derived from the conversion of L-arginine, could be incorporated into this group: that is, nitric oxide (NO) and agmatine. However, within the present context, it is more appropriate to evoke their relevance to descending controls within the Sections devoted to cholinergic (NO) (Section 9.1), noradrenergic (NO and agmatine) (Sections 5.9 and 5.10) and glutamatergic (NO) (Section 10.2) mechanisms, respectively.

Fourth, Section 12 critically discusses those strategies clinically employed for the alleviation of pain via the recruitment of descending controls. In addition to a consideration of the advantages and disadvantages of techniques for direct spinal drug delivery, several novel approaches currently in development are reviewed.

Finally, in Sections 13 and 14, the article concludes with a brief summary of certain major insights into the operation and pathophysiological significance of descending controls which have emerged over recent years and which are likely to influence future research in this field.

Each section is intended to be self-sufficient in information so as to preclude the need for constant consultation of other parts of the Review. Nevertheless, extensive reference is made throughout to other sections in which complementary information may be found concerning specific aspects under consideration.

The accompanying-comprehensive, but by no means exhaustive-citation list prioritises key articles, other reviews and, in particular, recent literature which has as yet to be cited elsewhere. For an interesting historical perspective on descending controls, the pioneering work of Meyer et al. (1971); Meyer and Price (1976); Akil et al. (1976) and Besson et al. (1978, 1981), as well as the following authoritative sequence of reviews (Fields and Basbaum, 1978, 1994, 1999; Basbaum and Fields, 1984), is recommended.

2. Organisation of descending input to the DH

2.1. Relationship of descending pathways to primary afferent fibres and intrinsic DH neurones

2.1.1. Neuronal circuitry in the DH

For an understanding of the operation of descending pathways, it is essential to briefly consider their relationship to PAFs and other neuronal elements in the DH (Fig. 1). There is a vast literature devoted to synaptic processing of nociceptive input in the DH and the reader is referred to several more thorough and technical accounts for additional information (Besson and Chaouch, 1987; Willis, 1988; Willis and Coggeshall, 1991; Levine et al., 1993; Todd and Spike, 1993; Coggeshall and Carlton, 1997; Willis and Westlund, 1997; Bevan, 1999; Doubell et al., 1999; Millan, 1999; Raja et al., 1999; Wall and Melzack, 1999; Yaksh, 1999a).

Small calibre, unmyelinated, C PAFs, and medium calibre, myelinated Aδ PAFs, both of which are responsive to noxious (tissue-damaging) chemical, thermal and mechanical stimuli, convey nociceptive information principally to superficial (laminae I/II) and deep (V/VI) laminae of the DH, as well as to the circumcanular lamina X. On the other hand, large calibre, myelinated, rapidly-conducting Aβ fibres transmit information concerning innocuous, mechanical stimuli (but see Section 2.2) to deeper laminae (III–VI). PAFs either directly stimulate PNs, which relay their messages to the brain, or indirectly engage PNs via excitatory interneurones (EXINs). Comprising a brake on these actions, PAFs also target inhibitory interneurones (ININs) which interact with PNs, EXINs or the terminals of PAFs themselves. Descending pathways may, then, modulate nociception via an interaction with several neuronal elements in the DH: (1) the terminals of PAFs; (2) PNs; (3) intrinsic EXINs and ININs and (4) terminals of other descending pathways. Indeed, each of these modes of interaction occurs (Willis and Coggeshall, 1991; Fields and Basbaum, 1999; Millan, 1999; Yaksh, 1999a).

2.1.2. Multiple roles of transmitters in descending pathways: inhibition and facilitation

As summarised in Figs. 1–4, this configuration provides a framework permitting expression of mechanisms of either DI or DF. To take the former as an example, pathways mediating DI attenuate release of pronociceptive mediators from nocisponsive PAFs (termed "pre-synaptic" actions) and, directly or indirectly (via ININs), suppress their

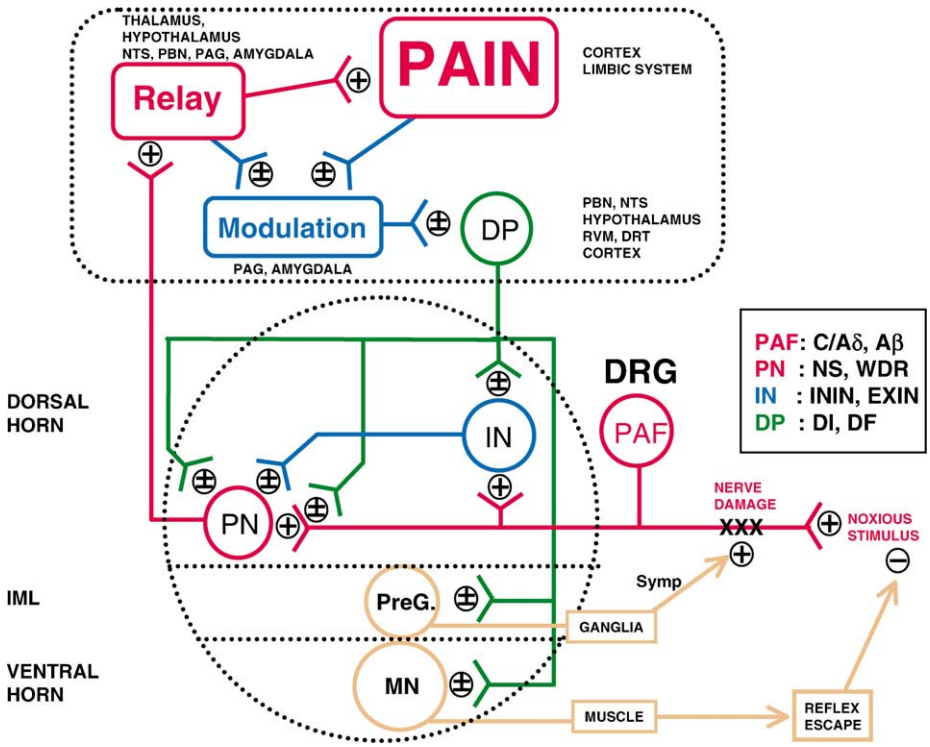

Fig. 1. Schematic illustration of the relationship between pathways descending to the spinal cord and intrinsic populations of neurones involved in the transmission and modulation of nociceptive information. Terminals of descending pathways (DP) originating in the rostroventral medulla (RVM) and other brainstem nuclei, the nucleus tractus solitarius (NTS), the parabrachial nucleus (PBN), the dorsal reticular nucleus (DRT), the hypothalamus and the cortex interact with afferent fibres (PAF), interneurones (INs) and projection neurones (PNs) in the DH. Actions at these sites, as a function of the influence of individual receptors upon cellular excitability, either suppress or enhance passage of nociceptive information to the periaqueductal grey (PAG), thalamus, hypothalamus, PBN, NTS, amygdala and other cerebral structures involved in its secondary processing. These stuctures transfer nociceptive information to corticolimbic regions, and interact with other centres to modulate the activity of descending pathways themselves. Descending pathways modulate sympathetic outflow by actions at preganglionic (PreG) sympathetic neurones in the intermediolateral cell column (IML). Following PAF injury, sympathetic efferents modify nociceptive input to the DH via actions in the dorsal root ganglia (DRG). Within the ventral horn, actions of descending pathways at motoneurones (MN) may indirectly modify nociceptive input by the initation of appropriate motor behaviours. Abbreviations are as follows: NS, nociceptive-specific; WDR, wide dynamic range: ININ, inhibitory interneurone and EXIN, excitatory interneurone. For further details, see text.

excitation of PNs (referred to as “post-synaptic” actions). This expression of DI at PAF terminals, PNs and EXINs presupposes an inhibitory influence of descending pathways upon neuronal activity. However, if DI is exerted via ININs, a facilitatory influence must be evoked necessitating either: (1) the involvement of an alternative neurotransmitter or (2) an action of the same transmitter mediated via a second receptor type differentially coupled to intracellular transduction mechanisms. The existence of several neurotransmitters in descending pathways-in certain cases, co-localised-permits the first of these possibilities. The second possibility appeals to a fundamental and universal insight into the actions of neurotransmitters which has progressively crystallised over recent years. That is, the existence of multiple receptors for individual transmitters which differentially modify neuronal activity. Descending controls conform well to this principle, as exemplified by 5-HT for which, as discussed in Section 7.4, at least 15 subtypes of receptor have been cloned. Of these, certain are excitatory and others inhibitory, corresponding to the bi-directional facilitatory and suppressive influence of 5-HT upon processing of nociceptive input in the DH (Boess and Martin, 1994; Millan, 1995, 1997; Barnes and Sharp, 1999). This assignment of contrasting roles to individual types of 5-HT receptor: (1) illustrates the complexity of studies designed to elucidate the roles of descending pathways; (2) indicates that the attribution of a single, unitary role to one transmitter, or to one class of descending pathway, may be erroneous and (3) more encouragingly, suggests that ligands which appropriately activate or block individual receptor types, or selected combinations of receptors, offer the possibility of highly-effective and well-tolerated analgesic agents (Section 12.5).

The earlier comments underline the complexity of descending controls. Furthermore, as pointed out in Sections 9 and 10, the occurrence of certain transmitters both in descending pathways and in intrinsic DH neurones and/or PAFs, further complicates the task of unravelling their respective roles. Evidently, a precise knowledge of: (1) neuronal architecture within the DH; (2) the identity of individual neurotransmitters released from descending pathways

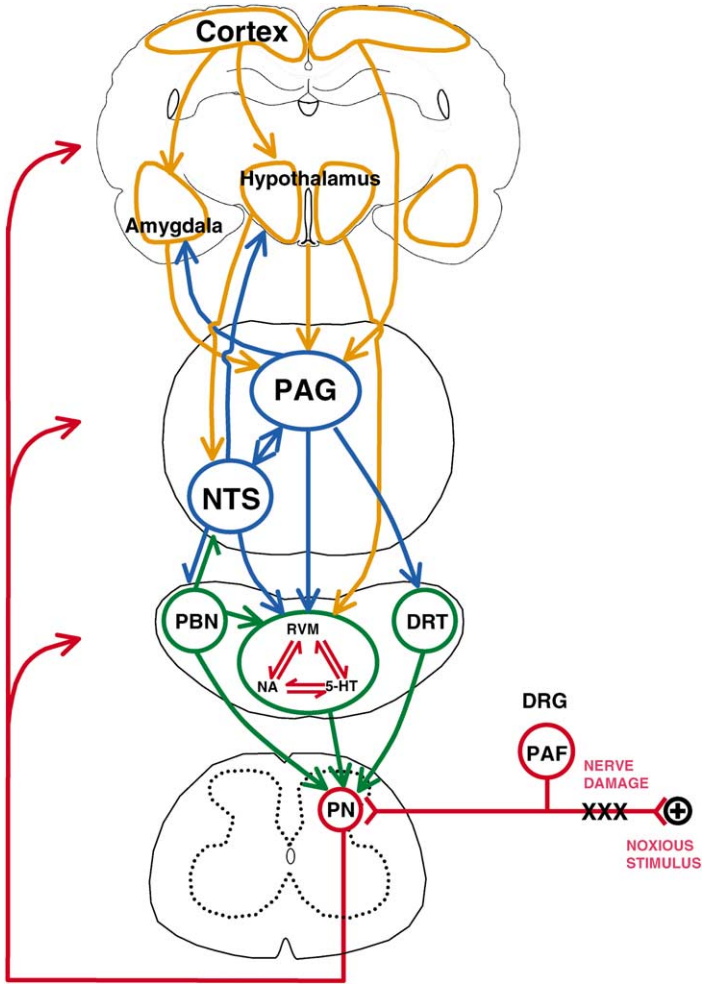

Fig. 2. Schematic view of the interrelationship between cerebral structures involved in the initiation and modulation of descending controls of nociceptive information. Note the strategic location of the periaqueductal grey (PAG) and the reciprocal nature of many interconnecting pathways. Direct projections from the cortex, hypothalamus and nucleus tractus solitarius to the DH are not indicated for clarity—direct pathways to the DH from the periaqueductal grey and amygdala are very sparse. Abbreviations are as follows: CX, cortex; Hypothal, hypothalamus; Amyg, amygdala; NTS, nucleus tractus solitarius; PBN, parabrachial nucleus; DRT, dorsoreticular nucleus; RVM, rostroventral medulla; NA, noradrenaline; perikarya 5-HT, serotonergic perikarya; PAF, primary afferent fibre and DRG, dorsal root ganglion. For further details, see text.

and (3) their influence upon neuronal activity via multiple, functionally-heterogenous receptors, is essential for a full understanding, and effective clinical harnessing, of mechanisms of DI and DF. In this light, it is important to remember that the output component of this system is constituted by PNs transmitting nociceptive information to the brain. In other words, the overall influence of specific drugs upon the activity of PNs is decisive. As a corollary, a thorough characterisation of the complete complement of inhibitory and excitatory receptors displayed by PNs, and of the precise influence of drugs upon their electrical activity, is of crucial importance. For example, the identification on PNs of receptors known to exert an inhibitory influence upon cellular excitability leads inexorably to the conclusion that their discrete activation will be associated with antinociception. Such information may provide insights into analgesic strategies permitting the circumvention of opposing actions of transmitters at multiple sites afferent to PNs.

2.2. Preferential modulation by descending pathways of nociceptive as compared to non-nociceptive information

In Fig. 1, the simplified schema of DH organisation does not incorporate those PAFs which normally transmit non-nociceptive information into the DH. In fact, certain nociceptive-specific PNs and interneurones (INs), predominantly localised in superficial laminae, respond only to noxious stimuli, whereas others, mostly in deeper laminae, are excited only by non-noxious input (Besson and Chaouch, 1987; Willis and Coggeshall, 1991; Wall and Melzack, 1999). Modulation of the former by descending pathways is of greater relevance to the appreciation of pain. An additional class of neurone is termed “wide-dynamic range” or “convergent”. Wide-dynamic range neurones, which are primarily encountered in deeper laminae, encode both innocuous and noxious information from the skin and other organs in a stimulus-dependent fashion

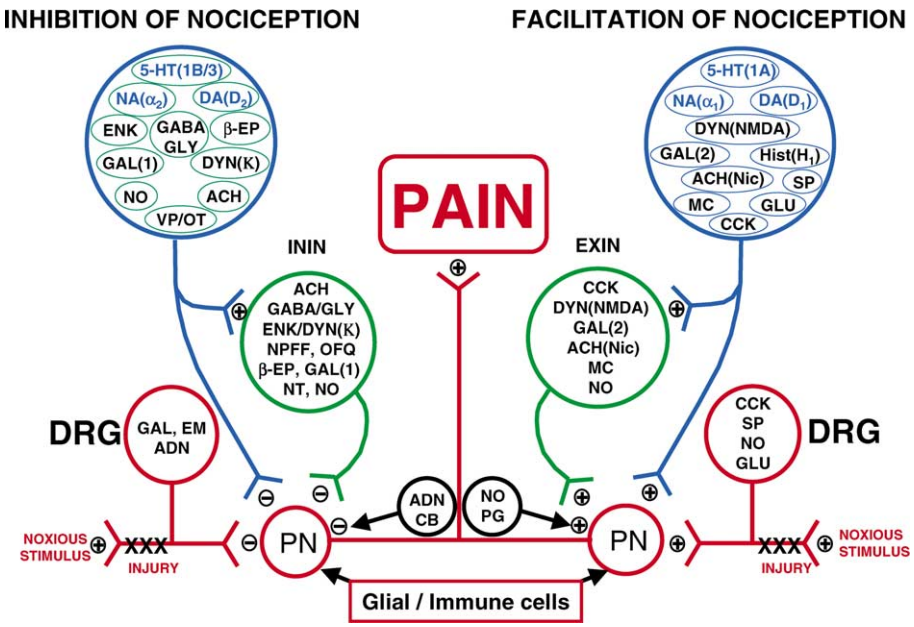

Fig. 3. Overview of the multiplicity of transmitters and other modulators involved in the modulation of nociceptive information in the DH. On the left-hand side, transmitters contributing to the induction of antinociception (descending inhibition) are indicated and on the right-hand side, those participating in pronociceptive processes (descending facilitation) are shown. This physical separation has, obviously, no anatomical foundation. The transmitters and modulators portrayed are those discussed in this review rather than an exhaustive compendium of all identified to date in the DH. For clarity, only principle localisation(s) are shown. Transmitters are contained in descending pathways themselves, inhibitory and excitatory interneurones (ININ and EXIN) and primary afferent fibre terminals. In addition, glial and immunocompetent cells are important sources of mediators modulating nociceptive processing in the DH. Two anatomically-undefined sources are shown: one incorporates the antinociceptive modulators, cannabinoids (CB) and adenosine (ADN) and the other includes nitric oxide (NO) and prostaglandins (PG). NO can both enhance and suppress nociceptive transmission, while prostaglandins act pronociceptively. Individual receptor types are indicated only for transmitters which appear at multiple loci and which exert opposite antinociceptive versus pronociceptive properties. Abbreviations are as follows; PN, projection neurone; DRG, dorsal root ganglion; CCK, cholecystokinin; SP, substance P; CGRP, calcitonin gene related peptide; GLU, glutamate; DYN, dynorphin; NMDA, *N*-methyl-D-aspartate; MC, melanocortin; 5-HT, serotonin; NA, noradrenaline; DA, dopamine; Hist, histamine; GAL, galanin; EM, endomorphin; ACh, acetylcholine; GABA, γ-hydroxy-butyric acid; GLY, glycine; ENK, enkephalin; NPFF, neuropeptideFF; OFQ, orphaninFQ (nociceptin); β-EP, β-endorphin; VP, vasopressin and OT, oxytocin. For details, see text.

(Besson and Chaouch, 1987; Willis and Coggeshall, 1991; Wall and Melzack, 1999). Their sensitisation by repetitive, nociceptive stimulation plays a key role in the induction of long-term, clinical, inflammatory and/or neuropathic painful states: i.e. pain involving tissue and/or nerve damage (Willis, 1994; Baranauskas and Nistri, 1998; Doubell et al., 1999; Millan, 1999). It is well-established that wide-dynamic range neurones are important substrates for the expression of descending controls (Willis, 1988; Fields and Basbaum, 1999; Millan, 1999). In this light, there is evidence that descending pathways can preferentially modify the response of a single wide-dynamic range neurone to nociceptive versus non-nociceptive modes of input (Willis, 1988; Fields and Basbaum, 1999; Millan, 1999). There are several explanations (outlined in the following sections for DI) for this seemingly paradoxical observation (Millan, 1999): (1) descending pathways may exclusively interact with the terminals of nocisponsive PAFs, either directly or via ININs; (2) they may selectively inhibit EXINs engaged by nocisponsive PAFs; (3) by virtue of compartmentalised, post-synaptic actions at discrete loci on the dendrites and/or soma of PNs, descending pathways may primarily inhibit their excitation via topographically-contiguous input from nocisponsive PAFs—that is, physically-adjacent terminals of descending pathways and nocisponsive PAFs may interact at a common site on PNs and (4) intracellular signals (soluble second messengers, protein kinases, ion currents, etc.) engaged by descending pathways in PNs may primarily modify signals transducing the actions of nocisponsive PAFs. This issue is of considerable practical importance inasmuch as analgesic strategies modifying DI or DF (like other forms of pain relief) should abrogate excessive nociceptive transmission without eliminating all forms of sensory input per se.

On the other hand, following tissue and, in particular, nerve damage, large calibre Aβ fibres play a crucial role in mediating mechanical allodynia: i.e. the pain elicited by normally innocuous mechanical stimuli, such as light touch (Woolf and Doubell, 1994; Doubell et al., 1999; Millan, 1999; Woolf and Mannion, 1999). Briefly, this can be explained by a change in the phenotype (pattern of neurotransmitter expression) of PAFs whereby they begin to synthesise excitatory neurotransmitters, such as substance P (SP), which are normally present only in nocisponsive, fine calibre PAFs. Further, upon injury, the aberrant re-orientation of PAFs into superficial DH laminae allows

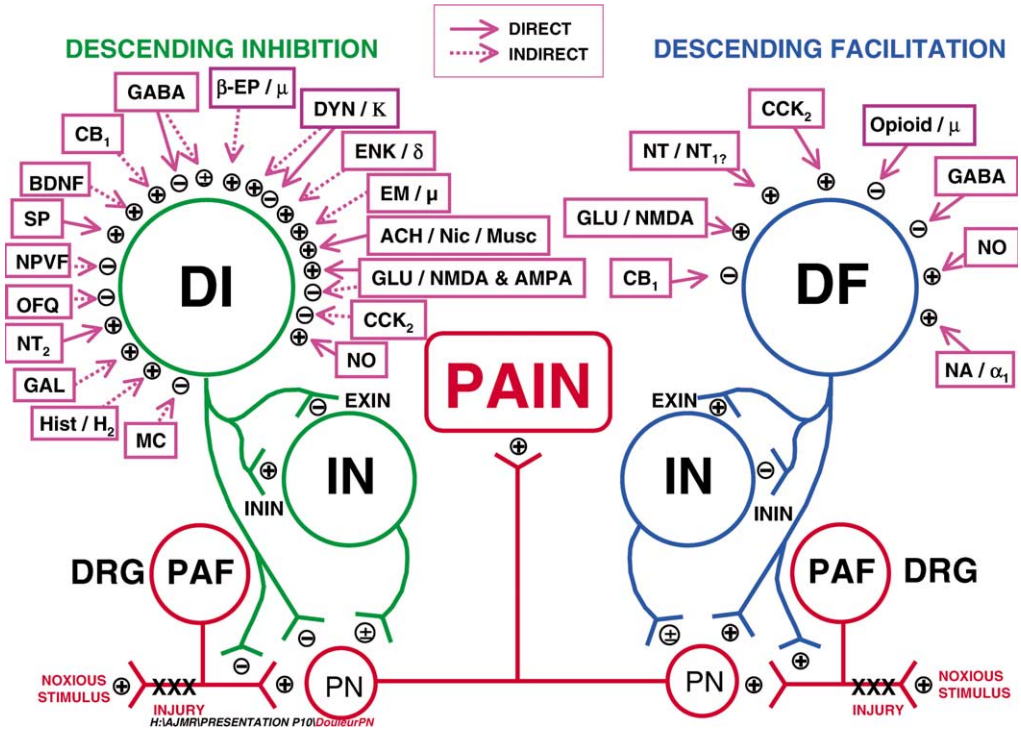

Fig. 4. Overview of the multiplicity of mechanisms involved in the modulation of the activity of pathways mediating descending inhibition as compared to descending facilitation. In the left and right panels, mechanisms modulating descending inhibition (DI) and facilitation (DF) are indicated, respectively. Certain act directly and others indirectly via intervening neurones. For mechanisms modulating DI, in many cases, actions at "OFF" cells in the rostroventromedial medulla and at serotonergic and noradrenergic neurones are involved, but additional mechanisms are certainly implicated. For mechanisms modulating DF, actions at "ON" cells in the rostroventromedial medulla and at descending pathways releasing transmitters indicated in Fig. 2 are likely implicated but they remain poorly defined. At the level of the DH, note that pathways mediating DI and DF exert opposite patterns of influence upon primary afferent fibre (PAF) terminals, projection neurones (PNs), excitatory interneurones (EXINs) and inhibitory interneurones (ININs). Abbreviations are as follows: DRG, dorsal root ganglion; NO, nitric oxide; CCK, cholecystokinin; NT, neurotensin; GLU, glutamate; NMDA, *N*-methyl-D-aspartate; ACh, acetylcholine; musc, muscarinic; nic, nicotinic; DYN, dynorphin; ENK, enkephalin; β-EP, β-endorphin; EM, endomorphin; GABA, γ-hydroxy-butyric acid; Hist, histamine; CB, cannabinoid; NA, noradrenaline; SP, substance P; NPVF, neuropeptide VF and OFQ, orphanin FQ (nociceptin). For details, see text.

them to escape pre-synaptic inhibitory controls and results in their contact with nociceptive-specific PNs which they would not otherwise access. These changes may contribute to the relative resistance of mechanical allodynia accompanying PAF injury to conventional analgesics such as opioids (Arner and Meyerson, 1988; Dellemijn and Vanneste, 1997; Bian et al., 1999; Suzuki et al., 1999; Catheline et al., 2001; Enggaard et al., 2001; Von Heijne et al., 2001). They also suggest that post-synaptic mechanisms for suppression of the influence of Aβ fibres upon nociceptive-specific PNs in the superficial DH may be particularly efficacious in the management of otherwise-intractable, neuropathic pain.

2.3. Role of volume transmission in the actions of descending pathways

Although the earlier discussion implicitly assumes direct, synaptic contact between descending pathways and other neuronal units, there is increasing evidence for "volume transmission" in the DH (Zoli and Agnati, 1996; Coggeshall and Carlton, 1997; Agnati et al., 2000; Duggan, 2000). This process, which is complementary to "hard-wiring" modes of communication, has been established for transmitters released from PAFs and is similarly applicable to transmitters, such as 5-HT and acetylcholine (ACh), derived from descending pathways (Ridet et al., 1993; Duggan, 2000; Cordero-Erausquin and Changeux, 2001; Kiss and Vizi, 2001). Volume transmission refers to the diffusion of transmitters to sites distant from the synaptic cleft: this permits persistent and widespread, rather than transient and localised, modulation of neuronal activity in the DH via effects at receptors not necessarily apposed to terminals of descending pathways. Such delayed and prolonged actions are markedly influenced by transmitter stability and reuptake and, broadly-speaking, are reminiscent of the effects of exogenous drug application onto the spinal cord via intrathecal (i.t.) catheters (Section 12.3).

2.4. Interactions of descending pathways with glial and immunocompetent cells

While preceding sections focused on the interrelationships between descending pathways and neurones, it is important to evoke their potential influence upon non-neuronal

units in the DH. That is: (1) resident glial cells (astrocytes, oligodendrocytes and immunocompetent microglia) and (2) immigrant, immunocompetent T cells. The latter can infiltrate the DH following damage to the spinal cord, to PAFs or to peripheral tissue, events provoking a loss of blood–brain barrier integrity (Millan, 1999; Watkins and Maier, 1999a,b; Bezzi and Volterra, 2001; DeLeo and Yezierski, 2001). The functional status of glial cells is subject to modulation by glutamate, ACh, SP, γ-amino-butyric acid (GABA), 5-HT, noradrenaline (NA), adenosine and other transmitters originating in descending pathways, PAF terminals and intrinsic DH neurones (Jalonen et al., 1997; Fujita et al., 1998; Hirst et al., 1998; Kulik et al., 1999; Millan, 1999; Verkhratsky et al., 1998; Watkins et al., 2001). Of particular note is the accumulation by glia of glutamate, GABA and glycine (Sections 9.2 and 10.2): that is, key excitatory versus inhibitory transmitters involved in nociceptive processing in the DH (Millan, 1999; Danbolt, 2001; Gadea and Lopez-Colomé, 2001a,b,c). Further, glial cells have been shown to regulate neuronal cholinergic transmission via secretion of a ACh-binding protein (Smit et al., 2001), and to control glutamatergic function by modification of the subunit composition of *N*-methyl-D-aspartate (NMDA) receptors on neurones (Daniels and Brown, 2001). Glial and immunocompetent cells generate a plethora of factors which can influence nociceptive processing in the DH: notably, cytokines (such as interleukins, neurotrophins and tissue necrosis factor α), nitric oxide (NO), prostaglandins, histamine, adenosine triphosphate (ATP) glycine, and glutamate (Millan, 1999; Kiss and Vizi, 2001; Nakajima et al., 2001; Vanegas and Schaible, 2001; Watkins et al., 2001). Further, upon "up-regulation" of the activity of glial cells in the DH by PAF injury or "illness" (Section 4.2), they make an important contribute to the expression of DF and the induction of pain (Meller et al., 1994; Watkins et al., 1997a, 2001; Millan, 1999; Watkins and Maier, 1999a,b; Sweitzer et al., 2001a,b). It is probable that interactions between descending pathways and non-neuronal units in the DH, which have to date been neglected, will emerge to be of broad importance to spinal nociceptive processing (Carmignoto, 2000; Bezzi and Volterra, 2001; Kiss and Vizi, 2001).

2.5. Actions of descending pathways in spinal cord regions other than the DH

2.5.1. Modulation of autonomic (sympathetic and parasympathetic) outflow

Sympathetic (intermediolateral cell column (IML)) and parasympathetic preganglionic nuclei of the thoracolumbar and sacral spinal cord, respectively, receive an intense innervation from several classes of descending pathway, notably, those containing 5-HT or NA, together with co-localised neuropeptides such as SP and thyrotropin releasing hormone (Sections 5.7 and 7.1.3) (Bowker et al., 1983, 1988; Wu et al., 1993; Ruda et al., 1986; Millan, 1997; Hökfelt et al., 2000). There are several important implications of this pronounced input from descending pathways to autonomic nuclei in the spinal cord (Fig. 1). First, in experimental studies, perturbation of cardiovascular parameters can confound interpretation of the influence of descending pathways upon pain thresholds. Second, even the direct, spinal administration of drugs in man does not permit complete dissociation of analgesia from (spinally-integrated) cardiovascular actions (Section 12.3) (Eisenach et al., 1996; Dougherty and Staats, 1999; Yaksh, 1999a,b). Third, modification of sympathetic and parasympathetic outflow may, via baroceptor-monitored changes in arterial pressure, lead to alterations in nociception mediated by descending pathways themselves (Randich and Maixner, 1984; Ren et al., 1991; Gebhart and Randich, 1992; Thurston and Helton, 1996; Taylor et al., 2000). Thus, through a supraspinal loop, principally involving vagal afferents to the nucleus tractus solitarius (NTS), descending pathways can modify their own activity via actions in autonomic centres of the spinal cord. Fourth, an alteration in sympathetic outflow can modify peripheral tissue inflammation and the associated nociception (Levine et al., 1993; Levine and Reichling, 1999; Millan, 1999; Raja et al., 1999). More importantly, neuropathic pain can be exacerbated by sympathetic stimulation of damaged PAFs following the diversion of sympathetic fibres into the dorsal root ganglion (DRG) (McLachlan et al., 1993; Woolf and Doubell, 1994; Kinnman and Levine, 1995; Elam et al., 1999; Millan, 1999; Raja et al., 1999; Woolf and Mannion, 1999; Kalmari et al., 2001). Correspondingly, inhibition of sympathetic output may be implicated in the spinal, analgesic actions of several drug classes including, for example, α_2-AR agonists (Yaksh et al., 1995; Millan, 1997; Yaksh, 1999a).

2.5.2. Modulation of motor function

Descending pathways also provide an intense input to the ventral horn (VH), wherein they exert a pronounced control of motor function. Interestingly, in analogy to the IML, the extent of co-localisation of neuropeptides and other transmitters (such as SP, thyrotropin releasing hormone, neuropeptide Y and glutamate) with the massive projections of monoaminergic tracts to the VH is far more pronounced than for the DH (Bowker et al., 1983; Todd and Spike, 1993; Wu et al., 1993; Maxwell et al., 1996; Millan, 1997; Hökfelt et al., 2000). Thus, a major source of potential error in experimental studies of the influence of drugs upon nociceptive processing in the DH is their modification of motor performance by effects in the VH. Moreover, it is imperative to consider any possible impact of drugs upon motor function prior to their clinical evaluation as potential analgesic agents. From a pathophysiological perspective, control of motor function may be of significance to nociception and its processing in that motor responses (reflexes and more elaborate, co-ordinated escape behaviours) permit termination of exposure to noxious stimuli (Fig. 1). Further, inhibition of motoneurone (MN) activity constitutes the output loop of processes encouraging immobility, and thereby recovery and recuperation following injury

(Millan, 1999). Finally, pain from the peritoneal region is characterised by a protective rigidification of the abdominal musculature (Millan, 1999). Clearly, then, the possible influence of drugs upon the motor component of spinal nociceptive reflexes must be carefully evaluated for a full appreciation of their overall influence upon painful states.

3. Supraspinal origins of pathways descending to the DH

3.1. Common sites of origin for mechanisms of descending inhibition and facilitation

There is no absolute anatomical separation between structures involved in the initiation of mechanisms of DI as compared to DF (Table 1). Common loci in both the rostroventromedial medulla (RVM) and NTS, for example, give rise to descending pathways engendering DI or DF, albeit via contrasting mechanisms. (Fields et al., 1991; Watkins et al., 1994; Wiertelak et al., 1997; Fields and Basbaum, 1999; McNally, 1999; Urban et al., 1999a,b,c; Nuseir and Proudfit, 2000). Indeed, even a single transmitter, such as 5-HT (Sections 7.3 and 7.4), may concurrently mediate DI and DF via activation of: (1) multiple subtypes of receptor differentially coupled to intracellular transduction mechanisms and (2) a single receptor type localised on functionally-distinct classes of target neuron in the DH (Millan, 1995, 1997; Garraway and Hochman, 2001a,b).

Descending pathways access the spinal cord via the dorsolateral and ventrolateral funiculi, and it has been suggested that these systems are differentially employed by mechanisms of DI and DF (Zhuo and Gebhart, 1997; Watkins et al., 1998; Wei and Dubner, 1998). For example, a prominent component of DI (likely involving noradrenergic and serotonergic pathways) elicited from the brainstem projects to the DH via the dorsolateral funiculius, while its ventrolateral counterpart contributes to mechanisms of DF evoked from this region (Zhuo and Gebhart, 1997; Watkins et al., 1998; Wei and Dubner, 1998). However, inasmuch as 5-HT mediates both pro and antinociceptive actions in the DH (Sections 7.3 and 7.4), the dorsolateral quadrant evidently also channels mechanisms of DF to the DH. Indeed, stimulation of the dorsolateral funiculus can excite neurons in the DH, while its disruption moderates the DF and excessive nociception associated with, for example, PAF injury (McMahon and Wall, 1988; Kovelowski et al., 2000; Ossipov et al., 2000; Vanderah et al., 2001a,b; Porreca et al., 2001). Thus, the precise descending routes to the DH adopted by various modes of DI and DF still require clarification.

Chemical (generally glutamate) and electrical stimulation of numerous cerebral structures can modulate nociception via spinal mechanisms, but such effects are not invariably

Table 1
Overview of monosynaptic pathways descending to the DH and the transmitters/receptors involved in their influence upon nociception

Structure	Primary transmitters(s)	Other transmitters	Anti	Pro
Hypothalamus				
Paraventricular	VP/OT	DYN, ENK, NO, NPFF	VP_{1a}/OT	–
Tuberomammillary	Histamine	GABA, GAL, ENK, ADN	–	H_1
Posterior periventricular (A_{11})	DA	CGRP	D_2	D_1
Arcuate	β-EP, MC	CART	μ-Opioid	MC_4
Parabrachial nucleus	?	GAL?	Yes	–
Nucleus tractus solitarius	?	GAL?, β-EP, OFQ, NPFF	Yes	Yes?
Brainstem				
NRM	5-HT	GABA, GLU, ENK, GAL, CCK, SP	$5\text{-HT}_{1B,2,3}$	$5\text{-HT}_{1A,2,3}$
RVM	ACh	GABA, glycine, ENK, CCK	Musc, Nic	Nic
A_5, A_6, A_7 nuclei	NA	GABA, GLU, ENK, GAL, NPFF	α_{2A}, $\alpha_{2B/2C}$?	α_{1A}, α_{1B}?
Dorsal reticular nucleus	?	?	Yes	Yes
Cerebral cortex				
Anterior cingulate	?	?	–	Yes
Frontal, parietal	?	?	Yes	–
Periaqueductal grey	CCK/SP	?	–	CCK_2/NK_1

The Table provides an overview of the principle pathways which directly innervate the DH of the spinal cord, and the transmitters/receptors involved in the expression of their functional actions: pro and antinociceptive. The influence upon nociception is indicated for the primary transmitter only. In certain cases, the neurotransmitters have not been concretely identified: in these cases, "Yes" indicates that a pro and/or antinociceptive role, respectively, has been attributed upon stimulation of the structure concerned. "Other transmitters" are not necessarily co-localised with primary transmitter(s) in single neurones. For the RVM, there is no real distinction between the "primary" (ACh) and "other" transmitters in terms of their relative importance. VP, vasopressin; OT, oxytocin; DYN, dynorphin; ENK, enkephalin; NO, nitric oxide; GABA, γ-amino-butyric acid; GAL, galanin; ENK, enkephalin; ADN, adenosine; DA, dopamine; CGRP, calcitonin gene related peptide; β-EP, β-endorphin; MC, melanocortin; CART, cocaine and amphetamine related transcript; NPFF, neuropeptideFF; OFQ, orphaninFQ; 5-HT, serotonin; GLU, glutamate; CCK, cholecystokinin; SP, substance P; ACh, acetylcholine; Musc, muscarinic; Nic, nicotinic; NA, noradrenaline; NK, neurokinin; NRM, nucleus raphe magnus and RVM, rostroventromedial medulla.

mediated by pathways descending directly to the spinal cord (Basbaum and Fields, 1984; Millan, 1986; Ruda et al., 1986; Willis, 1988; Fields et al., 1991; Stamford, 1995; Fields and Basbaum, 1999). Attention is focused herein upon descending pathways which monosynaptically innervate the spinal cord and, where known, upon those neurochemical mechanisms which modulate and mediate their actions.

Prior to a detailed consideration of the pertinence of specific transmitters, it is instructive to indicate those cerebral structures which modulate nociceptive processing via direct (monosynaptic) pathways to the DH (Fig. 2). For certain of these, the identity of transmitters expressing DI and/or DF remains to be ascertained (Table 1).

3.2. Supraspinal regions giving rise to pathways directly descending to the DH

3.2.1. Hypothalamus

Although the hypothalamus is not traditionally associated with nociceptive processing, it plays an important role in co-ordinating autonomic and sensory information, and it is the recipient of a major ascending pathway transmitting nociceptive information from the DH (Giesler, 1995; Paxinos, 1995; Millan, 1999). The hypothalamus is extensively interlinked with the NTS, PAG and RVM together with corticolimbic structures implicated in the affective and cognitive dimension of pain (Millan, 1999). Several nuclei are implicated in nociceptive processing and descending controls. The medial preoptic nucleus projects intensely to the periaqueductal grey, and also to the RVM (Sections 3.2.4 and 3.3), probably via glutamatergic pathways (Murphy et al., 1999; Jiang and Behbehani, 2001), but not to the DH. It plays an important role in the autonomic response to pain, and its stimulation inhibits the response of spinal neurones to noxious stimuli (Lumb, 1990). Stimulation of the anterior hypothalamus suppresses the response of wide-dynamic range neurones in the DH to noxious stimulation (Carstens, 1986; Workman and Lumb, 1997). Further, stimulation of the lateral hypothalamus elicits antinociception via (possibly glutamatergic) relays to the PAG and RVM (NRM), which ultimately trigger the activation of descending noradrenergic pathways (Aimone et al., 1988; Behbehani et al., 1988; Cechetto and Saper, 1988; Dafny et al., 1996; Franco and Prado, 1996; Holden and Naleway, 2001). Injection of opioids into the posterior, pre-optic and arcuate nuclei of the hypothalamus elicits behavioural antinociception (Manning and Franklin, 1998; Yaksh, 1999a), while lesions of its medial component and several other nuclei can elicit hyperalgesia (Section 9.3.5) (Millan, 1986; Hamba, 1988; Truesdell and Bodnar, 1987). The role of a neurochemically-defined pathway running from the ventromedial/dorsomedial hypothalamus to the PAG in the modulation of nociception is considered in Section 9.4. Finally, apart from the lateral hypothalamus-which provides a minor input to the DH (see above: Cechetto and Saper, 1988)-several hypothalamic centres, including the paraventricular nucleus (PVN) (Section 8.2), the arcuate nucleus (Section 9.3.5), the tuberomamillary nucleus (Section 8.1.1) and the posterior periventricular nucleus (Section 6.2) provide direct and neurochemically-defined pathways to the DH and other regions of the spinal cord.

3.2.2. Parabrachial nucleus

The parabrachial nucleus (PBN), which is situated within the dorsolateral pontomesencephalic tegmentum of the brainstem, mimics the hypothalamus in playing a major role in the integration of autonomic and somatosensory information, in being interlinked with higher structures involved in the emotional and cognitive dimension of pain and in receiving nociceptive (in particular, visceral) information directly from the medullary DH and spinal cord (Yoshida et al., 1997; Fields and Basbaum, 1999; Millan, 1999; Wei et al., 1999a; Bester et al., 2001; Bourgeais et al., 2001b; Wang et al., 2001a). Various sub-divisions of the PBN project to the NTS, RVM, spinal DH and the functionally-homologous trigeminal nucleus of the medulla (which subserves processing of nociceptive input from cranial tissues). Pathways emanating from the PBN predominantly target neurones localised in superficial DH laminae. Stimulation of the PBN suppresses the response of DH neurones to both nociceptive and non-nociceptive input (Beitz et al., 1987; Chiang et al., 1994; Yoshida et al., 1997).

3.2.3. Nucleus tractus solitarius

The NTS fulfils a key role in the processing of visceral information, receiving a major input from the vagal nerve, as well as afferents from superficial and deep DH neurones (Millan, 1999; Pan et al., 1999a; Gamboa-Esteves et al., 2001). Like the PBN, with which it is interconnected, the NTS behaves as an interface between autonomic and sensory systems, is reciprocally linked with the hypothalamus and limbic and cortical regions, provides a major input to the PAG and monoaminergic nuclei of the brainstem, and directly projects to the spinal cord (Lewis et al., 1987; Mtui et al., 1993; Randich and Meller, 1994; Tavares and Lima, 1994; Paxinos, 1995; Wiertelak et al., 1997; Pan et al., 1999a). Stimulation of the NTS can elicit antinociception (Aicher and Randich, 1990; Morgan et al., 1989b). On the other hand, several studies have focused on the importance of vagal input to the NTS in triggering mechanisms of DF via the RVM (Section 4.3) (Ren et al., 1991; Gebhart and Randich, 1992; Zhuo and Gebhart, 1992, 1997; Watkins et al., 1994; Wiertelak et al., 1997).

3.2.4. Rostroventromedial medulla

As discussed in detail in Sections 5.2 and 7.1, the brainstem contains several clusters of neurons from which monoaminergic pathways to the spinal cord are derived. Much attention has been focused on its rostroventromedial component, the RVM, which has been meticulously analysed as regards the involvement of specific transmitters and cell types in the induction of DF and DI. Although

the RVM may directly receive sensory input, the activity of descending pathways originating therein is primarily modified by afferents from the PAG, PBN, NTS and other structures involved in the supraspinal receipt and processing of nociceptive information (Fields et al., 1991; Fields and Basbaum, 1999; Millan, 1999; Zagon, 2001). It is a heterogeneous region incorporating several nuclei, each of which provides (largely direct) descending pathways to both superficial and deep DH laminae. Although nomenclature is confusing and not invariably consistent, one may recognise the following subdivisions: medially, the NRM, a structure rich in serotonergic perikarya, and more dorsally and/or laterally, the nucleus reticularis gigantocellularis, the nucleus gigantocellularis pars alpha and the nucleus reticularis paragigantocellularis lateralis (Basbaum and Fields, 1984; Fields et al., 1991; Watkins et al., 1998; Fields and Basbaum, 1999; McNally, 1999; Urban et al., 1999a,b,c; Urban and Gebhart, 1999; Wei et al., 1999b; Azami et al., 2001). For clarity, the present review confines terminology to the "RVM" or, where appropriate, specifies the NRM.

RVM-localised sites acting as substrates for DF and DI appear to be intermingled with no obvious pattern of topographical separation (Fields et al., 1991; Zhuo and Gebhart, 1997; Fields and Basbaum, 1999). Nevertheless, based on functional characteristics, several contrasting classes of neurone have been recognised (Fields et al., 1991; Fields and Basbaum, 1999; Mason, 1999). First, "OFF" cells are (indirectly) excited by opioids and inhibited by nociceptive input: they display a transient interruption in their discharge immediately prior to a nociceptive reflex and are thought to participate in the induction of DI. Second, "ON" cells are inhibited by opioids and excited by nociceptive input: they are thought to trigger DF (Bederson et al., 1990; Fields et al., 1991; Kaplan and Fields, 1991; Zhuo and Gebhart, 1992, 1997; Fields and Basbaum, 1999; Mason, 1999; Fields, 2000; Gao and Mason, 2000). The neurochemical signatures of OFF and ON cells remain to be deciphered. A further, related population of cells has been classified as "primary" or "secondary" in accordance with their contrasting phenotypes, responsivity to opioid agonists and roles in the descending modulation of nociceptive processing in the DH (Pan et al., 1990, 1993, 1997, 2000; Pan, 1998; Ackley et al., 2001). Certain primary and secondary cells appear to be serotonergic and GABAergic in nature, respectively (Sections 7.3.3 and 9.2.4).

Engagement of RVM-derived pathways mediating DI and/or DF plays a crucial role in the modulation of nociceptive processing under conditions of sustained pain due to tissue inflammation and PAF injury (Section 4.3) (Li et al., 1998; Wei et al., 1999b; Azami et al., 2001; Porreca et al., 2001).

3.2.5. Dorsal reticular nucleus of the medulla

The dorsal reticular nucleus, which is situated in the dorsolateral quadrant of the medulla just adjacent and lateral to the NTS, receives nociceptive input from both somatic and visceral tissue. It projects directly to superficial and deep laminae of the DH, including a population of PNs which themselves project to the dorsal reticular nucleus (Tavares and Lima, 1994), thereby closing a reverberating DH–dorsal reticular nucleus–DH loop. Stimulation of the dorsal reticular nucleus elicits hyperalgesia, while its lesioning abrogates inflammatory pain as revealed by cellular markers in identified, nocisponsive DH neurones (Almeida et al., 1993, 1996, 1999). Conversely, it has been postulated that a group of neurones in the dorsal reticular nucleus participates in the expression of "Diffuse Noxious Inhibitory Controls", the activation of which by tissue damage can elicit analgesia in other regions (Bouhassira et al., 1992) (Section 4.1). Thus, in analogy to numerous other supraspinal structures, it appears that mechanisms originating in the dorsal reticular nucleus can mediate either DF or DI. Unfortunately, little is known concerning the neurochemistry and modulation of output pathways from this structure.

3.3. Role of the periaqueductal grey in the modulation of descending controls

As discussed throughout this review, the PAG plays a pivotal role in the modulation of nociceptive processing: for example, GABAergic antagonists (Section 9.2.4), cannabinoids (Section 11.1.3), and μ-opioid agonists (Section 9.3.5) all initiate brainstem-integrated, monoaminergic mechanisms of DI via actions in this structure (Fields and Basbaum, 1978; Millan, 1982, 1986; Basbaum and Fields, 1984; Behbehani, 1995; Stamford, 1995; Fields and Basbaum, 1999; Yaksh, 1999a; Bajic et al., 2001).

The PAG is heterogeneous in terms of its cytoarchitectonic and neurochemical organisation (Fields et al., 1991; Bandler and Keay, 1994; Keay et al., 1997; Fields and Basbaum, 1999; Ruiz-Torner et al., 2001). It receives direct (and indirect) nociceptive input from the DH (Hylden et al., 1986; Besson and Chaouch, 1987; Millan, 1999) and is reciprocally interconnected with the hypothalamus, the PBN, the NTS and diverse corticolimbic structures, including the frontal cortex and amygdala, in line with their key roles in the control of emotion-in particular, anxiety and fear (Coffield et al., 1992; Gray and Magnuson, 1992; Fanselow et al., 1995; Paxinos, 1995; Brandao et al., 1999; Yaksh, 1999a; Bourgeais et al., 2001a; Odeh and Antal, 2001). Indeed, antinociception elicited from the amygdala-which only minimally projects to the spinal cord-may involve a PAG link to the brainstem (Mizuno et al., 1985; Helmstetter et al., 1998; Manning, 1998; Pavlovic and Bodnar, 1998; Ahn et al., 2001; Bourgeais et al., 2001a; Manning et al., 2001; Oliveira and Prado, 2001; Shane et al., 2001; Neugebauer and Weidong, 2002).

Direct links from the PAG to serotonergic and non-serotonergic neurones of the RVM, as well as to the A_7 noradrenergic nucleus of the medulla (Sections 5.3 and 7.3), are important pathways for expression of its role in the modulation of descending controls (Cameron et al., 1995;

Fields and Basbaum, 1999; Mason, 1999; Bajic et al., 2001; Odeh and Antal, 2001). Notably, excitatory pathways projecting from the PAG to brainstem neurones initiating DI are subject to tonic, inhibitory control by GABAergic ININs in the PAG: relief of GABAergic control by, for example, μ-opioids and cannabinoids, contributes to their induction of analgesia from the PAG (Sections 9.2.4, 9.3.5 and 11.1.3) (Fields and Basbaum, 1999; Christie et al., 2000; Vaughan et al., 2000; Hernandez and Vanegas, 2001). Glutamatergic, serotonergic (from the DRN) and neurotensin (NT)-containing neurones participate in this excitatory link between the PAG and the RVM (Beitz, 1982b, 1990; Beitz et al., 1983; Wiklund et al., 1988; Urban and Smith, 1993; Guimaraes and Prado, 1999; Kirifides et al., 2001). Glutamate may also be utilised by efferents from the PAG to the noradrenergic A_7 nucleus (Beitz, 1990; Cameron et al., 1995; Bajic and Proudfit, 1999; Bajic et al., 2001): however, direct support is lacking for this contention. Conversely, there is strong evidence that the release of SP from efferents travelling from the PAG to the A_7 nucleus initiates noradrenergic mechanisms of DI from this structure (Yeomans and Proudfit, 1992; Holden and Proudfit, 1994; Nakaya et al., 1994; Proudfit and Monsen, 1999).

A few inhibitory GABAergic and enkephalin (ENK)-containing neurones project from the PAG to the RVM, and a more substantial population innervates the A_7 noradrenergic nucleus (Prichard and Beitz, 1981; Holden and Proudfit, 1995, 1998). Direct contacts with neurones mediating DI and DF from these regions would, in principle, account for pro and antinociceptive actions, respectively. However, there is evidence from studies of the A_7 nucleus that such inhibitory pathways (from the PAG and elsewhere) primarily target local ININs. Their activation offers, thus, a substrate for the indirect, polysynaptic inception of DI via disinhibition of noradrenergic perikaria (Bajic et al., 2001).

Finally, a small population of fibres directly projects from the PAG to the trigeminal nucleus and DH. Although their neurochemical identity remains incompletely resolved, both SP and cholecystokinin (CCK) have been identified in a pathway running from the PAG to the spinal cord (Skirboll et al., 1983; Li et al., 1993; Noble and Roques, 1999).

3.4. The cerebral cortex and descending controls

The cognitive and emotional dimension of pain is of special importance as concerns both its experience and clinical management. Evidence is accumulating that cortical structures fulfil a more active role in nociceptive processing than hitherto appreciated (Bolles and Fanselow, 1980; Burkey et al., 1996; Casey, 1999; Millan, 1999; Shi and Davis, 1999; Bechara et al., 2000; Fields, 2000; Price, 2000; Hofbauer et al., 2001; Johansen et al., 2001; Keogh et al., 2001; Labuda and Fuchs, 2001). Indeed, via relays in other cerebral structures such as the PAG, stimulation of the insular and ventro-orbital cortex can evoke antinociception (Zhang et al., 1997b; Yang and Follet, 1998; Burkey et al., 1999; Millan, 1999; Shi and Davis, 1999). On the other hand, stimulation of the anterior cingulate cortex, a region involved in the "aversiveness" of pain, can elicit DF in the rat (Calejesan et al., 2000; Apkarian et al., 2001; Johansen et al., 2001). The frontal cortex projects strongly to the NRM (serotonergic neurones) and other regions of the RVM, while frontocortical, somatosensory and parietal regions of the cortex are a source of direct corticofugal projections terminating throughout the DH, and principally targeting intrinsic neurones (Miller, 1987; Hurley et al., 1991; Tsujio et al., 1998; Bushnell et al., 1999; Kuroda et al., 2001; Varga et al., 2001). It has been demonstrated that stimulation of these regions (and the motor cortex) modifies nociception in man and/or rodents, and it can be effective in the treatment of neuropathic pain (Kenshalo and Willis, 1991; Tsubokawa et al., 1993; Canavero and Bonicalzi, 1995; Willis and Westlund, 1997; Garcia-Larrea et al., 1999; N'guyen et al., 1999; Kuroda et al., 2001). A pathway travelling from the cortex to the dorsal column nucleus is of particular interest since, in addition to its role in the transmission of proprioceptive (tactile) information, the dorsal column nucleus is implicated in the induction of visceral and neuropathic pain (Houghton et al., 1999; Millan, 1999; Day et al., 2001; Martinez-Lorenzana et al., 2001; Porreca et al., 2001; Wang and Westlund, 2001). Irrespective of the transmitters involved—which have, as yet, eluded identification—the above observations reveal that even the highest supraspinal centres may directly (and indirectly) influence nociceptive processing in the DH via monosynaptic (and polysynaptic) descending pathways.

4. Physiological significance and functional roles of descending controls

4.1. Interplay of descending inhibition and facilitation in the signalling of nociceptive information

In general, for pain reflecting excessive stimulation of specialised nociceptors, there is an adaptive relationship between the signalling of noxious stimuli and actual or impending tissue damage, corresponding to the crucial warning function of pain. However, the "input–output" equation for nociceptive transmission is far from invariant and may be weighted either in favour of, or against, its passage by an abundance of mechanisms including DI and DF (Besson and Chaouch, 1987; Willis and Coggeshall, 1991; Maier et al., 1992; Rothman, 1992; Cesselin, 1995; Fields and Basbaum, 1999; McNally, 1999; Millan, 1999; Célérier et al., 2001). As concerns the determination of this "set-point", there likely exists a critical balance between mechanisms of DI and DF. This equilibrium can be rapidly and reversibly or, under certain (perhaps pathological) conditions, durably and irrevocably modified as a function of the internal and external environment of the organism.

Under resting conditions, DI dampens excessive sensitivity to noxious stimuli. This role may be counterbalanced

by DF which enhances the signal to noise ratio for perception of noxious stimuli and the ensuing initiation of evasive behaviour. As concerns the adaptive function of pain in signalling dangerous stimuli, it has been proposed that the tonic operation of DI optimises the fidelity of sensory discrimination by confining the extent of neuronal receptor fields in the DH (Laird and Cervero, 1990). Analogously, under conditions of noxious stimulation, the signal to noise ratio for signalling of nociception/tissue damage may be magnified by cerebrally-integrated "Descending Noxious Inhibitory Controls" (Le Bars et al., 1979; Bouhassira et al., 1992, 1995a,b; Danziger et al., 1999; Fields and Basbaum, 1999). This refers to observations that the exposure of a defined tissue region to noxious stimuli engages a supraspinal loop resulting in the "heterotropic" activation of DI at other tissue regions (e.g. surrounding tissue). The contrast is, thus, amplified between nociceptive input from damaged as compared to intact tissue and the perceived intensity of pain enhanced. Inherent to this hypothesis, which has received extensive experimental support, is the notion that descending controls can specifically modify nociceptive processing from circumscribed body regions. Indeed, the concept that recruitment of descending pathways can lead to localised alterations in nociceptive processing is attracting increasing attention (Fang and Proudfit, 1996, 1998; Kozela et al., 2001; Monhemius et al., 2001). The possible mechanistic bases remain to be resolved but likely reflect interactions between descending pathways and local events in specific segments of the spinal cord. Important insights into this question may well be gained by a consideration of referred pain: that is, localised alterations (increases) in nociception observed at sites remote from the location of tissue damage (Millan, 1999).

As concerns DF, it has been contended that "hyperalgesia" and "anti-analgesia" should be distinguished. That is, processes resulting in a decrease in basal nociceptive thresholds/increase in pain sensation in the absence of other stimuli (hyperalgesia), and processes countering mechanisms for the induction of antinociception (anti-analgesia) (Wiertelak et al., 1992, 1997; Watkins et al., 1998; McQuay et al., 1996). While this distinction is empirically valid, there appears to be substantial similarities in the neuronal circuits underpinning these phenonema and the distinction between hyperalgesia and anti-analgesia may break down under conditions of long-term pain in that both actions can be simultaneously expressed by a single transmitter (Sections 4.3 and 4.4) (Watkins et al., 1998; McNally, 1999).

4.2. Environmental stimuli adaptively engaging descending inhibition

The induction of DI from the RVM and other supraspinal centres by imposition of noxious and non-noxious, stressful stimuli results in a marked and generalised antinociception. Further, dangerous situations potentially associated with tissue damage, such as intra- and interspecific conflict and defeat, are similarly accompanied by the engagement of DI and the induction of antinociception. It has been maintained that this elevation in nociceptive thresholds will, upon the occurrence of tissue damage, reduce the risk that pain compromises performance. Thus, the participation of DI in the induction of antinociception under aversive circumstances can be assimilated into a broad panoply of adaptive behaviours and physiological responses activated by "stress" or "danger" which enhance performance under conditions of actual or impending tissue damage (Bolles and Fanselow, 1980; Fanselow et al., 1995; Millan, 1999; Rhudy and Meagher, 2000). Further accentuating the adaptive nature of DI, and indicative of the importance of cognitive-emotional factors in the regulation of descending controls, conditioned stimuli previously associated with aversive stimuli suffice to activate DI and elicit antinociception. Mechanisms of DI can, thus, be engaged in anticipation of potentially noxious stimuli, probably by neuronal circuits encompassing the PAG, amygdala and cortex, structures playing a key role in the control of emotivity and fear (Sections 3.3 and 3.4) (Watkins and Mayer, 1982; Helmstetter, 1992; Helmstetter and Tershner, 1994; Harris et al., 1995; Amanzio and Benedetti, 1999; Brandao et al., 1999; Shi and Davis, 1999).

4.3. Activation of multiple mechanisms of descending facilitation

In accordance with the preceding argument, the induction of DF following suspension of conflict and disengagement from potentially-dangerous conditions may be regarded as a homeostatic mechanism for a return to equilibrium in the transmission of nociceptive input. Indeed, "safety signals" announcing the termination of exposure to a potentially-damaging stimulus can activate mechanisms of DF and thereby normalise nociceptive sensitivity (Wiertelak et al., 1992; Watkins et al., 1994). This conditioned anti-analgesia involves supraspinal links in the dorsal raphe nucleus and NRM and is ultimately mediated by CCK in the DH (Section 9.5.2) (Wiertelak et al., 1992). Thus, relative to the resting state and within a temporal framework, in anticipation of and during "conflict/stress", DI predominates whereas, following its cessation, DF is enhanced.

Mechanisms of DF initiated in the RVM (including the NRM) can be engaged by inflammation of peripheral and visceral tissues, and by PAF injury (Fields, 1992; Morgan et al., 1994; Zhuo and Gebhart, 1997; Mansikka and Pertovaara, 1997; Pertovaara et al., 1998; Urban et al., 1999a,b,c; Wei et al., 1999b; Porreca et al., 2001). DF contributes, thus, to the hyperalgesia, and/or allodynia which characterises these conditions, including "secondary hyperalgesia", which is the zone of tenderness and spontaneous pain contiguous to the region of tissue damage (Treede et al., 1992; Millan, 1999). From a teleological perspective, then, in encouraging protective and recuperative behaviours, the engagement of DF limits the risk that tissue damage will be exacerbated. The DF evoked by tissue inflammation mimics conditioned

anti-analgesia inasmuch as the NRM is involved in its expression. However, it may be distinguished by the involvement of NO and NMDA receptors in the DH, possibly activated by glutamate derived from descending pathways, although a PAF source of glutamate cannot currently be excluded (Section 10.2) (Watkins et al., 1994; Wiertelak et al., 1997; Célérier et al., 2001). Similarly, the potential involvement of SP in inflammation-induced DF may reflect a source either in descending pathways and/or in PAF terminals (Section 10.1) (Watkins and Maier, 1999a,b).

Interestingly, as reproduced experimentally by administration of lithium, bacterial endotoxins or cytokines, "illness" similarly triggers mechanisms of DF (Watkins et al., 1994; Wiertelak et al., 1994). The neuronal network involved in the induction of hyperalgesia by illness involves activation of hepatic vagal afferents by interleukin$_{1B}$ liberated by macrophages in the liver. Vagal afferents project to the NTS (Section 3.2.3) which comprises a relay en route to the NRM, from which pathways descending to the DH mediate DF. CCK, SP, NMDA receptors and NO have all been implicated in this mechanism of DF. However, it remains unclear (vide supra) whether SP and glutamate are contained in the descending pathways themselves or whether they are recruited in PAF terminals (Watkins et al., 1994, 1998; Wiertelak et al., 1994; Rady et al., 1999; Watkins and Maier, 1999a,b; Célérier et al., 2001). In analogy to the pain engendered by tissue damage, DF triggered by illness encourages the avoidance of potentially aversive situations and thereby promotes and accelerates recovery from disease. A further potential similarity between sickness and inflammation concerns the probable role of microglial cells and astrocytes in aggravating the accompanying nociception (Section 2.4) (Watkins and Maier, 1999b; Watkins et al., 2001).

Underpinning the diversity and complexity of mechanisms of DF, activation of vagal afferents at the cervical level, via stimulation of baroceptors and a NRM link, recruits a further pathway of DF which acts via both 5-HT (Section 7.3.4) and dynorphin (DYN) (Section 9.3.3) in the DH (Ren et al., 1991; Gebhart and Randich, 1992).

In addition, though the neurochemical substrates are not clearly defined, induction of DF by ON cells in the RVM has been implicated in the withdrawal hyperalgesia which accompanies discontinuation of prolonged treatment with μ-opioid agonists (Bederson et al., 1990; Kaplan and Fields, 1991; McNally, 1999; Célérier et al., 2001; Vanderah et al., 2001a,b).

Finally, it has been established that, in interaction with mood, cognitive factors exert a pronounced influence upon the perception and response to nociceptive input, and alterations in attention may be associated with modification of descending controls (including DF). Notably, the "anxiety" which accompanies anticipation of (noxious) stimulus is associated with an enhancement in its intensity, possibly involving a reinforcement of DF (Bushnell et al., 1985; Fields and Basbaum, 1999; Millan, 1999; Ploghaus et al., 1999; Sawamoto et al., 2000; Keogh et al., 2001).

4.4. Influence of chronic, pathological pain upon descending inhibition and facilitation

The preceding discussion of the physiological significance of mechanisms of DI and DF focused upon their adaptive, reversible—and often transient—engagement: i.e. upon regulation of the equilibrium between DI and DF as a function of the immediate needs of the organism. Under conditions of more persistent, pathological pain due to tissue or PAF injury, accompanying—and influencing—changes in nociceptive processing in the periphery, spinal cord and higher centres (Willis, 1994; Woolf and Doubell, 1994; Baranauskas and Nistri, 1998; Danziger et al., 1999; Doubell et al., 1999; Millan, 1999; Woolf and Mannion, 1999), there is a pronounced and sustained alteration in the activity of descending controls.

Notably, long-term noxious stimulation is characterised by a progressive reinforcement in mechanisms of DI reflecting the recruitment of descending pathways originating in the RVM and, most strikingly, noradrenergic nuclei (Section 5.4) (Basbaum and Fields, 1984; Zhang et al., 1994; Ren and Dubner, 1996; Millan, 1997; Li et al., 1998; Martin et al., 1999b; Wei et al., 1999b; Azami et al., 2001; Suzuki et al., in press). Like the parallel engagement of opioidergic and GABAergic ININs in the DH (Section 9) (Basbaum and Fields, 1984; Millan, 1986, 1990, 1993, 1999; Yaksh, 1999a), this enhancement of DI "tone" counterbalances excessive nociceptive input and mitigates pain. Its recruitment conceivably reflects the increasingly urgent requirement to reassume normal activities (foraging, reproduction, etc.).

As argued elsewhere for nociceptive processing in general (Millan, 1999), it is questionable whether one should invariably impose an "adaptive" interpretation upon modifications in the activity of descending controls, in particular under conditions of chronic pain. Thus, chronic, pathological pain—which may even outlast peripheral or central tissue damage—is not necessarily accompanied by the favourable, adaptive regulation of DI, DF and other endogenous mechanisms of nociceptive control (Woolf and Doubell, 1994; Doubell et al., 1999; Millan, 1999). Long-term painful states reflect a PAF-triggered and maintained "sensitisation" of EXINs, PNs and other downstream units transmitting nociceptive information to higher centres: i.e. a marked (and perhaps irreversible) enhancement in their excitability due to a complex pattern of events involving alterations in signal transduction, gene expression and even the structure of synapses (Willis, 1992, 1994; Hökfelt et al., 1994; Baranauskas and Nistri, 1998; Doubell et al., 1999; McMahon and Bennett, 1999; Millan, 1999; Raja et al., 1999). Due to the progressive exhaustion or dysregulation of DI, to its limited efficacy, or to a loss of responsiveness of downstream mechanisms mediating its effects, DI may be unable to combat long-term painful states. This problem is compounded by a failure to disengage mechanisms of DF which continue to promote transmission of nociceptive information. Indeed, there is now a compelling body

of evidence that the persistant activation of DF amplifies neuronal sensitisation in the DH and contributes to chronic painful states (Fields, 1992; Urban et al., 1996a; Mansikka and Pertovaara, 1997; Wiertelak et al., 1997; Pertovaara, 1998; Wei and Dubner, 1998; Wei et al., 1999a,b; Hurley and Hammond, 2000; Kovelowski et al., 2000; Ossipov et al., 2000; Porreca et al., 2001).

4.5. Therapeutic manipulation of mechanisms of descending inhibition and facilitation

As noted above, there is convincing evidence that mechanisms of both DI and DF are reinforced under conditions of long-term pain. From a clinical perspective, there are essentially two (synergistic) strategies for the exploitation of descending controls to alleviate pain. First, mechanisms of DI can be enhanced, as exemplified by supraspinal actions of opioids and segmental actions of α_2-AR agonists, respectively (Sections 5 and 9.3). Second, for which no clinically-available drug can be cited, mechanisms of DF may be interrupted. It remains to be established whether the latter approach can yield sufficiently robust analgesia per se. Thus, in-line with the notion of anti-analgesia, strategies for interference with DF may most effectively be utilised in conjunction with those harnessing mechanisms of DI (Section 12.5).

4.6. Multiple neurotransmitters, multiple classes of receptor and descending controls

Within light of the aforegoing comments, the following sections focus on the roles of diverse neurotransmitters and their receptors in the induction, modulation and expression of mechanisms of DI and DF (Figs. 3 and 4). Not surprisingly, NA and 5-HT remain the most familiar and intensively-investigated transmitters implicated in descending controls. Knowledge of their contribution has increased exponentially over recent years, in particular as concerns divergent roles of multiple classes of α-AR and 5-HT receptor in the mediation of DI and DF. Despite the historical preoccupation with NA and 5-HT, descending projections containing a further monoamine, DA, and many other neurotransmitters (generally not co-localised with monoaminergic pathways) also play a crucial role in mechanisms of DI and/or DF. As outlined in Section 1, non-monoaminergic transmitters are successively discussed as follows: (1) those (like monoamines) only contained in descending pathways; (2) those contained in descending pathways and, predominantly, in intrinsic neurones and (3) those contained in descending pathways and, predominantly, in PAFs. Finally, modulators not produced by specific neuronal pathways are considered separately.

As will become evident from the ensuing discussion, receptor multiplicity and intracellular transduction mechanisms provide an indispensable framework for the comprehension and exploitation of the roles of individual transmitters in descending controls. For all transmitters, therefore, at least elemental information concerning these aspects is summarised.

5. Descending noradrenergic pathways and multiple adrenoceptors

5.1. Multiple classes of adrenoceptor

Three major classes of AR can be recognised: α_1-, α_2- and β-ARs (Ruffolo et al., 1993; Bylund et al., 1994; Hieble et al., 1995; Kukkonen et al., 2001; Piascik and Perez, 2001). Three subtypes of the former have been cloned: α_{1A}, α_{1B} and α_{1D}, which are collectively characterised by their positive coupling via Gq/11 to voltage-gated Ca^{2+}-channels and phospholipase C (PLC), activation of which mobilises intracellular pools of calcium. (The pharmacologically-defined α_{1C}-AR has been abandoned) Similarly, there are three classes of α_2-AR: α_{2A}, α_{2B} and α_{2C}, which are distinguished by their coupling via Gi/o to inhibition of adenylyl cyclase (AC), to enhancement of K^+-currents and to suppression of Ca^{2+}-currents. (The rat α_{2D}-AR is the species homologue of the human α_{2A}-AR to which it presents certain differences in its ligand binding profile) Although heterologous expression systems have revealed pleiotropic (promiscuous) coupling of various α_2-AR subtypes to multiple intracellular signals (earlier citations), a fundamental distinction to their α_1-AR counterparts is, then, an inhibitory as compared to facilitatory influence upon neuronal excitability. At least three and, probably, four classes of β-AR exist, simply termed β_1, β_2, β_3 and β_4, of which the latter awaits cloning. In contrast to α_2-ARs, they generally stimulate the activity of AC via engagement of Gs. Accordingly, they increase neuronal excitability.

5.2. Supraspinal sources of noradrenergic input to the spinal cord

The spinal cord is innervated both by adrenergic cell clusters in medullary C1 and C2 nuclei, and by noradrenergic nuclei localised in A_5, A_6 (locus coeruleus) and the pontine A_7 (subcoeruleus) regions (Tucker et al., 1987; Kwiat and Basbaum, 1992; Westlund, 1992; Tavares et al., 1996; Millan, 1997; Schreihofer and Guyenet, 1997; Simpson et al., 1997; Hökfelt et al., 2000). As mentioned earlier (Section 2.5), the IML and VH are both recipients of a massive noradrenergic input (most prominently from A_5 and A_6 groups, respectively), and all laminae of the DH pivotal to nociceptive processing (laminae I/II, IV/V and X) reveal an intense plexus of noradrenergic varicosities, to which the A_7 nucleus makes a particularly important contribution (Proudfit, 1992; Westlund, 1992; Nuseir et al., 1999). In the DH, noradrenergic terminals appose intrinsic neurones (PNs and INs) in line with the occurrence of mRNA encoding

α_1- and α_2-ARs in the DH (Sections 5.10 and 5.11.1). As judged by the preponderance of axo-somatic and axo-dendritic over axo-axonic synapses, pre-synaptic junctions on PAFs are rare despite the presence of mRNA encoding α_2-ARs in DRG and functional evidence that α_2-ARs control release from nocisponsive PAFs (Section 5.10) (Hagihira et al., 1990; Clark and Proudfit, 1991; Kwiat and Basbaum, 1992; Westlund, 1992; Willis, 1992; Coggeshall and Carlton, 1997; Millan, 1997). Both volume transmission and a role of ININs in mediating the influence of descending noradrenergic pathways upon PAFs may underlie the paucity of structural evidence for their direct contact with PAF terminals in the DH. Irrespective of the explanation, noradrenergic projections to the DH play a critical role in the modulation of nociceptive information prior to its transfer to higher centres, a contention underpinned by extensive functional studies summarised in the following paragraphs. Moreover, modulation of the activity of preganglionic neurones by descending noradrenergic pathways likely plays a role in the control of painful states aggravated by aberrant sympathetic activity (Yaksh et al., 1995; Millan, 1999; Raja et al., 1999).

5.3. Modulation of the activity of descending noradrenergic pathways

Anatomical observations outlined above provide a substrate for innumerable algesiometric (behavioural), neurochemical (intracellular markers) and electrophysiological (activity of DH neurones) studies demonstrating that: (1) spinal application of NA (Yaksh, 1985; Sullivan et al., 1992; Eisenach et al., 1996; Honoré et al., 1996; Millan, 1997; Supowit et al., 1998; Shinomura et al., 1999) and (2) electrical stimulation of cerebral noradrenergic cell nuclei elicit robust antinociception. In the latter respect, A_5, A_6 and in particular, A_7 nuclei appear to be involved (Proudfit, 1992; Stamford, 1995; Millan, 1997; Zhao et al., 1999b; Nuseir and Proudfit, 2000). As discussed in detail elsewhere (Millan, 1997; Yaksh, 1999a), there is irrefutable evidence for a key role of post-synaptic mechanisms (direct suppression of the excitation of PNs by nocisponsive PAFs) in the analgesic properties of NA in the DH. Though data are less compelling, pre-synaptic inhibition of release from PAF terminals may also be of significance.

Recruitment of descending noradrenergic pathways is implicated in the antinociception elicited upon stimulation of cerebral structures other than noradrenergic nuclei, including the PAG, probably via a RVM-A_7 link (Peng et al., 1996b; Millan, 1997; Budal et al., 1998; Caî et al., 1999) and—despite the original assumption of a key role of 5-HT—the NRM (Fields and Basbaum, 1978; Millan, 1982, 1995, 1997; Basbaum and Fields, 1984; Brodie and Proudfit, 1986; Gebhart and Randich, 1992).

Opioidergic mechanisms in the PAG relieve an excitatory link (directly or via the RVM) to the A_7 noradrenergic nucleus: this mechanism is implicated in the expression of stimulation- and stress-induced antinociception (Section 3.3) (Millan, 1986; Stamford, 1995; Holden and Proudfit, 1998; Fields and Basbaum, 1999; Grabow et al., 1999; Holden et al., 1999; Yaksh, 1999a). Correspondingly, there is evidence for a role of descending noradrenergic pathways in the mediation of supraspinal opioidergic antinociception, although the relative contribution of various noradrenergic nuclei remains under discussion (Wigdor and Wilcox, 1987; Sawynok, 1989; Gebhart and Randich, 1992; Millan, 1982, 1997; Grabow et al., 1999; Martin et al., 1999b; Yaksh, 1999a; Bohn et al., 2000; Bajic and Proudfit, 1999; Bajic et al., 2001; Morales et al., 2001a). Further, the role of noradrenergic mechanisms is not exclusive inasmuch as co-operative actions of NA, 5-HT and, possibly, other transmitters contained in descending pathways may be necessary for the full expression of supraspinal opioiodergic antinocieption (Sections 7.5 and 12.3.2) (Sawynok, 1989; Millan, 1997; Fields and Basbaum, 1999).

Several other mechanisms control the activity of centrifugal noradrenergic projections including local, inhibitory GABAergic neurones, antagonism of which elicits antinociception via disinhibition of noradrenergic pathways to the DH (Nuseir and Proudfit, 2000). Indeed, the activation of noradrenergic cell bodies by local administration of opioids probably reflects relief of this tonic, inhibitory GABAergic input (Naranjo et al., 1989; Proudfit, 1992; Holden and Proudfit, 1998; Nuseir and Proudfit, 2000). SP-containing fibres from the PAG, on the other hand, elicit antinociception by direct excitation of noradrenergic perikarya of the A_7 nucleus (Yeomans and Proudfit, 1992; Proudfit and Monsen, 1999). There also exists an excitatory link from the lateral hypothalamus to the A_7 nucleus, activation of which elicit DI (Section 3.2.1) (Yaksh, 1999a; Holden and Naleway, 2001). A role of descending noradrenergic pathways in the antinociception elicited by supraspinal administration of cannabinoids (Section 11.1.3.2) (Lichtman and Martin, 1991; Lichtman et al., 1996), cholinergic agonists (Section 9.1) (Brodie and Proudfit, 1986; Nuseir et al., 1999; Ma et al., 2001a) and neurotensin (Section 9.1) (Naranjo et al., 1989) has also been proposed. Interestingly, via a mechanism possibly related to antagonist actions at central NMDA receptors excitatory to GABAergic ININs, the general anesthetic, nitrous oxide, enhances the activity of pontine noradrenergic nuclei. Its analgesic properties are, ipso facto, dependent upon the integrity of noradrenergic pathways descending to the DH (Guo et al., 1996; Jevtovic-Todorovic et al., 1998a; Paquet and Smith, 2000; Sawamura et al., 2000). Finally, there is accumulating evidence that cyclooxygenase inhibitors can modulate nociception by interference with the generation of prostaglandins in the CNS (Millan, 1999). In this light, the discovery that noradrenergic cell bodies bear prostaglandin (EP_3) receptors, which are implicated in spinal pronociceptive mechanisms, is intriguing (Narumiya et al., 1999; Minami et al., 2001b; Nakamura et al., 2001).

5.4. Physiological roles of descending noradrenergic pathways

The degree of spontaneous activity of descending noradrenergic pathways appears to be modest. However, as a function of the internal and external environment of the organism, changes in their activity fulfil a major contribution to fluctuations in the intensity of DI (Yaksh, 1985; Millan, 1997; Green et al., 1998; Martin et al., 1999b; Millan et al., 2000a). Thus, acute imposition of high intensity, somatic (noxious) stimuli accelerates the release of NA in the spinal cord (Men and Matsui, 1994; Millan, 1997), consistent with a role of DH pools of NA in the mediation of (noxious and non-noxious) "stress-induced analgesia" (Oluyomi and Hart, 1990; Rochford et al., 1992; Millan, 1997; Gjerstad et al., 2000). Further, activation of noradrenergic neurones in the locus coeruleus has been reported in a model of allodynia (Milne et al., 2001). Under conditions of persistent noxious input, the potentiation of descending noradrenergic input to the DH is pronounced and plays a major role in the moderation of pain (Section 4.4). Thus, in analogy to spinal opioidergic ININs (Millan, 1993), the majority of studies indicate a sustained and marked compensatory enhancement in noradrenergic mechanisms of DI under conditions of pain due to PAF injury or peripheral inflammation (Stanfa and Dickenson, 1994; Cho et al., 1995; Satoh and Omote, 1996; Tsuruoka and Willis, 1996; Millan, 1997; Green et al., 1998; Omote et al., 1998; Martin et al., 1999b; Sawamura et al., 1999; Stone et al., 1999; Wei et al., 1999a,b; Xu et al., 1999b). Alterations in the activity of descending noradrenergic pathways have also been implicated in the mediation of antinociception elicited by acute induction of hypertension, and in alterations of nociception displayed by spontaneously-hypertensive rats (Thurston and Randich, 1990; Taylor et al., 2000). These observations are of note in view of the heavy noradrenergic input to the IML and of the important role of noradrenergic mechanisms in the interplay between cardiovascular and somatosensory function (McGrath et al., 1989; Millan, 1997).

5.5. Influence of cerebral noradrenergic mechanisms upon other descending pathways

While the preceding discussion focused on segmental actions of NA in the mediation of DI, it should be pointed out that many structures providing direct and indirect pathways to the DH are innervated by ascending noradrenergic pathways, including the PVN, arcuate and tuberomammillary nuclei of the hypothalamus, the cortex, the NTS, the PBN and the PAG (Moore and Bloom, 1979; Nicholas et al., 1993; Millan et al., 2000b; Brown et al., 2001; Glass et al., 2001; Onaka et al., 2001). Therein, NA likely fulfils an, as yet poorly explored, role in the modulation of nociception via indirect control of the activity of descending pathways. For example, α_2-ARs exert an inhibitory influence upon histaminergic pathways derived from the tuberomammillary nucleus of the hypothalamus (Section 8.1) (Gulat Marnay et al., 1989; Brown et al., 2001), while α_1-ARs are excitatory to oxytocin (OT)-containing neurones of the PVN (Onaka et al., 2001). Further, noradrenergic neurones originating in A_5, A_7 (and A_1) nuclei innervate the RVM which plays a key role in integrating central modulatory influences upon DI and DF (Section 3.2.4) (Fields et al., 1991; Kwiat and Basbaum, 1992; Tanaka et al., 1994; Meng et al., 1997). Therein, NA exerts a receptor-dependent (Section 5.11.3) modulation of the activity of descending pathways and, as a consequence, nociceptive thresholds (Fields et al., 1991; Mansikka et al., 1996; Meng et al., 1997). NA also modulates the activity of serotonergic pathways descending to the DH from the NRM, a structure which contains a high concentration of inhibitory α_2-AR receptors (pre- and post-synaptic), as well as excitatory α_1-ARs (Rosin et al., 1993; Guyenet et al., 1994; Nicholas et al., 1996; Millan et al., 2000b). Adrenergic and noradrenergic perikarya in medullary-pontine nuclei themselves possess α_2-AR autoreceptors, activation of which contributes to the motor-suppressive, sedative and hypotensive actions of α_2-AR agonists (Nicholas et al., 1993; Millan et al., 1994, 2000a,b; Talley et al., 1996; Aicher and Drake, 1999; Hein et al., 1999; Hein, 2000; Milner et al., 1999; Kable et al., 2000; Glass et al., 2001; Trendelenburg et al., 2001a,b).

It is conceivable that activation of α_2-ARs inhibitory to monoaminergic pathways mediating DI explains isolated findings of hyperalgesic actions of α_2-AR agonists upon microinjection into the RVM and adjacent tissues (Mansikka et al., 1996). Such possible effects of α_2-AR agonists must be borne in mind upon their systemic administration. However, they are generally of modest importance and masked by the robust antinociception evoked by simultaneous activation by α_2-ARs in the DH (Aantaa et al., 1993; Rosin et al., 1993; Guyenet et al., 1994; Millan et al., 1994, 2000a; Nicholas et al., 1996).

5.6. Antinociceptive actions mediated by α_2-adrenoceptors in the spinal cord

There is an overwhelming body of evidence that activation of segmental α_2-ARs elicits antinociception (Fig. 5) (Yaksh, 1985; Besson and Guilbaud, 1992; Eisenach, 1994; Dickenson and Besson, 1997; Millan, 1997). While the antinociceptive properties of α_2-AR agonists predominantly reflect moderation of the excitatory influence of PAFs at PNs, they also involve a reduction in the release of pronociceptive transmitters, such as SP and glutamate, from their terminals (Millan, 1997). Accordingly, in the general discussion above of the role of descending noradrenergic pathways, it is not unreasonable to assume that antinociceptive actions of NA in the DH reflect activation of α_2-ARs. Indeed, as reviewed elsewhere (Yaksh, 1985; Eisenach et al., 1996; Dickenson and Besson, 1997; Millan, 1997), neurochemical, electrophysiological and behavioural investigations, models of inflammatory and neuropathic painful states, studies of

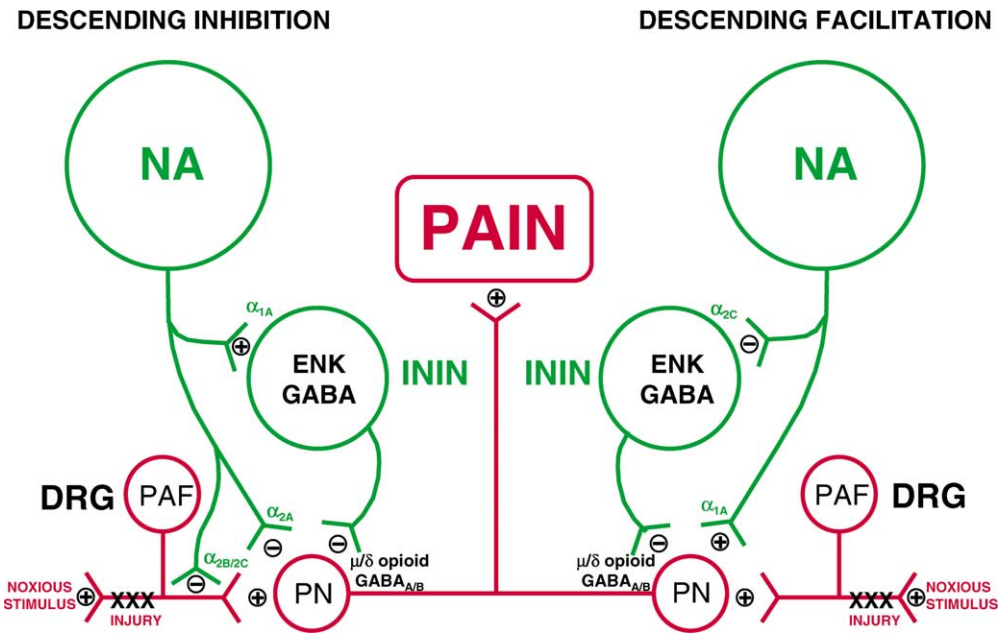

Fig. 5. Significance of multiple classes of adrenoceptor and of their divergent neuronal localisation to the modulation of nociceptive processing in the DH. On the left-hand side, mechanisms mediating descending inhibition are indicated and, on the right-hand side, those expressing descending facilitation are shown. Actions are exerted at terminals of primary afferent fibres (PAFs), projection neurones (PNs) and inhibitory interneurones (ININs). For clarity, excitatory interneurons are omitted, modulation of which would be essentially identical to PNs. Similarly, actions of ININs at PAF terminals are omitted for clarity. Enkephalin (ENK) and γ-hydroxy-butyric acid (GABA) are indicated as transmitters in ININs in view of their key antinociceptive roles and anatomical evidence that ENKergic neurones are targeted by noradrenergic input to the DH. Note that α_2-ARs suppress neuronal activity, whereas cellular excitability is enhanced by α_1-ARs. Abbreviations are as follows: DRG, dorsal root ganglia and NA, noradrenaline. For further details, see text.

diverse stimulus modalities, and analyses of the effects of systemic and spinal drug delivery, all converge towards the conclusion that DH-localised α_2-ARs play a crucial role in the mediation of DI by noradrenergic projections to the DH. Further, such actions are expressed both against acute nociceptive stimuli and, in most cases more markedly, under conditions of long-term peripheral inflammation (Kayser et al., 1992a,b, 1995; Idänpään-Heikkilä et al., 1994) and PAF injury (Yamamoto and Yaksh, 1991; Kayser et al., 1995; Leiphart et al., 1995; Yaksh et al., 1995; Hao et al., 1996; Wei and Pertovaara, 1997; Jasmin et al., 1998; Kontinen et al., 1998; Bitar and Pilcher, 2000; Kingery et al., 2000; Hord et al., 2001a; Malmberg et al., 2001; Suzuki et al., in press). The highly-reproducible ability of spinal administration of α_2-AR agonists to suppress mechanical allodynia in models of neuropathic pain deserves emphasis inasmuch as systemically-administered opioids are relatively ineffective, resembling their poor clinical efficacy against the mechanical allodynia of neuropathic pain (Section 2.2).

There is considerable clinical evidence that α_2-AR agonists elicit analgesia against a diversity of painful states, including neuropathic pain. These actions reflect the engagement of DH-localised α_2-ARs and are most convincingly expressed upon spinal (epidural or intrathecal) administration (Eisenach, 1994; Eisenach et al., 1995a, 1996, 1998, 2000; Glynn and O'Sullivan, 1995; Curatolo et al., 1997; De Kock et al., 1997; Millan, 1997; D'Angelo et al., 1999; Dougherty and Staats, 1999; Hall et al., 2000; Semenchuk and Sherman, 2000; Nader et al., 2001). The superior efficacy of α_2-AR agonists by spinal versus parental routes (Eisenach et al., 1996, 1998, 2000) in man supports experimental data indicating a segmental site of action (Millan, 1997). Pharmacokinetic studies in humans have shown proportionality between pain relief and lumbar (cerebrospinal fluid) concentrations of α_2-AR agonists. Further, analgesia is restricted to body regions interconnected with the spinal segments perfused. These observations support local actions of spinally-administered α_2-AR agonists (Eisenach et al., 1996; Asano et al., 2000a,b). Although the vast majority of clinical data have been acquired with the partial agonist, clonidine, (Eisenach et al., 1996), confirmatory observations have been acquired for systemic and spinal application of other α_2-AR agents, including the high efficacy agonist, dexmedetomidine (Berry and Hutchinson, 1988; Kauppila et al., 1991; Gosy, 2000; Hall et al., 2000; Semenchuk and Sherman, 2000; Hord et al., 2001a; Saper et al., 2001).

5.7. Cardiovascular and motor actions mediated by α_2-adrenoceptors in the spinal cord

The haemodynamic effects of α_2-AR agonists are complex and mediated by multiple central and peripheral loci, all of which can be recruited upon systemic drug administration (McGrath et al., 1989; Eisenach et al., 1996; Doda, 1997; Millan, 1997; Milner et al., 1999; Kable et al., 2000; Guimaraes and Moura, 2001). Segmental delivery of α_2-AR

agonists should, evidently, diminish potentially undesirable actions effected at sites other than the spinal cord (Section 12.3.1) (Eisenach et al., 1996). Correspondingly, in-line with experimental studies, spinal delivery of α_2-AR agonists in human subjects inhibits sympathetic outflow via actions at preganglionic neurones in the IML (Section 5.7). The magnitude of the hypotension and bradycardia provoked depends upon the precise location of catheter placement (Eisenach et al., 1996; Millan, 1997). There are, thus, both qualitative and quantitative differences in the cardiovascular profiles of α_2-AR agonists upon spinal versus systemic delivery. As concerns the sedative-hypnotic properties of α_2-AR agonists, these reflect engagement of α_2-AR autoreceptors in the locus coeruleus rather than the spinal cord (Schwinn et al., 1991; Hayashi and Maze, 1993; Eisenach et al., 1996; Millan et al., 2000b,c), and rostral diffusion of drugs to the brainstem following spinal delivery, as well as their redistribution via the systemic circulation upon epidural injection, may engender sedation. However, sedation is not necessarily a major drawback for sessile patient populations requiring treatment by spinal routes (Eisenach et al., 1996; Millan, 1997).

5.8. Mechanisms of α_2-adrenoceptor-mediated antinociception in the DH

5.8.1. Intracellular transduction

In recent years, several studies have examined the cellular mechanisms via which α_2-ARs mediate antinociception. As mentioned earlier (Section 5.1), although α_2-ARs can potentially couple to a diversity of intracellular cascades, their suppression of Ca^{2+}-currents, facilitation of K^+-currents and inhibition of AC are crucial to their inhibitory influence upon neuronal activity (Bylund et al., 1994; Hieble et al., 1995; Kukkonen et al., 2001). Several subtypes of G-protein which couple to these (and other) intracellular signals have been implicated in the antinociceptive actions of α_2-ARs-although only a few studies have specifically focused on spinal actions (Hayashi et al., 1995; Raffa et al., 1996; Garzon et al., 1999; Karim and Roering, 2000; Li and Zhuo, 2001). In accordance with the above comments, inhibition of (several classes of) voltage-dependent Ca^{2+}-channel has been implicated in the antinociceptive actions of α_2-AR agonists (Roering and Howse, 1996; Wei et al., 1996; Stone et al., 1997b; Wei and Roerig, 1998; Honma et al., 1999; Vanegas and Schaible, 2000; Saegusa et al., 2001). Similarly, activation of multiple classes of K^+-channel may be involved (Ocana et al., 1996; Stone et al., 1997b; Galeotti et al., 1999; Honma et al., 1999; Asano et al., 2000a,b).

Alterations in ion currents and AC activity elicited by stimulation of α_2-ARs modifies the functional status of protein kinase A and other protein kinases. Kinases play an important role in the modulation of cellular excitability and nociceptive processing in the DH: for example, by modifying the operation of GABAergic and NMDA receptors (Sections 9.5.2 and 10.1) (Bevan, 1999; Doubell et al., 1999; Millan, 1999). Correspondingly, although their precise roles remain unclear, protein kinases have been implicated in the expression of antinociceptive actions of α_2-ARs (Wei and Roerig, 1998; Nabekura et al., 1999). Indeed, the precise cellular events underlying induction of antinociception via α_2-ARs in the DH require additional clarification.

5.8.2. Interactions with other transmitters and mediators

It is likely that transmitters such as GAL, GABA and ENK, which are co-localised with NA in descending pathways (Table 1), interact with and modulate its effects in the DH (Iijima et al., 1992; Millan, 1997). As described in the following sections, interactions with mediators derived from other neuronal (and non-neuronal) sources are also of importance.

The diffusable second messenger, NO, is derived from L-arginine by an action of NO synthase, of which specific neuronal and non-neuronal forms exist (Millan, 1999; Wiesinger, 2001). NO is concentrated in the DH of the spinal cord, wherein it is derived from diverse sources (including glial cells). NO plays a complex role in the modulation of nociception (Gao and Qiao, 1998; Lin et al., 1999a,b,c; Millan, 1999; Luo and Cizkova, 2000; Milne et al., 2001; Sousa and Prado, 2001; Wen et al., 2001). Przesmycki et al. (1999) suggested that NO counters antinociceptive actions of α_2-AR agonists in the DH, in line with its pronociceptive properties (Gao and Qiao, 1998; Lin et al., 1999a,b,c; Millan, 1999; Wu et al., 2001c). Contrariwise, it has been suggested that NA induces NO synthase via engagement of α_2-ARs in the DH and that NO participates in the expression of its antinociceptive actions (Xu et al., 1996a, 1997; Pan et al., 1998a, 1999b). The interrelationship between α_2-ARs and NO is further complicated by a facilitatory influence of NO itself upon NA release. This action reflects, at least partly, its conjugation with NA to form 6-NO_2-NA which accesses noradrenergic terminals via NA transporters (Li et al., 2000). Consequently, it has been proposed that α_2-ARs mediate the ability of NO to attenuate allodynia due to PAF injury (Chen et al., 2000).

Complicating the situation even further, it has been suggested that NO is involved in spinal cholinergic antinociception and, correspondingly, that cholinergic ININs intervene in the induction of NO synthase and antinociception by α_2-AR agonists (Section 9.1) (Zhuo et al., 1993b; Xu et al., 1996a, 2000; Klimscha et al., 1997; Pan et al., 1998a). However, there is no obvious substrate for the recruitment of cholinergic ININs in the DH by α_2-ARs (Naguib and Yaksh, 1994; Paqueron et al., 2001). Moreover, in a reciprocal fashion, ACh (via an action at nicotinic receptors localised on adrenergic terminals) enhances the spinal release of NA which, via α_2-ARs, contributes to nicotinic mechanisms of antinociception in the DH (Section 9.1.3) (Gordh et al., 1989; Khan et al., 2001). Thus, the precise nature of the reciprocal interplay between α_2-ARs, NO and ACh in the DH remains in need of further delineation.

It has been suggested that adenosine participates in the antinociceptive actions of α_2-AR agonists in the DH

(Section 11.2.2) (Sweeney et al., 1987, 1989; Sawynok and Reid, 1992; Yang et al., 1998b; Zhao et al., 1999b). Although the precise underlying mechanisms remain to be elucidated, this is of interest since adenosine plays an important role in the mediation of antinociception in the DH: notably, adenosine mimicks the actions of α_2-AR agonists against neuropathic pain via actions at A_1 receptors (Rane et al., 1998; Sawynok, 1998, 1999; Belfrage et al., 1999; Suzuki et al., 2000; Collins et al., 2001; Johansson et al., 2001).

Spinal actions of the cytokine, tissue necrosis factor α, derived from glial and, possibly, neuronal sources have been implicated in the induction of inflammatory and neuropathic painful states (Section 2.4) (Ignatowski et al., 1999; Millan, 1999; Sweitzer et al., 2001a,b; Watkins et al., 2001). Interestingly, tissue necrosis factor α has been shown to suppress the release of NA and it may even be generated by noradrenergic neurones themselves (Ignatowski et al., 1997). Although the precise interrelationship between descending noradrenergic pathways and tissue necrosis factor α remains to be clarified, both experimental and clinical studies suggest that a reduction of its production may contribute to the analgesic actions of α_2-AR agonists (Ignatowski et al., 1997; Nader et al., 2001).

Despite this proliferation of potential mechanisms for expression of the antinociceptive actions of α_2-AR agonists in the DH, their direct inhibitory influence upon PNs, EXINs and sympathetic neurones in the IML should not be neglected (Millan, 1997; Yaksh, 1999a). As implied earlier, much remains to be resolved as regards the intricate and reciprocal pattern of interactions between α_2-AR and other mediators modulating spinal nociceptive processing. Notwithstanding such uncertainties, knowledge of the relationship of noradrenergic to other mechanisms controlling nociceptive processing in the DH is important in affording a framework for experimental and clinical observations that α_2-AR agonists can elicit antinociception co-operatively with other classes of analgesic agent.

5.9. Co-operative antinociceptive actions of α_2-adrenoceptor agonists and other classes of analgesic agent

5.9.1. Cholinergic agonists

The above-outlined interplay between α_2-ARs and cholinergic mechanisms in the DH is of pertinence to evidence for synergistic induction of antinociception by spinal administration of α_2-AR agonists and cholinesterase inhibitors in rats, the combined actions of which are attenuated by muscarinic—but not nicotinic-antagonists (Naguib and Yaksh, 1994; Abram and O'Connor, 1995; Abram and Winne, 1995; Eisenach, 1999). In line with these findings, the analgesic effects of epidural clonidine in man are potentiated by the cholinesterase inhibitor, neostigmine, which also attenuates its cardiovascular side-effects (Lothe et al., 1994; Eisenach et al., 1996; Hood et al., 1996).

5.9.2. Opioid agonists

Opioid receptors localised in the DH fulfil a crucial role in the mediation of antinociception (Section 9.3) (Basbaum and Fields, 1984; Millan, 1986, 1990; Herz et al., 1993; Dickenson and Besson, 1997; Yaksh, 1999a). Segmental populations operate in synergy with their supraspinal counterparts and, in-line with the role of descending noradrenergic pathways in the expression of supraspinal opioidergic antinociception, spinal α_2-ARs contribute to the "multiplicative" interaction between cerebral and segmental populations of opioid receptor (Kellstein et al., 1988; Roering and Fujimoto, 1989; Hylden et al., 1991; Millan, 1997; Stone et al., 1997a,b; Grabow et al., 1999; Hurley et al., 1999). Opioids (Section 9.3) and α_2-ARs (Section 5.1) share common intracellular transduction mechanisms, notably suppression of AC activity and a positive and negative influence upon K^+- and Ca^{2+}-currents, respectively. Further, they similarly inhibit the activity of nocisponsive PNs (and EXINs) upon which they are likely co-localised (Hieble et al., 1995; Connor and Christie, 1999; Yaksh, 1999a). Correspondingly, several studies have demonstrated mutual (generally synergistic) spinal antinociceptive properties of α_2-AR and opioid agonists against both acute and chronic inflammatory and neuropathic pain (Sullivan et al., 1987; Honoré et al., 1996; Millan, 1997; Ossipov et al., 1997; Przesmycki et al., 1997; Fairbanks et al., 2000; Horvath et al., 2001). Mu-opioid receptors are involved in these interactions, and α_2-AR agonists may similarly potentiate the antinociceptive actions of δ- and κ-agonists, although data are less extensive in this regard (Roerig et al., 1992; Millan, 1997; Grabow et al., 1999; Yaksh, 1999a).

Paralleling these experimental studies, it has been shown that α_2-AR agonists reduce opioid analgesic requirements in patients. Indeed, upon both systemic and spinal delivery, they enhance the magnitude and duration of opioid-induced analgesia without a deterioration of side-effects (Eisenach et al., 1996; Park et al., 1996; Millan, 1997; Goyagi et al., 1999; Nader et al., 2001).

There are reports of cross-tolerance between antinociceptive properties of α_2-AR agonists and opioids in the DH (Post et al., 1988; Millan, 1997). Nevertheless, Fairbanks and Wilcox (1999b) showed that the synergism between clonidine and morphine is maintained following induction of tolerance to morphine. These data indicate that adjunctive use of α_2-AR agonists with morphine may be beneficial even in patients who have become unresponsive to morphine, a possibility necessitating clinical verification.

5.9.3. GABAergic agonists

GABAergic ININs play a key role in nociceptive processing in the DH (Section 9.2.1). By analogy to α_2-AR agonists, induction of neuronal hyperpolarisation via the potentiation of K^+-currents contributes to the antinociceptive actions of $GABA_B$ agonists, such as baclofen (Barnard, 1996, 2000; Millan, 1999; Bowery and Enna, 2000; Loomis et al., 2001; Milne et al., 2001; Von Heijne et al., 2001). A further

analogy to α_2-AR agonists is provided by the enhancement in the analgesic efficacy of baclofen seen following PAF injury (Smith et al., 1994a; Millan, 1999). It is, thus, of interest that baclofen and GABAergic modulators supra-additively elicit antinociception upon administration with α_2-AR agonists to rats (Przesmycki et al., 1998; Nishiyama and Hanaoka, 2001).

5.9.4. NMDA receptor antagonists

α_2-AR agonists suppress glutamate release from PAFs and abrogate, by a post-synaptic mechanism, their excitation of PNs in the DH (Section 10.2) (Millan, 1997; Zhang et al., 1998a,b; Yaksh, 1999a). This inhibitory influence of α_2-ARs upon NMDA receptor-mediated nociceptive transmission provides a substrate for observations that spinal and systemic administration of α_2-AR agonists potentiates the antinociceptive potency of the NMDA receptor channel blocker, dizocilpine, in models of PAF injury (Lee and Yaksh, 1995; Jevtovic-Todorovic et al., 1998b). Further, clonidine enlarges the therapeutic window for doses acting antinociceptively as compared to those which provoke motor side-effects, a significant observation inasmuch as the troublesome motor and psychiatric actions of NMDA receptor antagonists impede their clinical development (Gorelick and Balster, 1995). Therapeutic use of NMDA channel blockers is also compromised by their neurotoxic properties, which are likewise attenuated by α_2-AR agonists (Farber et al., 1995). Thus, it would be of considerable interest to examine the influence of α_2-AR agonists upon alleviation of pain by the NMDA receptor channel blocker, ketamine, which is currently being exploited as a probe of the role of NMDA receptors in the induction of clinical pain. Indeed, applied in combination with epidural opioids and local anesthetics, ketamine enhances their analgesic actions (Choe et al., 1997; Abdel-Ghaffar et al., 1998; Himmelseher et al., 2001).

5.9.5. Local anesthetics

Local anesthetics, such as lidocaine, interfere with the propogation of action potentials principally via their actions at Na^+-channels, although Ca^{2+}- and K^+-channels may also be involved (Butterworth and Strichartz, 1993; Koppert et al., 2000). Possibly reflecting these properties, they diminish the NMDA receptor-mediated sensitisation of nocisponsive DH neurones (Fraser et al., 1992; Nagy and Woolf, 1996). Upon i.t. injection in rats, lidocaine synergistically elicits antinociception with clonidine (Kawamata et al., 1997; Hao et al., 2001) and numerous clinical studies have shown that spinal (and systemic) co-administration of clonidine with local anesthetics reproducibly and markedly enhances their analgesic efficacy (Eisenach et al., 1996; Millan, 1997; Benhamou et al., 1998; D'Angelo et al., 1999; Milligan et al., 2000).

5.9.6. Serotonergic ligands

There is considerable evidence for a functional, receptor subtype-dependent interrelationship between descending noradrenergic and serotonergic pathways as concerns their modulation of nociceptive processing (Section 7.5) (Sawynok, 1989; Post and Archer, 1990; Millan, 1995, 1997). Notably, there is evidence for the synergistic induction of antinociception by α_2-AR and 5-HT_{1B} receptor agonists (DeLander and Hopkins, 1987a,b; Sawynok, 1989; Post and Archer, 1990; Danzebrink and Gebhart, 1991b). Inasmuch as 5-HT_{1B} agonists and α_2-ARs are both clinically-available and are of therapeutic utility in the treatment of migraine headache, the nature of their interaction would be of interest to pursue further (Section 7.4.2) (Millan, 1997, 1999; De Vries et al., 1999; Mitsikostas and Del Rio, 2001; Saper et al., 2001). Moreover, the diverse influence of multiple subtypes of 5-HT receptor upon nociception (Section 7.4) suggests considerable scope for the more refined and targeted exploitation of the cojoint role of descending noradrenergic and serotonergic pathways in the induction of antinociception (Section 12.5).

5.9.7. Adenosine agonists

As mentioned earlier—and discussed in Section 11.2.2—experimental studies have provided evidence for a functional inter-play between descending noradrenergic pathways and DH pools of adenosine in the induction of spinal antinociception. Further, both α_2-AR agonists (Section 5.6) and adenosinergic agonists (Section 11.2.2.1) have been shown to elicit analgesia upon systemic and spinal administration to patients. It is, thus, of potential therapeutic pertinence that the co-administration of α_2-AR and adenosinergic agonists co-operatively elicited antinociception in rodents (DeLander and Hopkins, 1987b; Aran and Proudfit, 1990a).

5.9.8. Cyclooxygenase inhibitors

There is increasing interest in central pronociceptive and antinociceptive actions of prostaglandins and cyclooxygenase inhibitors, respectively (Millan, 1999; Narumiya et al., 1999; Minami et al., 2001b; Nakamura et al., 2001). It is, thus, of note that α_2-AR agonists and cyclooxygenase inhibitors have been shown to synergistically elicit antinociceptive upon i.t. administration (Malmberg and Yaksh, 1993).

5.9.9. Therapeutic significance

The above comments underpin the importance of studies examining functional inter-relationships amongst α_2-ARs and other DH-localised mechanisms mediating antinociception. From a theoretical point of view, synergistic analgesic actions of α_2-AR agonists and other drug classes may reflect the "physiological" mode of operation of descending pathways mediating DI, which concurrently engage multiple mechanisms of antinociception (Section 12.3.2). From a therapeutic perspective, such observations yield insights into novel multi-target drug strategies designed to optimise therapeutic benefit in the absence of disruptive side-effects (Section 12.5).

5.10. Multiple classes of α_2-adrenoceptor in the spinal modulation of nociceptive processing

5.10.1. Imidazoline sites, agmatine and multiple classes of adrenoceptor

5.10.1.1. Imidazoline receptors. Much of the earlier discussion of the actions of α_2-AR agonists (in particular, clinical data) is based on observations obtained with the prototypical (partial) α_2-AR agonist, clonidine. Like the majority of α_2-AR agonists, clonidine does not distinguish between various subtypes of α_2-AR. Further, in contrast to NA itself, it interacts with imidazoline $(I)_1$ and, less markedly, I_2 binding sites (Bylund et al., 1994; Hieble et al., 1995; Millan et al., 2000a). The significance of CNS population of I_1 sites in general, even after intensive investigation, remains nebulous, although they may participate in the induction of hypotension (Parini et al., 1996; Farsang and Kapocsi, 1999; Raddatz et al., 2000; Bruban et al., 2001). Further, though I_2 sites can be detected in the spinal cord, and have been implicated in the modulation of nociceptive processing, data remain fragmentary and it is controversial as to whether they enhance or suppress nociception (Houghton and Westlund, 1996; Kolesnikov et al., 1996; Diaz et al., 1997; Ruggiero et al., 1998; Sanchez-Blazquez et al., 2000; Raasch et al., 2001; Yesilyurt and Uzbay, 2001). The antinociceptive actions of clonidine and other α_2-AR agonists are resistant to I_1/I_2 antagonists, abolished by α_2-AR antagonists devoid of affinity for I_1/I_2 sites, attenuated by antisense probes against α_2-ARs and profoundly modified in transgenic mice lacking specific subtypes of α_2-AR (Millan, 1997; Fairbanks and Wilcox, 1999a; Robinson et al., 1999; Kable et al., 2000; Millan et al., 2000a; Sawamura et al., 2000; Malmberg et al., 2001). Thus, while more research into a possible role of I_1/I_2 sites in nociceptive processing is justified, it is improbable that they play a major role in the actions of clonidine or other α_2-AR agonists. Further, as indicated above, they are not involved in the actions of NA.

5.10.1.2. Agmatine. While the following paragraphs focus on the significance of multiple classes of α_1- and α_2-AR in mediating the actions of NA (and adrenaline), the potential existence of other endogenous ligands for α_2-ARs should be considered. Agmatine is a novel amine which is broadly distributed in the CNS including, in all probability, the DH (Raasch et al., 2001; Wiesinger, 2001). It is generated from L-arginine by decarboxylation, while a further metabolic pathway catalysed by NO synthase yields NO and L-citrulline (Section 5.8.2). Agmatine possesses modest (micromolar) affinity for α_2-ARs, as well as I_1 and I_2 sites, the latter of which remain in search of an endogenous ligand (Pinthong et al., 1995; Raasch et al., 2001). Although the functional significance of agmatine binding to α_2-ARs remains obscure inasmuch as it failed to manifest either agonist or antagonist properties in functional studies, facilitation of catecholamine release could lead to their indirect stimulation (Pinthong et al., 1995; Raasch et al., 2001).

In distinction to α_2-AR agonists, agmatine is ineffective in algesiometric models of phasic, noxious stimuli but, upon systemic and/or spinal application, it has been reported to inhibit persistant inflammatory pain and, like α_2-AR agonists, to enhance morphine-induced analgesia (MIA) (Kolesnikov et al., 1996; Horvath et al., 1999; Li et al., 1999b). In one recent study, moreover, α_2-AR antagonists blocked the antinociceptive actions of agmatine (Onal and Soykan, 2001). These findings require consolidation and the mechanisms underlying the influence of agmatine upon nociceptive processing remain poorly understood. Complicating their interpretation, amongst a plethora of idiosyncratic actions, agmatine behaves as an inhibitor of NO synthase and expresses antagonist properties at NMDA receptors (Galea et al., 1996; Yang and Reis, 1999; Raasch et al., 2001; Ferry and Landry, 2002). Each of these effects may engender antinociception and facilitate MIA (Sections 5.8.2 and 10.2). Thus, the physiological significance of agmatine remains uncertain. Nevertheless, more precise knowledge of its neuronal localisation and cellular actions in the DH should illuminate its potential role in the modulation of nociceptive processing in interaction with noradrenergic transmission, α_2-ARs and other modes of descending control.

5.10.1.3. Multiple classes of adrenoceptor. The important question arises as to the contribution of individual α-AR subtypes to the antinociceptive properties of NA, clonidine and other adrenergic agonists. The density of all β-AR subtypes on intrinsic neurones in the DH and in the DRG is feeble and there is little or no evidence for a functional role in the modulation of spinal nociceptive processing (Nicholas et al., 1991, 1993, 1996; Millan, 1997). The following discussion focuses, thus, on α_1- and α_2-ARs.

5.10.2. α_{2A}-adrenoceptors

5.10.2.1. Role in the induction of antinociception. A compelling body of evidence that segmental α_{2A}-ARs fulfil a major role in the induction of antinociception may be summarised as follows.

First, binding studies originally suggested that α_{2A}-ARs are prominent in the spinal cord of the rat (Millan, 1997) and immunohistochemical studies employing antisera exclusively recognising α_{2A}-ARs have corroborated their high density in the superficial DH, as well as in deeper laminae and lamina X (Rosin et al., 1993; Stone et al., 1998, 1999; Shi et al., 1999). Zeng and Lynch (1991) also found mRNA encoding α_{2A}-ARs to predominate over α_{2B}- and α_{2C}-ARs in rat spinal cord, and Nicholas et al. (1993) reported mRNA-positive neurones for α_{2A}-ARs in laminae II/III revealing their production by intrinsic DH neurones. In man, mRNA encoding α_{2A}-ARs is likewise concentrated in both superficial and deep DH laminae (Stafford-Smith et al., 1995). Consistent with their presence on intrinsic PNs

(and EXINs), it was reported that α_{2A}-ARs are poorly represented on opioidergic ININs (Stone et al., 1998). Further, double-labelling studies revealed that numerous α_{2A}-ARs are co-localised with SP and calcitonin gene related peptide (CGRP) on the terminals of nocisponsive PAFs (Stone et al., 1998). These observations are of significance in light of a curious lack of coherence from immunocytochemical and mRNA studies as concerns the density of α_{2A}-ARs in the DRG—although there is now a consensus that they are, indeed, present (Millan, 1997; Nicholas et al., 1997; Cho et al., 1997; Gold et al., 1997; Stone et al., 1998; Birder and Perl, 1999; Shi et al., 2000). While inflammation does not markedly affect levels of α_{2A}-ARs in DRG, they are generally increased by PAF injury (Cho et al., 1997; Birder and Perl, 1999; Stone et al., 1999; Shi et al., 2000), consistent with antinociceptive actions of α_{2A}-AR agonists against neuropathic pain (Section 5.6). Furthermore, the majority of investigations suggest that antinociceptive properties of α_2-AR agonists are enhanced under these conditions (Yaksh et al., 1995; Hao et al., 1996; Ossipov et al., 1997; Wei and Pertovaara, 1997; Kontinen et al., 1998; Bitar and Pilcher, 2000; Kingery et al., 2000; Malmberg et al., 2001; Von Heijne et al., 2001; Suzuki et al., in press). Of particular note is the increase in α_{2A}-ARs seen in large DRG cells following PAF injury (Birder and Perl, 1999) since Aβ fibres may be responsible for the accompanying mechanical allodynia (Woolf and Doubell, 1994; Doubell et al., 1999; Millan, 1999; Woolf and Mannion, 1999) which is consistently moderated by spinal administration of α_2-AR agonists (above references). From the earlier observations, it is apparent that α_{2A}-ARs are strategically located for the expression of antinociception by actions at both pre- and post-synaptic sites relative to the terminals of nocisponsive PAFs in the DH.

Second, extensive pharmacological analyses of the actions of systemic and spinal administration of agonists and antagonists interacting preferentially with α_{2A}- as compared to α_{2B}- and α_{2C}-ARs have been performed. They have conclusively shown that the former play a key role in the induction of antinociception against diverse qualities of noxious stimuli in rodents (Millan, 1992, 1997; Takano and Yaksh, 1992a, 1993; Millan et al., 1994, 2000a; Yaksh, 1999a; Li and Eisenach, 2001).

Third, in mice possessing dysfunctional α_{2A}-ARs, antinociceptive actions of α_2-AR agonists are markedly abrogated (including a model of neuropathic pain), and opioid/α_2-AR antinociceptive synergy is abolished (Hunter et al., 1997; Lakhlani et al., 1997; Stone et al., 1997a; Hein, 2000; Kable et al., 2000; Kingery et al., 2000; Malmberg et al., 2001).

5.10.2.2. Additional actions. There is, thus, unequivocal evidence that DH-localised α_{2A}-ARs mediate antinociception in rodents, although the relative contribution of populations localised on PAFs as compared to intrinsic DH neurones remains to be elucidated. In light of interest in the therapeutic utility of selective α_{2A}-AR agonists, the following comments should be made.

First, under conditions of PAF injury, it has been proposed that α_{2A}-ARs transported from the DRG to peripheral terminals of PAFs may participate in the detrimental, pronociceptive actions of NA released from sympathetic fibres-at least as regards thermal stimuli (Raja et al., 1999; Kingery et al., 2000; Shi et al., 1999). However, this contention may be questioned on the basis: of (1) studies of neuropathic pain in α_{2A}-AR knock-out mice; (2) evidence that α_{2C}-ARs and α_1-ARs contribute to the peripheral expression of sympathetic pain and (3) findings that α_{2A}-AR autoreceptors on sympathetic terminals inhibit NA release (Millan, 1999; Raja et al., 1999; Hein, 2000; Kable et al., 2000; Fuchs et al., 2001; Hord et al., 2001a; Malmberg et al., 2001). In-line with the latter argument, peripheral antinociceptive actions of α_2-AR agonists have been reported in inflammatory states, reflecting inhibitory actions at sympathetic terminals and, perhaps, local induction of the release of opioids (Nakamura and Ferreira, 1988; Gentili et al., 1997; Reuben and Connelly, 1999; Joshi et al., 2000).

Second, the earlier-cited (Section 5.10.2.1) pharmacological and gene knock-out studies revealed that α_{2A}-ARs mediate sedation and hypotension, indicating that such effects cannot be dissociated from the induction of analgesia by (systemic administration of) α_{2A}-AR selective agents (Millan et al., 1994, 2000c; MacMillan et al., 1996; Hunter et al., 1997; Millan, 1998; Robinson et al., 1999; Kable et al., 2000). Correspondingly, α_{2A}-ARs are enriched on (1) noradrenergic and adrenergic pathways running to the IML and (2) preganglionic neurones, where their engagement provokes hypotension. Actions at these sites may also participate in the suppression of neuropathic pain by reducing sympathetic outflow (Section 5.7) (McGrath et al., 1989; Yaksh et al., 1995; Doda, 1997; Hein et al., 1999; Hein, 2000; Trendelenburg et al., 2001a,b). The sedative actions of α_2-AR agonists involve activation of α_{2A}-autoreceptors in the locus coeruleus (Hayashi and Maze, 1993; Millan et al., 2000c) to which access can be limited by spinal administration of α_2-AR agonists (Eisenach et al., 1996). Although α_{2A}-ARs are found in the (human) VH (Stafford-Smith et al., 1995; Millan, 1997; Stone et al., 1998; Shi et al., 1999), the influence of their stimulation upon motor function remains unclear.

Third, reflecting their inhibitory influence upon ascending noradrenergic and serotonergic pathways, α_{2A}-ARs have been shown to mediate the anxiolytic actions of α_2-AR agonists, an important component of their overall utility for pain relief (Millan et al., 2000c; Schramm et al., 2001).

Thus, α_{2A}-ARs fulfil several functional roles other than the control of spinal nociceptive processing. Anxiolytic and, under certain conditions, sedative properties are favourable. However, agonists selective for α_{2A}-ARs will not permit the induction of analgesia in the absence of cardiovascular or autonomic side-effects, whether upon parenteral or spinal administration.

5.10.3. Other α_2-AR subtypes

5.10.3.1. "Non-α_{2A}-ARs" in the modulation of nociception. The final comment of the preceding Section 5.10.2 underlines continued interest in potential antinociceptive actions elicited by α_{2B}- and α_{2C}-ARs. Indeed, though their respective pertinence remains unclear, the following observations suggest that (an) α_2-AR(s) other than α_{2A}-ARs may mediate antinociception (Millan, 1997; Yaksh, 1999a).

First, notwithstanding the presence of α_{2A}-ARs on PAF terminals, α_{2C}-ARs appear to predominate (Cho et al., 1997; Gold et al., 1997; Nicholas et al., 1997; Stone et al., 1998; Birder and Perl, 1999; Shi et al., 2000). Moreover, there is a homogeneous body of data indicating that prazosin, which shows higher affinity for α_{2B}- and (though less markedly) α_{2C}- than α_{2A}-ARs, blunts the inhibitory influence of α_2-AR agonists upon SP, CGRP and glutamate release in the spinal cord (Ono et al., 1991; Takano and Yaksh, 1992b; Millan, 1997). Correspondingly, the preferential α_{2A}-AR agonist, oxymetazoline, did not modify stimulated release of glutamate in the DH whereas, a further (subtype-non-selective) α_2-AR agonist, ST91, is (prazosin-reversibly) effective (Ueda et al., 1995). Nevertheless, it should be noted that a more recent pharmacological analysis of the α_2-AR subtype modulatory to spinal GLU release from PAF terminals concluded that α_{2A}-ARs were principally involved (Li and Eisenach, 2001).

Second, in behavioural studies, the antinociceptive actions of ST91 were attenuated by prazosin, in contrast to other agonists, such as dexmedetomidine, to which ST91 did not display cross-tolerance (Takano and Yaksh, 1992a,b, 1993; Takano et al., 1992). These data reinforce the aforementioned, neurochemical studies in indicating that ST91 acts at a "second" population of spinal α_2-ARs different to α_{2A}-ARs.

Third, consistent with a role of two independent classes of α_2-AR, Graham et al. (1997) identified differences between the actions of ST91 versus dexmedetomidine in various rat strains and subsequently demonstrated (Graham et al., 2000) that they synergistically evoke antinociception.

Considerable prudence must be exercised in the interpretation of these data in view of the lack of α_2-AR subtype selectivity of ST91 (Renouard et al., 1994) and the potent α_1-AR antagonist actions of prazosin (Hieble et al., 1995; Millan, 1997). Nevertheless, it was recently shown that the α_2-AR agonist, moxonidine, elicits α_2-AR antagonist-reversible antinociception in mice lacking functional α_{2A}-ARs (Fairbanks and Wilcox, 1999a; Fairbanks et al., 2000). The resistance of its antinociceptive actions to prazosin perhaps questions the implication of α_{2B}-ARs (Shannon and Lutz, 2000), but this difference to clonidine and other α_2-AR agonists also suggests the existence of an additional "subtype" of α_2-AR mediating antinociception.

5.10.3.2. α_{2B}-ARs. While the above studies do not differentiate between the potential roles of α_{2B}-AR versus α_{2C}-AR, it has been demonstrated that mice displaying a null mutation for α_{2B}-ARs (but not for α_{2A}- or α_{2C}-ARs) fail to show an antinociceptive response to the anaesthetic, nitrous oxide (Sawamura et al., 1999, 2000). In addition, its antinociceptive actions are reduced by prazosin (Guo et al., 1999). α_{2B}-ARs in the DH may be engaged by NA released from disinhibited descending noradrenergic pathways following blockade by nitrous oxide of NMDA receptors excitatory to GABAergic interneurones in the brainstem (Jevtovic-Todorovic et al., 1998a; Paquet and Smith, 2000).

Unfortunately for the hypothesis that α_{2B}-ARs comprise the "missing" α_2-AR subtype underlying antinociception in the spinal cord, levels of mRNA encoding α_{2B}-ARs in the DRG have proven to be low in the majority of studies, and they are unaffected by PAF injury. Further, in the spinal cord itself, little mRNA encoding α_{2B}-ARs has been found in the rat (Zeng and Lynch, 1991; Nicholas et al., 1993; Cho et al., 1997; Gold et al., 1997; Shi et al., 1999, 2000). Nevertheless, immunocytochemical studies of α_{2B}-AR protein are required to furnish (or refute) a concrete anatomical substrate for functional studies outlined earlier. Moreoever, it should be emphasised that mRNA encoding α_{2B}-ARs is far more prominant in the superficial and deep DH of man than of the rat (Stafford-Smith et al., 1995).

Two caveats concerning the potential therapeutic utility of α_{2B}-AR agonists in man should be mentioned. First, it has been suggested that α_{2B}-ARs situated on sympathetic terminals aggravate nociception via the release of prostaglandins (Levine et al., 1986; Khasar et al., 1995; Levine and Reichling, 1999). Second, α_{2B}-ARs are highly expressed in both the IML and VH of man (Stafford-Smith et al., 1995; Levine and Reichling, 1999), from which one may surmise a role in the regulation of autonomic and motor outflow.

5.10.3.3. α_{2C}-ARs. As concerns a possible role of α_{2C}-ARs in the induction of spinal antinociception, their mRNA is poorly represented in human DH and they are present in the rat DH only at a density inferior to that for α_{2A}-ARs—though superior to α_{2B}-ARs (Zeng and Lynch, 1991; Nicholas et al., 1993; Shi et al., 1999). Interestingly, an immunocytochemical study confirmed the existence of α_{2C}-ARs in rat DH and indicated that their neuronal localisation differs markedly to that of α_{2A}-ARs. Thus, α_{2C}-ARs appear to be prevalent on intrinsic neurones, including both somatostatin—and ENK—containing ININs, though not, surprisingly, those NK_1 receptor-bearing neurones which likely correspond to nocisponsive PNs (Stone et al., 1998). This observation raises the question as to whether α_{2C}-ARs might actually exert a pro rather than antinociceptive role in the DH. That is, assuming that PNs are subjected to tonic, inhibitory control by ININs, α_{2C}-AR activation might account for certain (indirect) excitatory effects of descending noradrenergic pathways upon PNs in the DH (Section 5.4) (Millan, 1997). This remains to be clarified. Alternatively, α_2-AR subtypes are coupled to a diversity of transduction mechanisms (Section 5.1) and it is not inconceivable

that α_{2C}-ARs engage an excitatory mechanism at ININs permitting the expression of antinociception.

A further conundrum regarding the evidence that α_{2C}-ARs are principally situated on intrinsic neurones in the DH is that both mRNA and immunohistochemical studies have demonstrated high amounts of α_{2C}-ARs in DRG—primarily in small, but also on some large, neurones (Cho et al., 1997; Gold et al., 1997; Birder and Perl, 1999; Shi et al., 2000). In distinction to α_{2A}-ARs, the level of α_{2C}-ARs in DRG appears to decline upon PAF injury, though not inflammation (Cho et al., 1997; Gold et al., 1997; Birder and Perl, 1999; Shi et al., 2000). While this observation may be construed as questioning the relevance of α_{2C}-ARs on central PAF terminals to the mediation of antinociception by α_2-AR agonists in neuropathic pain, there is no straightforward relationship between receptor density and functional importance.

Further, this discussion devoted to α_{2C}-ARs may conclude with two comments. First, inhibitory α_{2C}-AR autoreceptors co-localised with α_{2A}-ARs on sympathetic terminals may, in suppressing their activity, reduce nociception due to PAF injury (Khasar et al., 1995; Levine and Reichling, 1999; Raja et al., 1999; Hein, 2000; Trendelenburg et al., 2001a,b). Second, although mRNA encoding α_{2C}-ARs has been observed in the VH of rats, levels appear to be low in man (Rosin et al., 1993; Stafford-Smith et al., 1995; Shi et al., 1999).

5.11. α_1-Adrenoceptors in the spinal modulation of nociceptive processing

5.11.1. Localisation of α_1-adrenoceptors in the spinal cord

Despite increasing interest in the role of peripheral α_1-ARs in the transduction of pronociceptive actions of NA released from sympathetic fibres onto PAF terminals (Treede et al., 1992; Millan, 1999; Fuchs et al., 2001; Hord et al., 2001b), segmental populations of α_1-ARs have been virtually ignored in comparison to their α_2-AR counterparts. Nevertheless, a reasonable body of evidence suggests that α_1-ARs modulate nociceptive processing in the DH. Therein, they are located principally on intrinsic neurones rather than on PAFs. However, employing a highly-sensitive detection technique, a recent study reported modest levels of mRNA encoding α_1-ARs in rat DRG (Xie et al., 2001), while functional evidence for up-regulation of α_1-ARs in peripheral terminals of PAFs has been acquired both in models of PAF injury and in clinical investigations of neuropathic pain (Pieribone et al., 1994; Nicholas et al., 1997; Millan, 1999; Fuchs et al., 2001; Hord et al., 2001b). In addition to their presence in the DH, α_1-ARs are expressed at a high density in both the IML and the VH, corresponding to their role in mediating the excitatory influence of noradrenergic pathways upon sympathetic and motor units, respectively (Shao and Sutin, 1991; Ono and Fukuda, 1995; Domyancic and Morilak, 1997; Millan, 1997). Such actions complicate behavioural evaluation of their role in nociceptive processing in the DH.

5.11.2. Anti and pronociceptive roles of α_1-ARs in the DH

As mentioned earlier (Section 5.1), reflecting their positive coupling to PLC and Ca^{2+}-currents, and their inhibitory influence upon K^+-channels, α_1-ARs exert a robust excitatory influence upon neuronal activity (Hieble et al., 1995). Inasmuch as engagement of α_2-ARs is generally associated with a suppression of neuronal activity in the DH (Bylund et al., 1994; Hieble et al., 1995; Budal et al., 1998; Suzuki et al., in press), activation of α_1-ARs provides an appealing interpretation for observations of a direct excitatory influence of NA upon DH neurones (North and Yoshimura, 1984; Millar and Williams, 1989; Fields et al., 1991; Fleetwood-Walker, 1992; Jones, 1992; Millan, 1997), Assuming that a sub-population of neurones excited by NA/α_1-ARs represents ININs, this would account for isolated reports that α_1-ARs mediate antinociception at the segmental level (Howe et al., 1983; Jones, 1992; Loomis and Arunachalam, 1992; Kawabata et al., 1994; Grudt et al., 1995; Hord et al., 2001a). However, behavioural antinociception with high concentrations of NA and α_1-AR agonists may be an artifact of motor disruption due to actions in the VH, and low doses of α_1-AR agonists appear to enhance nociception in the DH (Aran and Proudfit, 1990a,b; Millan, 1997; Holden et al., 1999; Nuseir and Proudfit, 2000).

Such a pro rather than antinociceptive function for α_1-ARs requires their "transposition" from ININs to EXINs and PNs. In-line with this contention, Budal et al. (1998) revealed a facilitatory, post-synaptic influence of α_1-ARs upon a subset of DH neurones (probably PNs) excited by glutamate and noxious stimulation. These neurones were also inhibited by α_2-AR agonists. Thus, pro and antinociceptive actions mediated via α_1- and α_2-ARs, respectively, on a common population of PNs in the DH may account for the bidirectional influence of the stimulation of A_7 noradrenergic neurones upon nociception (Iwamoto and Marion, 1993; Fang and Proudfit, 1998; Holden et al., 1999; Nuseir et al., 1999; Nuseir and Proudfit, 2000; Holden and Naleway, 2001). It is possible that NA exerts such opposing actions on individual DH neurones via α_1-AR versus α_2-AR following simultaneous release from a single descending tract, or even terminal. Alternatively, it has been speculated that two different sub-populations of noradrenergic neurone arising in the A_7 region yield pathways underlying α_1-AR-mediated DF and α_2-AR-mediated DI, respectively (Holden et al., 1999).

5.11.3. Significance of pronociceptive actions of α_1-ARs

In recent years, the notion—founded on their opposite influence upon cellular excitability—that α_1-AR versus α_2-AR differentially influence nociceptive processing in the DH has crystallised into roles in the expression of DF and DI, respectively. Pronociceptive properties of α_1-ARs are of importance for two reasons.

First, in addition to a spinal role in mediating DF, α_1-ARs in other structures may likewise potentiate transmission of nociceptive information. Thus, (1) α_1-AR-mediated enhancement of sympathetic outflow from the IML may

aggravate sympathetic-dependent pain triggered by PAF injury; (2) presumably following their induction in the DRG, and in response to sympathetic stimulation, α_1-ARs on the terminals of PAFs mediate pronociceptive actions under conditions of inflammation (Hong and Abbott, 1996) and PAF injury (Ali et al., 1999; Lee et al., 1999; Millan, 1999; Raja et al., 1999; Fuchs et al., 2001; Hord et al., 2001b) (3) in contrast to α_2-ARs, activation of α_1-ARs in the RVM enhances the activity of ON cells (Section 3.2.4), thereby triggering DF and eliciting behavioural hyperalgesia (Willcockson et al., 1984; Fields et al., 1991; Meng et al., 1997; Heinricher et al., 1999) and (4) likewise, in the thalamus, divergent pro and antinociceptive actions of α_1- and α_2-ARs, respectively, have been described (Zhang et al., 1998a).

Second, as a corollary, the degree of residual activity of centrally-active α_2-AR agonist analgesics at α_1-ARs becomes a crucial issue. Absolute selectivity is difficult to achieve and actions at α_1-ARs may, clearly, compromise analgesia exerted via α_2-ARs located in the DH. Moreover, enhancement of sympathetic outflow by α_1-AR agonists may worsen sympathetic-dependent painful states and perturb cardiovascular function. As concerns motor function, stimulation of α_1-ARs counters the hypnotic-sedative properties of α_2-AR agonists (Schwinn et al., 1991; Hayashi and Maze, 1993; Millan et al., 2000c). In theory, then, α_1-AR agonist properties might be advantageous in abrogating the motor-suppressive actions of α_2-AR agonists for patients not desiring sedation. However, calculations based on the cancellation of two contrary effects can often prove misleading. Further, owing to motor-stimulant effects exerted via activation of α_1-ARs, it has been emphasised that, in a perioperative environment, exceptional selectivity for α_2- over α_1-ARs is a prerequisite for the utilisation of α_2-AR agonists in the induction of anesthesia (Schwinn et al., 1991; Hayashi and Maze, 1993).

5.11.4. Subtypes of α_1-AR

In the aforegoing discussion, no distinction was made between various α_1-AR subtypes. Recent anatomical studies have begun to shed light on the potential significance of α_{1A}-, α_{1B}- and α_{1D}-ARs. Studies of radioligand binding suggest that, overall, α_{1A}-ARs are preponderant throughout the spinal cord of the rat, including both the DH and the VH, with a comparatively low density of α_{1D}-ARs and an intermediate concentration of α_{1B}-ARs (Wilson and Minneman, 1989; Wada et al., 1996). mRNA studies have underpinned the presence of a substantial quantitity of α_{1A}-ARs, and suggest that both α_{1B}-ARs and α_{1D}-ARs may be produced in more significant amounts than revealed by binding studies (Pieribone et al., 1994; Day et al., 1997; Domyancic and Morilak, 1997). Such mRNA studies indicate synthesis of α_1-AR subtypes in situ by intrinsic DH neurones. This observation is of importance since mRNA encoding α_{1A}-, α_{1B}- and α_{1D}-ARs was virtually undetectable in the DRG in early in situ hybridisation studies (Nicholas et al., 1993, 1996). However, a more sensitive RNase protection assay recently demonstrated a modest level of mRNA encoding α_{1A}-ARs, and a lower level encoding α_{1B}- and α_{1D}-ARs (Xie et al., 2001). In view of the implication of α_1-ARs on peripheral terminals of PAFs in the facilitation of neuropathic pain (Section 5.11.3), it is of particular interact that PAF injury enhanced the expression of α_{1B}-ARs. In contrast, mRNA encoding α_{1A}-ARs was decreased and that of α_{1D}-ARs unaffected (Xie et al., 2001). Both α_{1A}-ARs and, less prominently, α_{1B}-ARs are expressed in presympathetic ganglia of the IML, and all three subtypes are found in the VH, with α_{1A}-ARs again predominant (Pieribone et al., 1994; Nicholas et al., 1996; Wada et al., 1996; Domyancic and Morilak, 1997; Millan, 1997; Volgin et al., 2001).

The importance of species differences in the distribution of α-AR subtypes should be borne in mind (Section 5.10.2). Stafford-Smith et al. (1999) have reported that mRNA encoding α_{1D}-ARs is abundant in the human spinal cord. Moreover, while mRNA corresponding to all three subtypes was enriched in the VH and both sympathetic and parasympathetic components of the IML, virtually no signal was discernible in the DH. This unanticipated finding requires confirmation at the protein level and may reflect technical limitations (insufficient assay sensitivity).

In-line with the predominance of α_{1A}-ARs in the DH and VH of the rat, this subtype has been implicated in the induction of nociception and expression of allodynia, and in the facilitation of MN activity, respectively (Bervoets et al., 1993; Millan et al., 1994; Wada et al., 1996). Other information concerning the role of segmental α_1-AR subtypes in the modulation of nociception does not appear to be available. This would be an opportune moment to initiate such investigations inasmuch as selective agents differentiating α_1-AR subtypes have recently become available, as well as transgenic mice deficient in specific classes of α_1-AR (Piascik and Perez, 2001; Spreng et al., 2001).

5.12. New ligands for α_2-adrenoceptors: improving on clonidine for pain relief

5.12.1. The search for novel α_2-adrenoceptor agonists

As noted earlier, there is a convincing body of evidence for a critical role of spinal α_2-ARs in the expression of DI whereas α_1-ARs primarily mediate DF. The α_{2A}-AR subtype indubitably plays a crucial role in antinociceptive processes under a diversity of conditions, and a potential antinociceptive role of α_{2B}- and α_{2C}-ARs remains under investigation. Segmental α_{1A}-ARs likely mediate pronociceptive actions, but the functional significance of α_{1B}- and α_{1D}-ARs remains obscure. Although α_2-AR mediated antinociception is arguably the predominant effect mediated by descending noradrenergic pathways, NA exemplifies the tenet whereby it is inappropriate to attribute a single function to an individual transmitter in the spinal cord (Table 1 and Fig. 5).

The above observations underpin continuing interest in α_2-ARs as targets for improved analgesic agents, either for utilisation alone or in association with other drug classes: indeed, several novel α_2-AR agonists (potential analgesics) have been described recently (Millan, 1998; Williams et al., 1999; Boyd, 2000; Boyd et al., 2001; Millan et al., 2000a,c; Ross et al., 2000). These have been extensively characterised and shown to display robust antinociceptive properties upon spinal and systemic administration in models of acute and chronic, inflammatory and neuropathic pain (Millan et al., 2000a,c; Suzuki et al., in press). Nevertheless, clinical experience has principally been acquired with clonidine, which cannot be regarded as an ideal α_2-AR analgesic. In this respect, two interrelated issues arise: (1) which factors underlie the limitations of clonidine for pain relief and (2) what are the perspectives for improved analgesic agents acting via spinal α_2-ARs?

5.12.2. Principle characteristics of clonidine

First, in cellular models of coupling to intracellular transduction mechanisms, clonidine behaves as a weak partial agonist at all subtypes of α_2-AR (Hieble et al., 1995; Millan et al., 2000a). This has several functional implications. (1) The efficacy of α_2-AR agonists required for expression of specific functional actions differs between autoreceptors (high receptor reserve and high sensitivity) and post-synaptic receptors (low sensitivity and low receptor reserve). α_2-AR autoreceptors contribute to motor and autonomic actions of α_2-AR agonists, whereas post-synaptic sites transduce their antinociceptive actions (Millan, 1997; Millan et al., 2000a; Kable et al., 2000). Partial agonism actually favours, therefore, the former, i.e. partial agonism may limit the therapeutic window of α_2-AR agonists. (2) More generally, low intrinsic activity at post-synaptic (DH-localised) α_2-ARs may impose a ceiling on the maximal degree of antinociception which can be obtained. This supposition is borne out by experimental studies undertaken with clonidine in comparison to higher efficacy agents (Takano and Yaksh, 1991, 1993; Yaksh, 1999a; Millan et al., 2000a). More seriously, the relatively weak intrinsic activity of clonidine suggests that at α_2-AR sites saturated by NA—a full agonist—clonidine might even attenuate its antinociceptive properties. This may explain rare and paradoxical findings of weak antinociceptive actions of clonidine under conditions where release of NA from descending pathways is amplified, such as PAF injury (Sections 5.4 and 5.6). (3) The efficacy of drugs at α_2-ARs is also of pertinence to their actions upon repetitive administration, inasmuch as the relatively low potency and efficacy of clonidine was suggested to underlie rapid induction of tolerance (Stevens and Yaksh, 1989; Takano and Yaksh, 1993). This suggests a further drawback of low efficacy. However, recent mechanistic studies of other systems suggest that processes of desensitisation may be less readily initiated by partial agonists, indicating that low efficacy may actually be advantageous in postponing the development of tolerance (Clark et al., 1999). This question necessitates, thus, additional study.

Second, the lipophilicity of clonidine is high, encouraging its redistribution by the systemic circulation to cerebral and peripheral tissues following spinal delivery (Eisenach et al., 1996; Yaksh, 1999a). Assuming lipophilicity sufficient to penetrate CNS tissue and attain α_2-ARs mediating antinociceptive properties, agonists of less pronounced lipophilicity would be of interest to examine by the spinal route.

Third, clonidine is poorly-selective for α_2- relative to α_1-ARs (Hieble et al., 1995; Millan et al., 2000a). As emphasised earlier (Section 5.11.3), stimulation of α_1-ARs in the DH and other structures may attenuate antinociceptive actions elicited via α_2-ARs and modify both cardiovascular and motor function. Under certain circumstances, the suppression of α_2-AR-mediated hypnotic-sedative actions (induction of anesthesia) by α_1-AR stimulation is unfavourable (Section 5.11.3).

Fourth, clonidine is a potent ligand of I_1 receptors. There is continuing controversy (Section 5.10.1.1) over the relationship of these sites to expression of the hypotensive actions of α_2-AR agonists (Farsang and Kapocsi, 1999; Hein, 2000; Kable et al., 2000; Bruban et al., 2001). Nevertheless, actions at I_1 sites may underlie deleterious cardiovascular and other secondary actions of clonidine and are unlikely to afford any benefit in terms of pain relief.

5.12.3. Novel α_2-AR agonists as analgesics

These comments should not detract from the importance of clonidine as a spinally-deliverable, clinically-useful analgesic agent. However, they suggest that α_2-AR agonists possessing differing characteristics (improved efficacy and selectivity, and diminished lipophilicity) justify therapeutic evaluation as potentially-improved analgesics. A final and obvious issue is the inability of clonidine to discriminate α_2-AR subtypes (Renouard et al., 1994; Hieble et al., 1995). The key role of α_{2A}-ARs in the mediation of antinociception was described earlier (Section 5.10.2). Thus, it would seem desirable to characterise the antinociceptive profiles of agonists interacting solely with α_{2A}-ARs. Contrariwise, in light of the influence of α_{2A}-ARs upon cardiovascular and motor function, there is a clear need to evaluate agonists acting selectivity at α_{2B}- and/or α_{2C}-ARs, which may also contribute to the modulation of spinal nociceptive processing (Section 5.10.3).

Finally, as emphasised earlier (Section 5.9), combination therapies associating α_2-AR agonists with other classes of analgesic agent have proven particularly efficacious in the induction of antinociception—without aggravating side-effects. Rather than the combination of separate drugs, it would be of interest to develop agents integrating two (or more) complementary mechanisms of antinociceptive activity, such as dual agonists at α_2-ARs and μ-opioid receptors. This would be analagous to the design of antipsychotics manifesting non-dopaminergic properties with the aim of both reinforcing therapeutic efficacy and diminishing

side-effects (Brunello et al., 1995; Chakos et al., 2001). This concept of multireceptorial analgesic agents permitting optimisation of the separation between desirable, analgesic and undesirable, secondary effects is further elaborated in Section 12.5.

6. Descending dopaminergic pathways and multiple dopamine receptors

6.1. Multiple classes of dopamine receptor

Dopamine (DA) receptors are classified into two families: D_2-like, incorporating D_2 and closely-related D_3 and D_4 receptors, and D_1-like which includes D_1 and closely-related D_5 receptors (Missale et al., 1998; Vallone et al., 2000). Stimulation of D_2, D_3 and D_4 receptors leads, via Gi/o, to the inhibition of AC. Activation of D_2 receptors also suppresses and potentiates Ca^{2+}- and K^+-currents, respectively, although such actions have proven difficult to detect for their D_3 and D_4 counterparts. Contrariwise, the engagement of D_1 and D_5 receptors results, via Gq, in a stimulation of AC activity. Thus, mirroring the opposite influence of α_1-AR versus α_2-AR upon cellular excitability (Section 5.1), activation of D_2 receptors inhibits, whereas activation of D_1 receptors augments, neuronal activity (Missale et al., 1998; Vallone et al., 2000).

6.2. Supraspinal sources of dopaminergic input to the spinal cord

Compared with the enormous literature devoted to NA and 5-HT, spinal actions of DA have received scant attention. Lumbar and thoracic spinal segments are virtually devoid of dopaminergic cell bodies although, at the cervical level in the rat, a few perikarya may be present around the central canal and in an area corresponding to preganglionic neurones (Mouchet et al., 1986). Further, the purported existence of a small population of DA-synthesising cells in the DRG (Price and Mudge, 1983) has been confirmed (Weil-Fugazza et al., 1993; Bertrand and Weil-Fugazza, 1995). Nonetheless, the dopaminergic innervation of the spinal cord is largely derived from cerebral structures. A minor component may originate in the substantia nigra pars compacta and the PVN of the hypothalamus, but the periventricular, posterior (A_{11}) region of the hypothalamus is the principle source of descending dopaminergic pathways (Commissiong et al., 1978; Commissiong and Neff, 1979; Swanson and Kuyper, 1980; Björklund and Skagerberg, 1982, 1984; Skagerberg et al., 1982, 1988; Skagerberg and Lindvall, 1985; Holstege and Kuypers, 1987; Yoshida and Tanaka, 1988; Mouchet et al., 1992; Ridet et al., 1992). Dopaminergic fibres can be detected in the IML and, despite initial contradictory reports, in the VH (Coole et al., 1981; Barasi and Duggal, 1985; Yoshida and Tanaka, 1988; Shirouzu et al., 1990; Lahlou, 1998), but the most extensive network of fibres is seen in the DH and lamina X (Skagerberg et al., 1982, 1988; Holstege and Kuypers, 1987; Yoshida and Tanaka, 1988; Mouchet et al., 1992; Ridet et al., 1992). Like other monoaminergic pathways descending to the spinal cord, dopaminergic neurones originating in the A_{11} nucleus colocalise other mediators which potentially modulate nociceptive processing at the segmental level (Orazzo et al., 1993).

6.3. Localisation of multiple classes of dopamine receptor in the spinal cord

6.3.1. D_2 receptor family: D_2, D_3 and D_4 receptors

Binding studies employing selective, radiolabelled ligands have demonstrated that D_2 receptors occur in the DH. Higher-resolution, immunocytochemical studies concur with this approach in localising D_2 receptors principally in superficial laminae and lamina X (Dubois et al., 1986; Yokoyama et al., 1994; Van Dijken et al., 1996). Studies of mRNA encoding D_2 sites revealed its presence in lamina I as well as in deeper laminae (II–VI) demonstrating synthesis of D_2 receptors by intrinsic DH neurones involved in nociceptive processing (Van Dijken et al., 1996). The detection of mRNA encoding D_2 receptors in the DRG suggests that D_2 receptors may be expressed by central terminals of PAFs (Peterfreund et al., 1995; Lazarov and Pilgrim, 1997; Xie et al., 1998). D_2 receptors have also been visualised in the IML and in the VH, although the latter contention has been challenged and remains somewhat controversial (Yokoyama et al., 1994; Van Dijken et al., 1996; Levant and McCarson, 2001).

A recent study showed that D_3 receptors mimic the preferential localisation of D_2 receptors in the DH (in particular in superficial laminae), although their absolute density is substantially inferior (Levant and McCarson, 2001). While it remains to be proven that D_3 receptors in the DH are produced by intrinsic neurones, the presence of mRNA encoding D_3 receptors in rat DRG suggests their location pre-synaptically on the terminals of PAFs projecting to the DH (Xie et al., 1998). mRNA encoding D_4 receptors is highly expressed in human spinal cord (Matsumoto et al., 1996). Although systematic examination of the potential presence of D_4 receptors in rodent spinal cord is awaited, mRNA has been detected in the DRG indicating their possible occurrence on PAF terminals in the DH (Xie et al., 1998).

Inasmuch as the majority of "D_2-selective" ligands do not reliably discriminate D_2 from D_3 and/or D_4 sites, it should be borne in mind that actions ascribed in the following sections to D_2 receptors may ultimately transpire to be mediated by D_3 or D_4 receptors. The respective roles of D_2, D_3 and D_4 receptors can now be resolved by the use of recently-described, highly-selective antagonists, as well as by studies with "knock-out mice" lacking these receptors (Sibley, 1999; Hrib, 2000; Crider and Scheideler, 2001).

6.3.2. D_1 receptor family: D_1 and D_5 receptors

As concerns the second "family" of D_1-like receptors, binding studies indicated the presence of D_1 receptors

throughout the spinal cord, including the DH. Although little precise information was generated by these original studies (Dubois et al., 1986; Bhargava and Gulati, 1990), a more recent, quantitative report corroborated the presence of D_1 receptors in all regions of the spinal cord and revealed that their density is superior to that of D_2 receptors (Levant and McCarson, 2001). mRNA studies formally demonstrating expression of D_1 sites by intrinsic neurones do not, regrettably, appear to have been undertaken although this approach has detected mRNA encoding D_1 receptors in DRG, suggesting that central PAF terminals in the DH bear D_1 receptors (Lazarov and Pilgrim, 1997; Xie et al., 1998). No information on the segmental co-localisation D_5 sites is, as yet, available, but they are well-represented in the trigeminal complex (Ariano et al., 1997; Ciliax et al., 2000).

6.4. Modulation of the activity of descending dopaminergic pathways

Little is known of the pathophysiological modulation of spinal dopaminergic transmission, although both acute and sustained noxious input accelerates DA turnover in the DH suggesting an enhancement in the activity of descending dopaminergic pathways (Weil-Fugazza and Godefroy, 1993; Men and Matsui, 1994; Hore et al., 1997; Gao et al., 2001b). Dopaminergic mechanisms may participate in the accompanying antinociception (Tricklebank et al., 1984). There are clinical reports that cerebrospinal fluid levels of DA are decreased in certain types of chronic pain-though this change is not necessarily related to an alteration in dopaminergic transmission at the spinal level (Bouckoms et al., 1992; Jääskeläinen et al., 2001).

6.5. Contrasting influence of segmental D_2 versus D_1 receptors upon nociception

Despite evidence that systemic morphine administration modifies spinal levels of DA (Weil-Fugazza and Godefroy, 1991), studies of the influence of dopaminergic antagonists upon MIA suggest that segmental dopaminergic mechanisms are unlikely to fulfil a significant role in its mediation (Kiristy-Roy et al., 1989; Rooney and Sewell, 1989; Gatch et al., 1998; King et al., 2001). Nevertheless, there are several reports (Ben-Sreti et al., 1983; Rooney and Sewell, 1989; Zarrindast and Moghaddampour, 1989) that D_2 agonists potentiate opioidergic antinociception. Though not all authors concur with these observations (Cook et al., 1999, 2000), a facilitation of MIA would be of interest inasmuch as the systemic administration of D_2 receptor agonists (alone) generally elicits antinociception. In distinction, D_1 receptor agonists elicit pronociceptive effects both alone and in interaction with D_2 agonists or opioids, although conflicting results have been presented (Ben-Sreti et al., 1983; Rooney and Sewell, 1989; Zarrindast and Moghaddampour, 1989; Hore et al., 1997; Zarrindast et al., 1999; Gao et al., 2000; Verma and Kulkarni, 1993). Occasional reports of pronociceptive effects of D_2 agonists in models involving thermal noxious stimuli likely reflect an artifact of their induction of hypothermia (Roane et al., 1998).

These observations indicate that, in line with their opposite coupling to intracellular signals, D_2 as compared to D_1 receptors differentially modify nociception. More direct support for a role of D_2 sites in the mediation of DI is provided by the following observations. First, stimulation of the A_{11} dopaminergic nucleus reduces the behavioural response to noxious stimulation, an action reproduced by D_2 agonists and abrogated by D_2 antagonists (Carr, 1984). Similarly, stimulation of the A_{11} nucleus selectively suppresses the response of convergent PNs in the superficial and deep DH to noxious stimuli, an action mimicked by D_2 agonists and blocked by D_2 antagonists (Fleetwood-Walker et al., 1988). Second, in line with these findings, ionophoretic application of DA onto PNs suppresses their response to the PAF transmitter, glutamate (Willcockson et al., 1984; Garraway and Hochman, 2001c). Further, DA hyperpolarises a subset of PNs in lamina II (Nakatsuka et al., 1999). Third, i.t. delivery of D_2 agonists elicits an antinociception which is selectively reversed by antagonists at D_2 but not D_1 receptors (Jensen and Smith, 1982; Jensen and Yaksh, 1984; Barasi and Duggal, 1985; Barasi et al., 1987; Liu et al., 1992; Gao et al., 2001a). Fourth, D_2 agonists, consistent with a specific influence upon sensory as compared to motor processes, selectively interrupt nociceptive reflexes without interfering with monosynaptic motor reflexes (Barasi and Duggal, 1985; Shannon et al., 1991). Fifth, i.t. administration of D_2 agonists suppresses the excitation of thalamic neurones provoked by noxious stimulation, an action dissociable from any influence upon cardiovascular parameters (Clatworthy and Barasi, 1987). Sixth, although data with spinal application of D_1 receptor agonists are scare, Gao et al. (2001a) recently suggested that their engagement enhances nociception, consistent with a role in the expression of DF.

Recruitment of descending dopaminergic pathways and spinal D_2 receptors may participate in the induction of antinociception by PAG stimulation (Akil et al., 1976), cannabinoids (Section 11.1.3) (Carta et al., 1999) and several novel analgesic agents (Esposito et al., 1986; Ohkubo et al., 1991). The NMDA receptor open channel blocker, ketamine, is widely employed for evaluation of the significance of segmental glutamatergic mechanisms in nociceptive processing (Section 5.9.4) (Luczak et al., 1995). Ketamine was recently shown to behave as a partial agonist at dopamine D_2 receptors (Kapur and Seeman, 2001) raising the intriguing possibility that stimulation of D_2 sites might contribute to its influence upon nociception and other functions. On the other hand, in contradiction of early findings, the antinociceptive properties of the catecholamine releaser, cocaine, cannot be attributed to spinal dopaminergic mechanisms (Kiristy-Roy et al., 1989). The latter

finding emphasises that effects of the systemic administration of dopaminergic agents cannot necessarily be attributed to actions at the spinal level. Indeed, forebrain dopaminergic pathways are also implicated in antinociceptive processes (Section 6.8).

6.6. Mechanisms for modulation of nociception by D_2 versus D_1 receptors in the DH

The most parsimonious explanation for the induction of antinociception via spinal D_2 receptors is a direct inhibitory action at either nocisponsive PAF terminals or PNs, a contention congruent with anatomical and electrophysiological data outlined earlier (Section 6.3). This would also be consistent with the inhibitory influence of D_2 receptors upon neuronal excitability mediated via inhibition of AC and suppression and activation of Ca^{2+}- and K^+-currents, respectively (Section 6.1) (Missale et al., 2000; Vallone et al., 2000). Indeed, an inhibitory influence of D_2 receptors upon Ca^{2+}-currents has been recorded in DRG cells and provides a potential mechanism for a pre-synaptic reduction of release from PAF terminals in the DH (Formenti et al., 1998). Such a role of D_2 receptors in the interference with PAF input would concur with the presence of mRNA encoding D_2 sites in the DRG (Xie et al., 1998). However, D_2 agonists did not modify the release of CGRP or SP in the DH (Bourgoin et al., 1993; Molokanova and Tamarova, 1995) so this possibility remains to be further evaluated. On the other hand, potentiation of the spinal liberation of CGRP and SP by D_1 agonists is in line with the presence of excitatory D_1 receptors in the DRG, and suggests that D_1 agonists may enhance nociception, at least partially, by strengthening input from nocisponsive PAFs onto PNs (Bourgoin et al., 1993). This proposition is coherent with evidence for pronociceptive actions of DA in the periphery via excitatory actions at D_1 receptors on PAF terminals (Nakamura and Ferreira, 1987; Bertrand and Weil-Fugazza, 1995; Formenti et al., 1998; Xie et al., 1998).

While it has been suggested that GABAergic ININs, acting via $GABA_A$ receptors, may intervene in the antinociceptive actions of DA (at D_2 receptors) in the DH (Yang et al., 1996b), it is difficult to reconcile this proposition with the suppression of neuronal firing by actions of DA at D_2 receptors. Similarly, the suggestion that opioid receptors mediate spinal D_2 receptor-mediated antinociception appears unlikely (Michael-Titus et al., 1990). Although there are isolated data examining a possible relationship between dopaminergic, noradrenergic and serotonergic mechanisms for modulation of nociceptive processing in the DH, no consistent pattern of data has emerged (Jensen and Yaksh, 1984; Fleetwood-Walker et al., 1988; Liu et al., 1992). Thus, as indicated earlier, the anti and pronociceptive actions of D_2 and D_1 agonists, respectively, are mostly likely expressed directly via actions on PNs and/or on PAF terminals.

6.7. Influence of DA upon autonomic and motor outflow

The influence of dopaminergic input, and of specific subtypes of dopamine receptor, upon MNs in the VH remains unclear. Reports of excitatory and inhibitory actions probably correspond to actions at D_1 and D_2 receptors, respectively (Ono and Fukuda, 1984; Kamijo et al., 1993; Smith et al., 1995; Van Dijken et al., 1996). Irrespective of this uncertainty, the potential modification of motor function by spinal administration of dopaminergic agents should be borne in mind in both experimental, and if performed, clinical investigations. In addition, via actions at preganglionic neurones in the IML, spinal application of dopaminergic agonists elicits a pronounced hypotension and bradycardia, probably via activation of D_2 receptors (Pelissier and Demenge, 1991; Lahlou, 1998). Whether suppression of sympathetic outflow translates into antinociceptive actions against neuropathic pain remains to be determined.

6.8. Supraspinal dopaminergic mechanisms in the modulation of descending controls

Mesolimbic, mesocortical and nigrostriatal dopaminergic pathways are involved in the modulation (inhibition) of nociception, primarily its affective component (Morgan and Franklin, 1991; Ariano and Sibley, 1994; Chulder and Dong, 1995; Altier and Stewart, 1998, 1999; Burkey et al., 1999; Gear et al., 1999; Gao et al., 2000; Gilbert and Franklin, 2001a). In addition, antinociceptive actions of dopaminergic agonists have been seen upon their introduction into the NRM, presumably due to modulation of descending controls, although the precise mechanism involved remains to be elucidated (Phillips et al., 1992). Despite the presence of DA and multiple dopaminergic receptors in structures giving rise to descending pathways, the question of their influence upon descending modulation of nociceptive processing remains to be functionally addressed (Ariano and Sibley, 1994; Ariano et al., 1997; Ciliax et al., 2000; Kitahama et al., 2000).

As pointed out above, in view of the important role of ascending dopaminergic pathways in the induction of antinociception, observations obtained upon systemic drug administration should not automatically be assigned to a spinal—or supraspinal—mechanism of action in the absence of additional, relevant information. The importance of defining neuroanatomical loci involved in dopaminergic mechanisms modulating nociception, and the conditions under which they are recruited, is underscored by a recent study in mice. In this study: (1) deletion of the gene encoding D_2 receptors or (2) i.c.v. administration of an antisense probe directed against D_2 receptors potentiated antinociception elicited by μ- and κ-opioid agonists in a reflexive, algesiometric procedure (King et al., 2001). It will be of importance to confirm these observations and to reconcile them with pharmacological studies in rats (vide supra) indicative of antinociceptive functions of spinal and

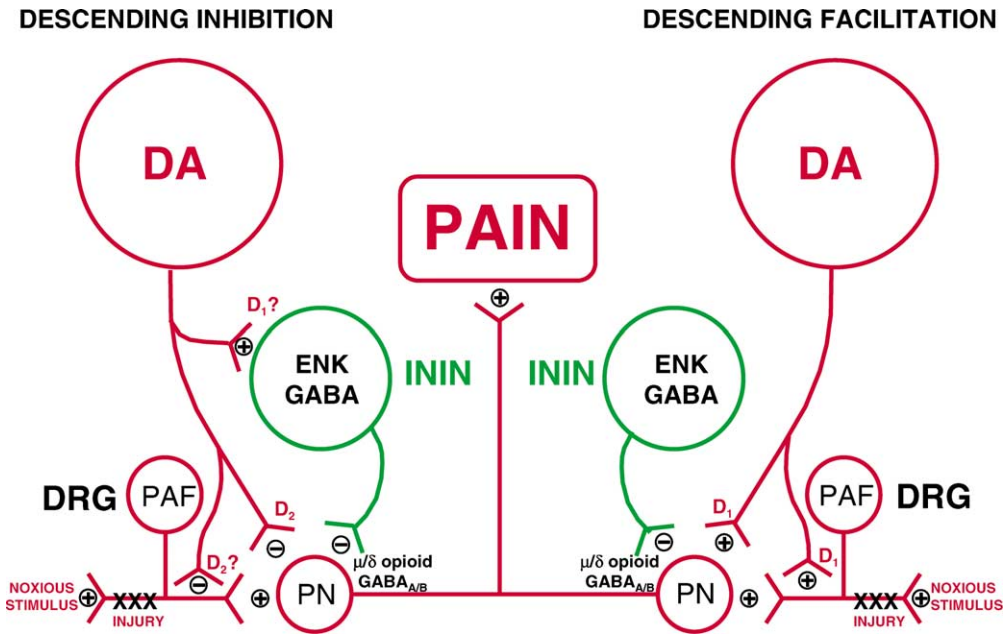

Fig. 6. Significance of multiple classes of dopamine receptor and of their divergent neuronal localisation to the modulation of nociceptive processing in the DH. On the left-hand side, mechanisms mediating descending inhibition are indicated and, on the right-hand side, those expressing descending facilitation are shown. Actions are exerted at terminals of primary afferent fibres (PAFs), projection neurones (PNs) and inhibitory interneurones (ININs). For clarity, excitatory interneurons are omitted, modulation of which would be essentially identical to PNs. Similarly, actions of ININs at PAF terminals are omitted for clarity. Enkephalin (ENK) and γ-hydroxy-butyric acid (GABA) are indicated as transmitters in ININs in view of their key antinociceptive roles. Note that D_2 receptors suppress neuronal activity, whereas cellular excitability is enhanced by D_1 receptors. Actions attributed to "D_2" receptors may emerge to involve closely-related D_3 or D_4 sites, and actions at "D_1" sites may involve closely-related D_5 receptors. Abbreviations are as follows: DRG, dorsal root ganglia and DA, dopamine. For further details, see text.

supraspinal populations of D_2 receptors, but which do not differentiate D_2 vs D_3/D_4 sites.

6.9. Clinical relevance of spinal dopaminergic mechanisms for the modulation of nociception

To summarise, despite only cursory interest in segmental dopaminergic mechanisms for the control of nociceptive processing, reasonable evidence has accumulated that antinociceptive (DI) and, perhaps, pronociceptive (DF) actions are mediated by spinal D_2 and D_1 sites, respectively. As pointed out earlier, drugs to date employed in the evaluation of the functional significance of spinal D_2 and D_1 sites do not differentiate them from their D_3/D_4 and D_5 counterparts, respectively, suggesting that a reassessment of their role(s) may be necessary once data from more selective ligands and transgenic models become available.

Interestingly, there have been sporadic reports of the use of D_2 agonists and the DA precusor, L-dihydroxyphenylalanine (generally referred to as L-DOPA), for relief of neuropathic pain (Ertas et al., 1998) but no solid clinical data are available. With the possible exception of Parkinsonian patients, autonomic, somatic and affective actions of systemically-applied D_2 agonists exerted at supraspinal and peripheral sites could severely compromise any potential utility as analgesic agents. Further, tempering enthusiasm for the (parenteral) utilisation of D_2 receptor agonists for pain relief, activation of hypersensitive dopaminergic (D_2) receptors localised on cerebral vessels may be implicated in the pathogenesis of migraine headaches as concerns both autonomic symptoms and the accompanying pain (Peroutka, 1997; Millan, 1999; Montagna, 2000). Nevertheless, it would appear justified to clinically explore whether spinal administration of D_2 agonists—alone, or in combination with other classes of analgesic agent—can afford pain relief in the absence of unacceptable side-effects.

Irrespective of these questions, the contrasting influence of segmental populations of D_2 versus D_1 receptors upon nociceptive processing in the DH underpins the argument that differential coupling to intracellular transduction mechanisms likely presages an opposite influence upon nociception (Fig. 6). These observations also exemplify the contention that a unitary function cannot realistically be assigned to individual transmitters in the DH.

7. Descending serotonergic pathways and multiple serotonin receptors

7.1. Organisation of serotonergic input to the spinal cord

7.1.1. Origins and projection patterns to the DH

Although a small population of 5-HT-immunoreactive cell bodies has been identified ventral to the central canal in

primates (LaMotte, 1988), virtually the entire serotonergic innervation of the spinal cord in these and other species is derived from supraspinal sources. In this regard, a modest proportion of serotonergic neurones from the dorsal raphe nucleus—which predominantly innervates the thalamus, dorsal hippocampus, striatum, cerebral cortex-sends collaterals to the spinal cord and the trigeminal nucleus, the structural and functional equivalent of the DH (Beitz, 1982a; Kazakov et al., 1993; Li et al., 1993; Cesselin et al., 1994; Wang and Nakai, 1994; Li et al., 1997; Kirifides et al., 2001). However, the predominant source of serotonergic input to the spinal cord (and trigeminal nucleus) arises within the vicinity of the RVM and, most prominently, from the NRM (Björklund and Skagerberg, 1982; Bowker et al., 1983; Bullitt and Light, 1989; Jones and Light, 1992; Kwiat and Basbaum, 1992; Wang and Nakai, 1994; Mason, 1999). It was recently proposed that the NRM is composed of sub-classes of serotonergic neurone, based upon combined anatomical and functional criteria (Gao and Mason, 2001). Serotonergic fibres display widespread co-lateralisation throughout the spinal cord, trigeminal nucleus and medullary nuclei (Bowker et al., 1983; Bowker and Abbott, 1990).

There is an extensive network of serotonergic fibres throughout the spinal cord: varicosities are most abundant in superficial zones (laminae I/II), but deeper laminae (IV–VI) also present a dense plexus of serotonergic terminals (Basbaum and Fields, 1984; Ruda et al., 1986; Besson and Chaouch, 1987; Halliday et al., 1995; Maxwell et al., 1996; Li et al., 1997; Stewart and Maxwell, 2000). Numerous axo-somatic and dendritic contacts of serotoninergic terminals are seen in the DH, some of which reveal contact between serotonergic terminals and PNs projecting to, for example, the thalamus and the PBN (Ruda et al., 1986; Ruda, 1988; Marlier et al., 1991; Wu and Wessendorf, 1992; Grudt et al., 1995; Li et al., 1997; Millan, 1997). In view of anatomical evidence for 5-HT receptors on PAFs (Section 7.4), there is remarkably little evidence for apposition of serotonergic fibres at central PAF terminals in the DH and trigeminal nucleus (above citations; Cesselin et al., 1994; Millan, 1997; Hamon and Bourgoin, 1999). Nevertheless, PAF activity may be modulated non-synaptically by volume transmission (Section 2.3) (Ridet et al., 1993) or, alternatively, via local ININs, including ENK- and GABA/glycine-containing populations which receive an input from descending serotonergic pathways (Ruda et al., 1986; Ruda, 1988; Alhaider et al., 1991; Fields et al., 1991; Millan, 1997; Tsuchiya et al., 1999). As discussed in the following sections, in addition to the presence of 5-HT receptors on PAF terminals, their dual localisation on both ININs and PNs provides a conceptual and neuronal

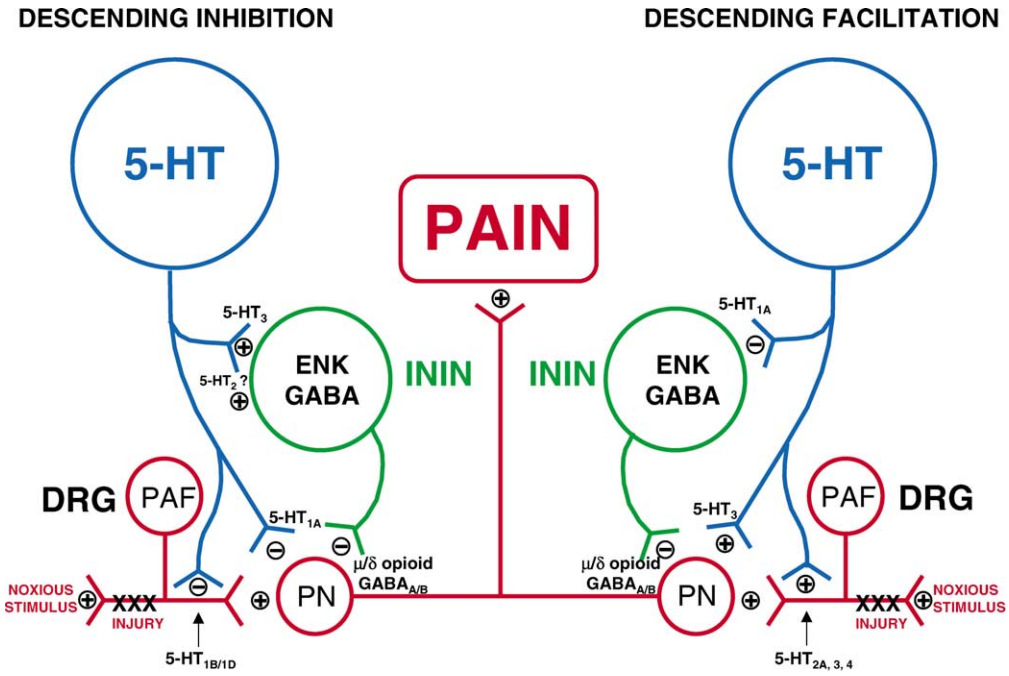

Fig. 7. Significance of multiple classes of 5-HT receptor and of their divergent neuronal localisation to the modulation of nociceptive processing in the DH. On the left-hand side, mechanisms mediating descending inhibition are indicated and, on the right-hand side, those expressing descending facilitation are shown. Actions are exerted at terminals of primary afferent fibres (PAFs), projection neurones (PNs) and inhibitory interneurones (ININs). For clarity, excitatory interneurons are omitted, modulation of which would be essentially identical to PNs. Similarly, actions of ININs at PAF terminals are omitted for clarity. Enkephalin (ENK) and γ-hydroxy-butyric acid (GABA) are indicated as transmitters in ININs in view of their key antinociceptive roles and anatomical evidence that they are targeted by serotonergic input to the DH. Note that 5-HT_{1A} and 5-$HT_{1B/1D}$ receptors suppress neuronal activity, whereas cellular excitability is enhanced 5-HT_2, 5-HT_3 and 5-HT_4 receptors. The subtype of 5-HT_2 receptor localised on ININs (A, B or C) is not indicated as this remains unclear. Other classes of 5-HT receptor may likewise exert a complex pattern of influence upon nociceptive processing (see text). Abbreviations are as follows: DRG, dorsal root ganglia and 5-HT, serotonin. For further details, see text.

framework for understanding the complex pattern of pro- and antinociceptive actions of 5-HT in the DH (Fig. 7).

7.1.2. Co-localisation of 5-HT with other transmitters

Like the dorsal raphe nucleus (Kirifides et al., 2001), the NRM does not constitute a pure population of serotonergic perikarya. Rather, it contains numerous other classes of neurone synthesising ACh, thyrotropin-releasing hormone, GABA, glycine, somatostatin, SP, ENK, dynorphin (DYN), galanin (GAL) and/or CCK (Bowker et al., 1983, 1988; Jones and Light, 1992; Kwiat and Basbaum, 1992; Nicholas et al., 1992; Wu and Wessendorf, 1992; Wu et al., 1993; Millan, 1995, 1997; Maxwell et al., 1996; Hökfelt et al., 2000). A subset of serotonergic neurones projecting to the DH reveals co-localisation with certain of these neurotransmitters (notably SP, thyrotropin-releasing hormone, GABA, DYN and ENK), which likely interact with 5-HT in the modulation of nociceptive processing upon their concomitant release in the DH. Athough the precise degree of co-existence remains under discussion (earlier citations), it appears that a substantial proportion (25%) of serotonergic neurones targeting superficial laminae contain GABA, whereas they are largely devoid of neuropeptides (Millhorn et al., 1988; Stamp and Semba, 1995; Antal et al., 1996; Maxwell et al., 1996). On the other hand, in deeper lamina V, there is little indication for GABA in serotonergic fibres wherein a sub-population contains SP, thyrotropin-releasing hormone and/or GAL (Wessendorf and Elde, 1987; Bowker and Abbott, 1990; Wu and Wessendorf, 1992; Maxwell et al., 1996). Clearly, whether co-localised with 5-HT or not, several transmitters contained in NRM-derived neurones projecting to the DH play an important role in the spinal modulation of nociceptive processing. Indeed, as outlined in Section 7.3, irrespective of the extent of co-existence of 5-HT with other transmitters, the designation of antinociception elicited by stimulation of NRM as purely serotonergic would be erroneous.

7.1.3. Serotonergic input to the intermediolateral cell column and ventral horn

In contrast to the DH, the pronounced serotonergic input to the IML (preganglionic sympathetic nuclei), to parasympathetic preganglionic neurones and to the VH is principally derived from the nucleus raphe pallidus, the nucleus raphe obscurus and the para-olivary nucleus/parapyramidal area. The extent of neuropeptide (though not GABA) co-localisation with 5-HT in these populations of descending serotonergic neurones is more pronounced (particularly for GAL, thyrotropin-releasing hormone and SP) than in their NRM-derived counterparts innervating the DH (Björklund and Skagerberg, 1982; Millhorn et al., 1987; Vera et al., 1990; Wu and Wessendorf, 1992; Izzo et al., 1993; Wu et al., 1993; Maxwell et al., 1996; Millan, 1997; Hökfelt et al., 2000). It is probable that 5-HT and co-localised neuropeptides display functional interactions upon their concurrent release from terminals in the IML and VH (Yang and Helke, 1995). An excitatory serotonergic drive upon preganglionic neurones is important in maintaining vasomotor tone and arterial pressure (Loewy, 1990; Vera et al., 1990; McCall and Clement, 1994; Millan, 1995). Tonic serotonergic input to the VH also plays an important role in regulating the functional status of motoneurones (Millan, 1995, 1997).

7.2. Modulation of the activity of descending serotonergic pathways

Both acute and chronic exposure to noxious stimuli has been demonstrated to activate serotonergic neurones in the RVM and to accelerate the turnover of 5-HT in the spinal cord (Weil-Fugazza, 1990; Puig et al., 1992; Taguchi and Suzuki, 1992; Men and Matsui, 1994; Li et al., 1999c; Mason, 1999; Gao and Mason, 2000; Zhang et al., 2000c). Supraspinal opioid mechanisms have been implicated in this stimulation of descending serotonergic transmission by noxious stimuli (Zhang et al., 2000a,b,c). These neurochemical findings are coherent with observations that manipulation of serotonergic pathways modifies the “stress-induced analgesia” with accompanies exposure to noxious stimuli. In this respect, contradictory reports of an attenuation or enhancement of stress-induced analgesia by interference with serotonergic transmission likely reflect the dual role of serotonergic mechanisms in the expression of DI and DF (Hutson et al., 1982; Le Bars, 1988; Gamble and Milne, 1990; Tjolsen et al., 1991; Millan, 1997). In distinction to models of chronic inflammatory pain (Weil-Fugazza, 1990; Li et al., 1999c; Zhang et al., 2000a,b,c), certain studies indicate that the activity of descending serotonergic pathways may be diminished upon PAF injury (Satoh and Omote, 1996; Suh et al., 1996b; Sandrini et al., 1997; Padayatti and Paulose, 1999; Bardin et al., 2000a). Under such conditions of PAF damage, there is evidence for alterations in the organisation of serotonergic input to the DH, including sprouting of serotonergic terminals (Marlier et al., 1991; Wang et al., 1999c). Although the functional significance of such structural changes remains uncertain, they provide an intriguing analogy to the profound restructuring of PAF input to the DH which is triggered by their injury (Woolf and Doubell, 1994; Millan, 1997, 1999; Doubell et al., 1999; Woolf and Mannion, 1999). Further, they may reflect the possession by descending serotonergic pathways of “trk” receptors for brain derived neurotrophic factor and other neurotrophins, as well as their constitutive expression of the growth factor and calmodulin-binding protein, “GAP-43” (Ching et al., 1994; Wotherspoon et al., 1997; King et al., 1999; Millan, 1999). Alterations in 5-HT metabolism have been documented in chronic pain patients, but it remains to be clarified whether they can be attributed to an increase—or decrease—in the activity of descending serotonergic pathways (Le Bars, 1989; Von Knorring, 1990; Hamon and Bourgoin, 1999).

7.3. Recruitment and actions of descending serotonergic pathways

7.3.1. Pro- and antinociceptive roles of descending serotonergic pathways

Traditionally, actions of 5-HT in the DH have been considered as dedicated to the suppression of nociceptive transmission (Basbaum and Fields, 1978; Millan, 1982; Le Bars, 1988; Eide and Hole, 1993). In contradiction of this assumption, much evidence has accumulated questioning whether descending serotonergic pathways play a generalised role in suppressing the flow of nociceptive information to higher centres (Le Bars, 1988; Eide and Hole, 1993; Millan, 1995, 1997, 1999; Hamon and Bourgoin, 1999; Yaksh, 1999a). Indeed, as outlined in the following sections, studies of electrical brain stimulation, MIA and the effects of direct administration of 5-HT onto the spinal cord collectively converge towards the conclusion that descending serotonergic pathways exert a bidirectional influence upon nociceptive processing in the DH, mediating processes of both DI and DF (Millan, 1995, 1997). This recognition of pro and antinociceptive actions of 5-HT in the DH permits the reconciliation of a plethora of contradictory data and can best be accommodated within a framework encompassing opposite actions of 5-HT as a function of: (1) individual classes of 5-HT receptor, which either enhance or decrease neuronal activity, and (2) the contrasting localisation of specific 5-HT receptor types on DH elements either facilitating (PAF, EXINs and/or PNs) or attenuating (ININs) the passage of nociceptive information to the brain (Fig. 7).

7.3.2. Involvement of serotonergic mechanisms in descending inhibition and facilitation

Much of the older literature advocates a role of descending serotonergic pathways in mediation of the antinociception elicited by electrical stimulation of the PAG and NRM (Besson et al., 1978, 1981; Besson, 1990; Fields and Basbaum, 1978; Millan, 1982; Basbaum and Fields, 1984; Rivot et al., 1984; Besson and Chaouch, 1987; Le Bars, 1988; Fields et al., 1991; Cameron et al., 1995; Yaksh, 1999a). However, studies: of (1) the influence of PAG and NRM stimulation upon the electrical activity of serotonergic neurones, and upon the spinal release and turnover of 5-HT and of (2) the influence of lesions of serotonergic pathways and the administration of serotonergic antagonists upon stimulation-produced analgesia (SPA), have yielded an, at best, equivocal body of evidence concerning the putative antinociceptive role of descending serotonergic pathways (Le Bars, 1980; Gamble and Milne, 1990; Gao et al., 1997; Millan, 1997). Indeed, non-serotonergic, descending GABAergic, glycinergic, cholinergic and ENKergic neurones originating in the RVM, as well as efferent projections to noradrenergic neurones in the A_7 nucleus, all contribute to SPA elicited from the PAG and NRM (Hammond et al., 1985; Zhuo and Gebhart, 1990a,b; McGowan and Hammond, 1993a,b; Lin et al., 1994; Fang and Proudfit, 1996; Millan, 1997; Cui et al., 1999).

Thus, activation of descending serotonergic pathways appears to be neither necessary nor sufficient for the induction of antinociception by stimulation of the NRM or PAG (Sawynok, 1989; Millan, 1995, 1997). Moreover, dependent upon stimulus parameters, stimulation of the RVM can elicit hyperalgesia and an extensive body of evidence shows that descending serotonergic pathways contribute to the induction of DF from this structure (Zhuo and Gebhart, 1990a, 1991a, 1992, 1997). Providing an interesting analogy to this cojoint recruitment—by RVM stimulation—of descending serotonergic pathways mediating both pro and antinociceptive actions, low and high intensity stimulation of vagal afferents (which access the RVM via a NTS relay) triggers DF and DI, respectively, in each case involving descending serotonergic mechanisms (Ren et al., 1988, 1991). Evidence that serotonergic mechanisms of DF contribute to neuropathic pain has also been presented (Pertovaara et al., 2001).

Simultaneous engagement of serotonergic mechanisms of DI and DF parallels evidence for the bidirectional control of spinal nociceptive processing by stimulation of the noradrenergic A_7 nucleus (Section 5.11.2, Fig. 5) with α_2- as compared to α_1-ARs mediating DI and DF, respectively. As discussed in Section 7.4, contrasting roles of multiple classes of 5-HT receptor likewise account for the cojoint expression of DI and DF by descending serotonergic pathways (Fig. 7).

7.3.3. Influence of supraspinal opioidergic and other mechanisms upon descending serotonergic pathways

As for models of supraspinal SPA, despite initial enthusiasm for a key role of descending serotonergic pathways in the mediation of MIA, it has become apparent that their contribution is at most partial and dependent upon a diversity of parameters, including the precise site and dose of morphine injection and the algesiometric paradigm employed (Besson et al., 1978, 1981; Fields and Basbaum, 1978; Millan, 1982, 1995, 1997; Basbaum and Fields, 1984; Rivot et al., 1984; Le Bars, 1988; Sawynok, 1989; Besson, 1990; Fields et al., 1991; Borszcz et al., 1996a,b; Hamon and Bourgoin, 1999; Yaksh, 1999a). For example, neurotoxin and pharmacological interruption of descending serotonergic transmission variably modifies MIA, and morphine does not consistently activate serotonergic neurones projecting from the NRM to the DH (Chiang and Xiang, 1987; Gao et al., 1998; Le Bars, 1988; Sawynok, 1989; Schaus et al., 1990; Matos et al., 1992; Puig et al., 1993; Borszcz et al., 1996a,b; Peng et al., 1996c; Suh et al., 1996b; Millan, 1997; Hamon and Bourgoin, 1999; Li et al., 2001). Thus, descending serotonergic pathways do not play an indispensable role in the mediation of MIA, whether elicited by systemic or cerebral administration of morphine. Further, in this context, it should be mentioned that serotonergic neurones in the RVM correspond neither to those ON nor OFF categories which are candidates for modulation of descending controls

by opioids and other mechanisms (Section 3.2.4) (Fields et al., 1991; Fields and Basbaum, 1999; Mason, 1999).

However, as indicated earlier, it is important to appreciate the significance of multiple 5-HT receptor types in the DH, certain of which transduce, and certain of which counter MIA, dependent upon their influence upon cellular excitability and their neuronal localisation. Further, this lack of a universal role for descending serotonergic pathways in the expression of MIA does not deny the existence of specific neuronal circuits whereby supraspinal opioidergic neurones can modify nociception via serotonergic mechanisms. In this light, it must be recognised that supraspinal populations of μ-, δ- and κ-opioid receptor differentially interact with descending serotonergic pathways.

Within the RVM, κ-opioid receptors fulfil a dual role in: (1) indirectly triggering serotonergic mechanisms of DI and (2) directly reducing their engagement by μ- and δ-opioid receptors (Pan et al., 1997, 2000; Pan, 1998). Several recent studies have advanced an explanation for these opposing actions of κ-opioid receptors based upon their influence upon two different classes of cell in the RVM, termed "primary" and "secondary", respectively. These neurones display contrasting phenotypes, patterns of synaptic connectivity, excitability and responsiveness to opioids. Primary cells, which comprise ∼30% of cells in the RVM contain 5-HT and are directly inhibited by κ-opioids and by a larger population of secondary GABAergic cells (Pan et al., 1990, 1993, 1997, 2000; Jones et al., 1991; Gao and Mason, 1997, 2000; Pan, 1998). The inhibition of secondary, GABAergic neurones by μ- and δ-opioid agonists disinhibits their serotonergic, primary counterparts resulting in antinociception (Pan et al., 1990; Vaughan et al., 1999; Li and Wang, 2001). Accordingly, direct inhibition of primary cells by κ-opioid receptors accounts for their interference with the antinociceptive properties of μ- and δ-opioid agonists (Pan et al., 1997; Gutstein et al., 1998; Kalyuzhny and Wessendorf, 1999; Vaughan et al., 1999). On the other hand, a suppression of excitatory glutamatergic input to secondary GABAergic cells by κ-opioid agonists underlies their intrinsic antinociceptive actions inasmuch as this action relieves the GABAergic inhibitory tone upon primary cells (Ackley et al., 2001). This cellular mechanism may account for certain older findings of the dependence of supraspinal κ-opioid receptor-induced antinociception upon serotonergic mechanisms (Vonvoigtlander et al., 1984; Czlonkowski et al., 1987; Ho and Takemori, 1989; Millan, 1990; Kunihara et al., 1992; Nemmani et al., 2001).

Although the anatomical foundations of such interactions would benefit from additional study, they are of considerable interest in that they provide a potential neuronal substrate for the contrasting influence of diverse classes of opioid receptor upon descending serotonergic pathways and, consequently, nociception. Further, they suggest that descending serotonergic pathways may mediate a component of MIA via a defined supraspinal network—even though the contribution to the overall antinociceptive actions of systemically-applied μ-opioidagonists is modest. The earlier comments also indicate that descending serotonergic pathways participate in the antinociception elicited by cerebral (RVM-integrated) actions of κ-opioid agonists (Section 9.3.3) and GABA antagonists (Section 9.2.4).

There is evidence implicating descending serotonergic pathways in the antinociception elicited by a diversity of mechanisms. These include supraspinal populations of nicotinic receptors (Section 9.1.3). Further, cerebral administration of brain derived neurotrophic factor elicits analgesia via the rapid recruitment of descending serotonergic pathways, possible indirectly via β-endorphin (β-EP)-containing neurones (Section 9.3.5.1) (Siuciak et al., 1994, 1995; King et al., 1999; Cirulli et al., 2000; Wang et al., 2001b). The recent finding that serotonergic neurones bear prostaglandin (EP_3) receptors also merits attention in the light of accumulating evidence that central actions of cycloxygenase inhibitors participate in their modulation of nociception and other functions. EP_3 receptors have been specifically implicated in the modulation of nociception at the segmental level (Millan, 1999; Narumiya et al., 1999; Minami et al., 2001b; Nakamura et al., 2001). Recruitment of serotonergic neurones in the DH may underlie the potent, spinal analgesic actions of the 32 amino acid neuropeptide, calcitonin (Bourgoin et al., 1988).

7.3.4. Functional actions of 5-HT in the DH

As emphasised in the aforegoing paragraphs, activation of descending serotonergic fibres is not synonymous with the induction of analgesia in view of the concomitant engagement by 5-HT of pronociceptive (DF) and antinociceptive (DI) mechanisms in the DH.

Correspondingly, the influence of 5-HT upon the activity of nocisponsive neurones in the DH is heterogeneous, with observations of both inhibition and, albeit less frequently, excitation. Such actions are seen: (1) upon neurones in superficial and deep DH laminae; (2) upon their resting activity and their response to nociceptive PAF input; (3) in interaction with the pronociceptive PAF transmitters, glutamate and SP, and (4) at both nociceptive-specific and wide-dynamic range (convergent) neurones (Jordan et al., 1979; Willcockson et al., 1984; Le Bars, 1988; Ali et al., 1994; Lopez-Garcia and King, 1996; Millan, 1997; Li and Zhuo, 1998; Khasabov et al., 1999; Garraway and Hochman, 2001a,b,c). Modulation of the excitatory effects of glutamate and SP (Section 10) underpins a post-synaptic site of action relative to PAFs and, in line with anatomical observations, most evidence supports direct (excitatory and inhibitory) actions of 5-HT upon both PNs and ININs (Muraze et al., 1990; Grudt et al., 1995; Lopez-Garcia and King, 1996; Millan, 1997; Lopez-Garcia, 1998; Garraway and Hochman, 2001a,b,c). Nevertheless, notwithstanding reservations concerning the presence of axo-axonic serotonergic contacts in the DH (Section 7.1), modulation of nociceptive processing by 5-HT in the DH may also involve a pre-synaptic influence upon transmitter release from PAF terminals: in this regard,

there are similarly indications for both an inhibitory and facilitatory influence (Del Mar et al., 1994; Cardenas et al., 1995, 1997a,b, 1999; Arvieu et al., 1996; Hori et al., 1996; Lopez-Garcia and King, 1996; Travagli and Williams, 1996; Inoue et al., 1997; Khasabov et al., 1998; Peng et al., 2001). These actions of 5-HT in the DH modulate the instantaneous response of PNs to transient, phasic PAF input and may also influence their progressive sensitisation upon recurrent PAF stimulation, a phenonemon of particular relevance to the induction of long-term, painful states (Baranauskas and Nistri, 1998; Doubell et al., 1999; Millan, 1999).

In-line with the these observations, spinal administration of 5-HT generally elicits behavioural antinociception, but its effects are test-dependent and a function of stimulus quality and modality. Indeed, in line with an excitatory influence upon the activity of PNs, certain studies have reported the induction of behavioural hyperalgesia. Moreover, 5-HT displays poor antinociceptive activity in models of persistent neuropathic and inflammatory pain (Zemlan et al., 1983; Solomon and Gebhart, 1988; Wilcox and Alhaider, 1990; Cesselin et al., 1994; Alloui et al., 1996; Bardin et al., 1997a,b, 2000a,b; Millan, 1997; Wang et al., 1999c; Li et al., 2001; Obata et al., 2001). These findings are probably related to experimental and clinical indications that drugs inhibiting 5-HT as compared to NA reuptake in the DH are relatively inefficacious as analgesic agents (Section 12.3.2.2) (Max et al., 1992; Onghena and Van Houdenhove, 1992; McQuay et al., 1996; Jeff et al., 1997; Millan, 1997; Eschalier et al., 1988; Kawamata et al., 1999; Sawynok et al., 1999; Sahebgharani and Zarrindast, 2001). Pronociceptive effects of 5-HT in electrophysiological and behavioural paradigms are congruent with reports that depletion of spinal pools of 5-HT attenuates the nociception associated with peripheral inflammation and vagal stimulation, and enhances the antinociceptive effects of stress and diverse types of analgesic agent (Sections 7.2 and 7.3) (Sawynok, 1989; Ren et al., 1991; Tjolsen et al., 1991; Cesselin et al., 1994; Millan, 1997). Further, blockade of spinal serotonergic transmission attenuates neuropathic pain provoked by PAF injury (Pertovaara et al., 2001).

Collectively, the above observations suggest that 5-HT does not invariably inhibit nociceptive processing in the DH. Rather, it elicits a spectrum of pro- and antinociceptive actions. As discussed in detail in the following sections, contrasting actions of 5-HT at various receptor subtypes differentially coupled to intracellular transduction mechanisms offer a compelling explanation of this ostensible paradox.

7.4. Roles of individual classes of 5-HT receptor in the spinal modulation of nociception

7.4.1. 5-HT$_{1A}$ receptors

7.4.1.1. Coupling and localisation. 5-HT$_{1A}$ receptors are negatively coupled to AC, and their activation opens and closes K^+- and Ca^+-channels, respectively (Bobker and Williams, 1989; Boess and Martin, 1994; Cardenas et al., 1999, 2001; Barnes and Sharp, 1999). They exert, thus, a pronounced inhibitory influence upon neuronal excitability.

HT$_{1A}$ receptors are found in a high concentration in the DH, most strikingly in superficial layers, but also in deeper laminae and lamina X (Marlier et al., 1991; Radja et al., 1991; Laporte et al., 1992, 1996; Thor et al., 1993; Coggeshall and Carlton, 1997; Hamon and Bourgoin, 1999). The fraction of 5-HT$_{1A}$ sites localised on PAFs remains unclear since, despite a modest reduction in their density upon elimination of nocisponsive PAF input to the spinal cord, mRNA encoding 5-HT$_{1A}$ receptors has not been reproducibly detected in substantial quantities in the DRG (Pompeiano et al., 1992; Pierce et al., 1996a,b, 1997; Chen et al., 1998; Wu et al., 2001d). Further, no consistent pattern of data has emerged in functional studies of the potential influence of 5-HT$_{1A}$ receptor ligands upon release of pronociceptive transmitters from PAF terminals (Bourgoin et al., 1993; Del Mar et al., 1994; Millan, 1997; Hamon and Bourgoin, 1999). Thus, a substantial component of the influence of 5-HT$_{1A}$ receptors upon nociceptive processing is mediated by direct actions at intrinsic DH neurones. As pointed out in Sections 7.4.1.2 and 7.4.1.3, both ININs and PNs (EXINs) are of relevance in this regard. 5-HT$_{1A}$ sites are poorly represented in the VH and IML (Millan, 1995; earlier citations).

7.4.1.2. Pronociceptive actions in the DH. Employing a diversity of algesiometric paradigms, numerous behavioural studies have reported hyperalgesic actions upon spinal administration of 5-HT$_{1A}$ agonists (Zemlan et al., 1983; Murphy et al., 1992; Alhaider and Wilcox, 1993; Ali et al., 1994; Millan, 1997; Bardin et al., 2000b; Zhang et al., 2001b). In addition, an extensive body of data indicates that activation of spinal 5-HT$_{1A}$ receptors interferes with the supraspinal induction of μ-opioid receptor mediated antinociception (MIA)—though not with κ-opioidergic antinociception (Millan, 1995, 1997; Millan et al., 1996). Stimulation of 5-HT$_{1A}$ receptors also attenuates induction of antinociception by the antidepressant, clomipramine (Ardid et al., 2001), as well as by nicotine (Damaj et al., 1994), calcitonin (Ormazabal et al., 1999), stress (Rodgers et al., 1991; Canto-de-Souza et al., 1998), GABAergic agonists and α_2-AR agonists (Clatworthy et al., 1988; Millan, 1997). These observations suggesting that engagement of segmental 5-HT$_{1A}$ receptors counters nociception are consistent with their implication in the DF elicited by stimulation of the RVM, excitation of vagal afferents and peripheral inflammation (Ren et al., 1991; Zhuo and Gebhart, 1991a; Calejesan et al., 1998). Stimulation of segmental 5-HT$_{1A}$ receptors conceivably accounts for older electrophysiological observations that DH-localised PNs can be (indirectly) excited by 5-HT (Jordan et al., 1979; Willcockson et al., 1984). Although concrete evidence could not then be acquired owing to a lack of selective ligands, more recent studies of wide-dynamic range neurones in deep DH laminae indicate that 5-HT$_{1A}$ receptors enhance their response

to inflammation and C/Aδ fibre stimulation, and augment their receptor field territories (Ali et al., 1994; Zemlan et al., 1994; Garraway and Hochman, 2001a,b; Zhang et al., 2001b).

Since pronociceptive actions of (inhibitory) 5-HT_{1A} receptors cannot be directly expressed at PNs, it is necessary to interpose an ININ. Although no anatomical proof has, to date been obtained, such ININs are likely to be GABAergic in nature by analogy to their expression of 5-HT_3 receptors (Section 7.4.4.3). Supporting this assertion, functional studies have shown that i.t. administration of GABAergic agonists blocks the induction of mechanical allodynia evoked by activation of segmental 5-HT_{1A} receptors (Millan et al., 1996). An alternative proposition locating 5-HT_{1A} receptors upon ENKergic ININs seems less probable inasmuch as opioidergic agonists do not modify the allodynia elicited by activation of spinal 5-HT_{1A} sites (Basbaum and Fields, 1984; Lopez-Costa et al., 1994; Millan et al., 1996; Yaksh, 1999a). In addition, there is evidence that 5-HT_{1A} receptors—by an unclear mechanism—can induce the gene expression of DYN in the DH, an opioid peptide for which pronociceptive actions have been reported (Section 9.3.3) (Millan, 1990, 1993, 1995, 1997; Lucas et al., 1993).

7.4.1.3. Antinociceptive actions in the DH. Notwithstanding this wealth of support for pronociceptive actions of 5-HT_{1A} receptors in the DH, dependent upon the parameter evaluated, the stimulus modality and various other factors, antinociceptive actions have also been documented in certain behavioural studies of 5-HT_{1A} agonists (Cervo et al., 1994; Millan et al., 1996; Oyama et al., 1996; Robles et al., 1996; Millan, 1997; Newman-Tancredi et al., 1997; Bardin et al., 2000b, 2001). These observations coincide with electrophysiological reports of an inhibitory influence of 5-HT_{1A} agonists upon DH neurones—albeit exerted indiscriminately against noxious and innocuous stimuli (El-Yassir et al., 1988; Gjerstad et al., 1996; Garraway and Hochman, 2001a,b). Further, it was proposed that 5-HT_{1A} receptors participate in the mediation of SPA from the PAG (El-Yassir and Fleetwood-Walker, 1990; Lin et al., 1996a). These findings, and the hyperpolarisation by 5-HT_{1A} agonists of superficial DH neurons in the trigeminal nucleus (Grudt et al., 1995; but see Cumberbatch et al., 1998a,b), almost certainly involve 5-HT_{1A} receptors localised on PNs (Lin et al., 1996a; Travagli and Williams, 1996). It should be noted that early reports for a role of α_2-ARs in the mediation of antinociception by "selective"5-HT_{1A} receptor agonists may reflect their direct agonist actions at α_2-ARs (Post and Archer, 1990; Millan, 1997).

7.4.1.4. Supraspinal 5-HT_{1A} receptors: modulation of descending controls. Noradrenergic cell bodies in the brainstem, notably in the locus coeruleus, are subject to an indirect facilitory influence of 5-HT_{1A} receptors. They exert their actions by: (1) post-synaptic inhibition of local, GABAergic ININs inhibitory to noradrenergic perikarya and (2) an autoreceptor-mediated suppression of serotonergic transmission leading to the relief of a tonic, facilitatory influence of 5-HT_{2C} receptors upon these GABAergic ININs (Gobert et al., 2000; Millan et al., 2000b). This positive influence of 5-HT_{1A} agonists upon noradrenergic neurones has been comprehensively characterised for their destinations in forebrain structures, and it may be inferred that the activity of descending noradrenergic pathways is likewise accelerated by 5-HT_{1A} receptor agonists (Bobker and Williams, 1989; Rosin et al., 1993; Guyenet et al., 1994; Gobert et al., 1995, 2000; Nicholas et al., 1997; Barnes and Sharp, 1999; Millan et al., 2000b). On the other hand, as alluded to earlier, inhibitory 5-HT_{1A} autoreceptors located on serotonergic perikarya in the NRM and other serotonergic nuclei exert a pronounced inhibitory influence upon the release of 5-HT throughout the CNS, including the spinal cord (Bobker and Williams, 1989; Hentall et al., 1993; Pan et al., 1993; Gobert et al., 1995; Vilim et al., 1999; Barnes and Sharp, 1999; Millan et al., 2000b). Interestingly, the increase in 5-HT_{1A} receptor gene expression in the NRM evoked by peripheral inflammation was suggested to reflect a feedback effect compensating for the parallel elevation in 5-HT release in the spinal cord (Zhang et al., 2000a,b,c). In view of the complex role of descending serotonergic pathways in the modulation of nociceptive processing via specific receptor types (this Section 7.4), it would be misleading to assign any nominal pro- or antinociceptive role to supraspinal populations of 5-HT_{1A} autoreceptors.

Activation of post-synaptic, 5-HT_{1A} receptors in the PAG mimics the facilitatory influence of opioids upon K^+-currents in isolated neurones (Jeong et al., 2001a). The possibility that this action is related to the engagement of DI is favoured by the finding that μ-opioids and 5-HT_{1A} agonists synergistically suppress GABA release in the PAG (Section 9.2.4) (Kishimoto et al., 2001). Finally, an as yet unidentified population of cerebral 5-HT_{1A} receptors has been suggested to mediate antinociception via the (indirect) recruitment of descending cholinergic pathways (Galeotti et al., 1997).

7.4.2. 5-HT_{1B}, 5-HT_{1D} and 5-HT_{1F} receptors

7.4.2.1. 5-HT_{1B} receptors. 5-HT_{1B} receptors are negatively coupled to AC and their activation enhances K^+-currents, actions contributing to their inhibitory influence upon neuronal excitability (Boess and Martin, 1994; Barnes and Sharp, 1999; Le Grand et al., 2000).

Binding sites for 5-HT_{1B} receptors are found throughout the DH, in particular in superficial laminae I and IV (Marlier et al., 1991; Thor et al., 1993; Cesselin et al., 1994; Laporte et al., 1996). These spinal populations of 5-HT_{1B} receptors are principally situated post-synaptic to serotonergic fibres, an observation of significance inasmuch as 5-HT_{1B} receptors in the spinal cord and elsewhere operate as inhibitory autoreceptors on serotonergic terminals (Matsumoto et al., 1992; Barnes and Sharp, 1999; Millan et al., 2000b). mRNA

encoding 5-HT_{1B} receptors is expressed in the DH—as well as in the VH—indicating that 5-HT_{1B} sites are synthesised by intrinsic spinal neurones (Pascual et al., 1996; Castro et al., 1997; Bonaventure et al., 1998a). This contention is underpinned by functional studies showing that antinociceptive actions are expressed via 5-HT_{1B} receptors localised on PNs (El-Yassir and Fleetwood-Walker, 1990) (see the following sections). Moreover, elimination of fine calibre PAF input to the DH deletes only a minority of 5-HT_{1B} receptors in the spinal cord (Cesselin et al., 1994; Coggeshall and Carlton, 1997).

The partial depletion of spinal pools of 5-HT_{1B} sites by removal of nocisponsive PAF input suggests, nonetheless, their presence on the central terminals of PAFs in the DH. This supposition is supported by the visualisation of mRNA encoding 5-HT_{1B} receptors in the DRG of various species—most prominently in rodents as compared to guinea pigs and man (Bruinvels et al., 1992, 1994; Bouchelet et al., 1996; Laporte et al., 1996; Pierce et al., 1996a,b, 1997; Longmore et al., 1997; Bonaventure et al., 1998a; Millan, 1999; Hou et al., 2001; Ma et al., 2001b; Wu et al., 2001d). Interestingly, co-existence of 5-HT_{1B} receptors with fine calibre fibres expressing both SP and the pronociceptive, vasodilatory neuropeptide, CGRP, was demonstrated in the guinea pig trigeminal nucleus (Bonaventure et al., 1998b). Surprisingly, in the rat trigeminal nucleus, the presence of 5-HT_{1B} receptors on SP-containing PAFs could not be corroborated by Wotherspoon and Priestley (2000), despite their identification on CGRP-containing elements and other populations of PAF. However, more recently, Ma et al. (2001b) found that C and Aδ fibres in the rat trigeminal nucleus do express 5-HT_{1B} receptors together with CGRP and SP. Further, Hou et al. (2001) similarly reported co-localisation of 5-HT_{1B} receptors with CGRP and SP in the human trigeminal ganglion.

DRG-produced 5-HT_{1B} receptors are transported to peripheral terminals where they fulfil a well-documented inhibitory influence upon PAF release of SP and CGRP in cerebral blood vessels, which can be monitored as a reduction in neurogenic extravasation. Neurogenic extravasation is implicated, together with direct vasodilation of cerebral blood vessels, in the pathogenesis of migraine headache. However, the significance of an inhibition of neurogenic extravasation to pain relief is controversial and the contribution of 5-HT_{1B} receptors to this process in man as compared to rodents is relatively minor (Moskowitz, 1992; Longmore et al., 1997; Yu et al., 1998; De Vries et al., 1999; Millan, 1999; Goadsby, 2000; Ma, 2001; Mitsikostas and Del Rio, 2001). The ability of 5-HT_{1B} agonists, such as sumatriptan, to attenuate spinal release of SP and CGRP indicates that a pre-synaptic mechanism for the induction of antinociception may similarly be applicable to 5-HT_{1B} sites localised on the central terminals of fine calibre nocisponsive PAFs (Arvieu et al., 1996; Durham and Russo, 1999; Carruthers et al., 2001). Indeed, there is increasing interest in the possibility that 5-HT_{1B} agonists clinically employed in the management of migraine headache exert actions at central 5-HT_{1B} sites in the trigeminal nucleus—principally at sites post-synaptic to PAF terminals (Ghelardini et al., 1996; Cumberbatch et al., 1997, 1998a,b; Goadsby and Knight, 1997; Bonaventure et al., 1998a; De Vries et al., 1999; Millan, 1999; Ellrich et al., 2001; Mitsikostas and Del Rio, 2001).

In correspondance with the aforegoing discussion, there is evidence that 5-HT_{1B} receptors participate in the expression of SPA from the NRM, in the induction of supraspinal MIA and in the spinal antinociceptive effects of the anti-inflammatory agent, acetaminophen (El-Yassir and Fleetwood-Walker, 1990; Alhaider and Wilcox, 1993; Ali et al., 1994; Gjerstad et al., 1997; Millan, 1997; Hain et al., 1999; Courade et al., 2001). As indicated earlier, both direct inhibition of PNs (primarily) and suppression of release from central terminals of PAFs are implicated in these observations. The occurrence of 5-HT_{1B} sites on ININs in the DH cannot be formally discounted and, by analogy to 5-HT_{1A} receptors, this would provide a substrate for occasional reports of pronociceptive actions of 5-HT_{1B} agonists (Gherstad et al., 1997; Zhang et al., 2001b). Notwithstanding such findings, 5-HT_{1B} receptors arguably comprise the class of 5-HT receptor for which the most robust and coherent pattern of antinociceptive actions has been acquired at the spinal (and trigeminal) level. Further, as indicated above, antinociceptive properties of 5-HT_{1B} agonists are also mediated in the periphery, both at 5-HT_{1B} receptors on PAF terminals in the meninges, and at vasoconstricting 5-HT_{1B} sites located in the endothelium of cerebral blood vessels (De Vries et al., 1999; Millan, 1999; Goadsby, 2000; Mitsikostas and Del Rio, 2001).

As concerns supraspinal structures, the marked density of 5-HT_{1B} receptors in the PAG and NTS is of note, although no concrete indication for a role of 5-HT_{1B} sites in the modulation of nociceptive processing via descending pathways is available (Bruinvels et al., 1994; Ghelardini et al., 1996; Castro et al., 1997; Bonaventure et al., 1998a). Moreover, although 5-HT_{1B} autoreceptors inhibit release from serotonergic terminals, initial reports of a modulatory influence of 5-HT_{1B} sites upon cerebral release of DA and NA have not been substantiated in studies with highly-selective ligands (Millan et al., 2000b). Thus, it is unlikely that modulation of descending monoaminergic pathways is involved in the influence of 5-HT_{1B} receptor ligands upon nociception. Finally, despite the well-documented inhibitory influence of 5-HT_{1B} receptors upon ascending cholinergic pathways, a similar modulation of their descending counterparts remains to be demonstrated (Barnes and Sharp, 1999).

7.4.2.2. 5-HT_{1D} receptors. 5-HT_{1D} receptors are closely-related to 5-HT_{1B} sites in terms of their primary structure, patterns of cellular coupling and ligand binding profiles (Barnes and Sharp, 1999). It has, further, been shown that 5-HT_{1D} receptors form functionally-active heterodimers with 5-HT_{1B} receptors upon expression in the same cell (Xie et al., 1999b). This observation is of interest inasmuch as there is functional evidence that serotonergic

neurones bear both 5-HT_{1B} and 5-HT_{1D} receptors on their soma—though a rigorous anatomical demonstration is still awaited (Bonaventure et al., 1998a; Millan et al., 2000b).

5-HT_{1D} receptors are highly expressed in the DRG and, in contrast to rodents, both in guinea pigs and in man, they predominate over 5-HT_{1B} receptors in trigeminal PAFs innervating the cerebral vasculature. Moreover, they may be distinguished from 5-HT_{1B} sites by their absence from the endothelium of cerebral blood vessels (Rebeck et al., 1994; Bouchelet et al., 1996; Castro et al., 1997; Longmore et al., 1997; Bonaventure et al., 1998a,b; Cutrer et al., 1999; De Vries et al., 1999; Hou et al., 2001; Ma, 2001; Ma et al., 2001b; Mitsikostas and Del Rio, 2001). At peripheral PAF terminals in the meninges, like their 5-HT_{1B} counterparts, 5-HT_{1D} receptors participate in the inhibition of transmitter release and, as a corollary, inhibit extravasation-though such actions may not suffice to terminate migraine headaches (Longmore et al., 1997; Cutrer et al., 1999; De Vries et al., 1999; Nilsson et al., 1999; Cutler et al., 2000; Goadsby, 2000; Gomez-Mancilla et al., 2001; Mitsikostas and Del Rio, 2001; Williamson et al., 2001). Interestingly, in contrast to spinal 5-HT_{1B} receptors which co-exist with SP and CGRP in PAFs (Section 7.4.2.1), 5-HT_{1D} receptors were co-localised only with a sub-population of PAFs releasing CGRP in the DH in the guinea pig (Bonaventure et al., 1998b). However, in man, 5-HT_{1D} receptors have been identificated on trigeminal neurones expressing both SP and CGRP (Hou et al., 2001).

The preceding comments suggest that 5-HT_{1D} receptors modify release from the central terminals of nocisponsive PAFs in the DH, though this remains to be directly demonstrated (Matsumoto et al., 1992; Arvieu et al., 1996; Bouchelet et al., 1996; Longmore et al., 1997; Millan, 1999; Goadsby, 2000; Hou et al., 2001; Ma, 2001; Ma et al., 2001b; Wu et al., 2001d). There is also evidence for generation of 5-HT_{1D} receptors by intrinsic neurones in the trigeminal nucleus of the guinea pig, and in lamina X of the cervical spinal cord. Thus, although no equivalent information for other species has to date been forthcoming, the occurrence of 5-HT_{1D} receptors upon intrinsic DH neurones throughout the spinal cord appears probable (Waeber and Moskowitz, 1995; Bonaventure et al., 1998a; Goadsby, 2000).

These comments indicate that activation of central 5-HT_{1D} receptors on central PAF terminals and, perhaps, intrinsic DH neurones may mediate antinociception. However, the definition of their precise roles in comparison to those of 5-HT_{1B} receptors will require functional studies with: (1) highly-selective ligands distinguishing these sites—which have recently become available and (2) transgenic mice bearing deletions of 5-HT_{1B} or 5-HT_{1D} receptors (Cutrer et al., 1999; Cumberbatch et al., 1998a,b; Mogil and Grisel, 1998; De Vries et al., 1999; Goadsby, 2000). In this respect, it will be important to take account of earlier-mentioned species differences in the localisation and functional significance of 5-HT_{1D} as compared to 5-HT_{1B} receptors.

The presence of inhibitory 5-HT_{1D} receptors on the dendrites of serotonergic perikarya should be evoked, though their selective activation or antagonism exerts little influence upon central serotonergic—or catecholaminergic—transmission ((Millan et al., 2000b)). 5-HT_{1D} sites are concentrated neither in the PAG nor in other structures involved in the modulation of descending controls (Bruinvels et al., 1994; Castro et al., 1997; Bonaventure et al., 1998a; Millan et al., 2000b; Bidmon et al., 2001). Indeed, little is known as concerns a potential role of supraspinal 5-HT_{1D} receptors in modulation of the activity of descending pathways.

7.4.2.3. 5-HT_{1F} receptors. 5-HT_{1F} receptors are closely-related to 5-HT_{1B} receptors and similarly possess high affinity for sumatriptan and several other 5-HT_1 agonists clinically effective in the relief of migraine headache (Waeber and Moskowitz, 1995; Barnes and Sharp, 1999; Goldstein et al., 1999; Mitsikostas and Del Rio, 2001). They likewise mimic 5-HT_{1B} sites in their negative coupling to AC and in their localisation on PAFs innervating the meninges. Correspondingly, activation of 5-HT_{1F} receptors has been implicated in the control of neurogenic extravasation within the dura, though not all data concur in this respect (Bouchelet et al., 1996; Johnson et al., 1997; Longmore et al., 1997; Phebus et al., 1997; Millan, 1999; Razzaque et al., 1999; Shepheard et al., 1999; Mitsikostas and Del Rio, 2001). In line with such a role of 5-HT_{1F} sites on the peripheral terminals of PAFs, the DRG contains mRNA encoding 5-HT_{1F} receptors, and they have been identified on the central terminals of trigeminal PAFs. Further, they are present on intrinsic neurones in the superficial trigeminal nucleus (Bruinvels et al., 1994; Waeber and Moskowitz, 1995; Pascual et al., 1996; Adham et al., 1997; Castro et al., 1997). It is possible then, that 5-HT exerts antinociceptive actions in the trigeminal nucleus at 5-HT_{1F} sites localised both pre and post-synaptically with respect to PAF input (Waeber and Moskowitz, 1995; Shepheard et al., 1999; Mitsikostas and Del Rio, 2001). However, in the spinal cord itself, 5-HT_{1F} sites appear to be confined to PAF terminals, rather than generated by intrinsic DH neurones (Bruinvels et al., 1994; Adham et al., 1997; Castro et al., 1997; Ma, 2001; Wu et al., 2001d). Whether this lack of 5-HT_{1F} sites on intrinsic DH neurones relates to relatively weak antinociceptive actions of "5-HT_{1B}" agonists against painful conditions other than migraine would be of interest to evaluate (Roberts-Thomson et al., 1996; Longmore et al., 1997; Shepheard et al., 1999; Goadsby, 2000).

Contrary to initial reports, comparatively few 5-HT_{1F} sites appear to be localised on serotonergic neurones, and they have not been detected in medullary noradrenergic perikarya. Nonetheless, their presence in the PAG and NTS justifies mention as concerns an, as yet unexplored, role in the modulation of descending pathways (Bruinvels et al., 1994; Adham et al., 1997; Castro et al., 1997).

A final receptor presenting structural, coupling and pharmacological homologies to 5-HT_{1B} sites, the 5-HT_{1E} receptor, though detected in the PAG and medulla-pons, does

not require further consideration here inasmuch as neither anatomical nor functional data have, to date, indicated a relationship to descending mechanisms of nociceptive processing (Fugelli et al., 1997; Barnes and Sharp, 1999).

7.4.2.4. Differentiation of actions at 5-HT$_{1B}$, 5-HT$_{1D}$ and 5-HT$_{1F}$ receptors. From the preceding comments, there is clearly considerable support for a major role of 5-HT$_{1B}$, 5-HT$_{1D}$ and/or 5-HT$_{1F}$ receptors, localised on central PAF terminals and/or intrinsic DH neurones, in the mediation of antinociception both in the trigeminal nucleus and in the DH of the spinal cord. Together with transgenic mice (Mogil and Grisel, 1998), the recent discovery of selective ligands differentiating these sites (Barnes and Sharp, 1999) should accelerate and simplify the task of characterising their individual roles and potential therapeutic relevance in the expression of DI.

7.4.3. 5-HT$_{2A}$, 5-HT$_{2B}$ and 5-HT$_{2C}$ receptors

7.4.3.1. Similar coupling and ligand binding profiles. All three subtypes of 5-HT$_2$ receptor, 5-HT$_{2A}$, 5-HT$_{2B}$ and 5-HT$_{2C}$, are positively coupled to PLC and exert an inhibitory influence upon K^+-currents, actions underlying their robust excitatory influence upon neuronal activity (Boess and Martin, 1994; Barnes and Sharp, 1999; Cussac et al., 2002). In terms of ligand recognition, their pharmacological profiles are similar and, of traditionally-used antagonists, only ketanserin distinguishes 5-HT$_{2A}$ (high affinity) from their 5-HT$_{2B}$ and 5-HT$_{2C}$ counterparts. Further, selective ligands clearly dissociating 5-HT$_{2B}$ and 5-HT$_{2C}$ receptors have only recently become available and no appropriate radioligand has, as to date, been identified for their selective labelling (Cussac et al., 2002). Thus, in the older literature, in which a diverse pattern of mixed pro- and antinociceptive roles of "5-HT$_2$" receptors has been described, it is difficult to assign effects to any particular 5-HT$_2$ receptor subtype. This interpretational difficulty is compounded by: (1) marked motor and cardiovascular effects mediated by 5-HT$_2$ receptors in the VH and IML, respectively, and (2) the frequent use of drugs by systemic administration, which cannot exclude actions exerted at the supraspinal level (Le Bars, 1988; Eide and Hole, 1993; Cesselin et al., 1994; Millan, 1995, 1997; Hamon and Bourgoin, 1999; Bardin et al., 2000b).

7.4.3.2. 5-HT$_{2A}$ receptors. Both binding studies and immunohistochemical analyses employing antibody probes have yielded a concensus that the level of 5-HT$_{2A}$ receptor (protein) in rat and human DH is low. The majority of authors have likewise reported low levels of mRNA encoding 5-HT$_{2A}$ sites in the DH (Helton et al., 1994; Millan, 1995, 1997; Coggeshall and Carlton, 1997; Maeshima et al., 1998; Cornea-Hébert et al., 1999), though one recent report mentions a modest level of mRNA, the expression of which was amplified by peripheral inflammation (Zhang et al., 2001a). The presence of mRNA encoding 5-HT$_{2A}$ receptors in rodent and human DRG (Pierce et al., 1996a,b, 1997; Fonseca et al., 2001; Wu et al., 2001d) suggests that the modest population of 5-HT$_{2A}$ sites visualised in the DH may primarily be situated on central PAF terminals.

Inasmuch as 5-HT$_{2A}$ receptors sensitise peripheral terminals of PAFs via the suppression of K^+-currents (Cardenas et al., 1997b; Todorovic et al., 1997; Tokunaga et al., 1998; Bevan, 1999; Millan, 1999), stimulation of their central terminals would provide a substrate for pronociceptive actions of 5-HT$_{2A}$ receptors in the DH (Wilcox and Alhaider, 1990; Eide and Hole, 1993; Millan, 1997; Khasabov et al., 1998; Kjorsvik et al., 2001). On the other hand, bearing in mind anatomical qualifications mentioned earlier, it has been forwarded that 5-HT$_{2A}$ receptors situated on PNs mediate pronociceptive actions (Wilcox and Alhaider, 1990; Eide and Hole, 1993; Hori et al., 1996; Kjorsvik et al., 2001). Further, "5-HT$_2$" sites have been suggested to inhibit NA release in the spinal cord, a "pronociceptive" action which must be effected indirectly (Celuch et al., 1992; Millan, 1999).

Obviously, emplacement of 5-HT$_{2A}$ receptors on ININs would permit antinociceptive actions and, in line with this possibility, 5-HT$_{2A}$ receptors have been shown to trigger GABAergic/glycinergic inhibitory potentials in the spinal cord (Sugiyama and Huang, 1995; Abi-Saab et al., 1999). Indeed, employing appropriately-selective ligands, 5-HT$_{2A}$ sites were documented both to mediate anti-allodynic actions in rats sustaining PAF injury and to suppress inflammatory nociception (Obata et al., 2001; Sasaki et al., 2001). Moreover, in a further recent study, it was postulated that 5-HT$_{2A}$ (but not 5-HT$_{2B}$ or 5-HT$_{2C}$) receptors participate in the antinociception elicited by spinal administration of inhibitors of cyclo-oxygenase 2 (Ochi and Goto, 2000; Courade et al., 2001).

While the precise density of 5-HT$_{2A}$ sites (and their mRNA) in the IML remains unclear, they occur at a high density in the VH (Laporte et al., 1996; Coggeshall and Carlton, 1997; Maeshima et al., 1998; Cornea-Hébert et al., 1999; Fonseca et al., 2001). Functional studies indicate that 5-HT$_{2A}$ receptors mediate a pronounced, tonic, excitatory influence upon the activity of preganglionic cells and MNs, actions reflected in a modification of autonomic and motor function respectively (Lewis et al., 1993; McCall and Clement, 1994; Larkman, 1995; Millan, 1995, 1997). Interestingly, in the light of evidence that 5-HT$_{2A}$ receptors indirectly suppress the activity of PNs in the DH via engagement of ININs, there are indications for an indirect, inhibitory influence of 5-HT$_{2A}$ receptors upon neurones in the IML and VH expressed via the recruitment of glycinergic ININs (Lewis et al., 1993; McCall and Clement, 1994; Larkman, 1995).

At the supraspinal level, modest levels of 5-HT$_{2A}$ receptors are found in the PBN, NTS, RVM and PAG. Further, mRNA is found in the NRM and, at a low level in the locus coeruleus, origins of descending serotonergic and

noradrenergic pathways, respectively (Pompeiano et al., 1994; Wright et al., 1995; Cornea-Hébert et al., 1999; Fay and Kubin, 2000; Fonseca et al., 2001; Zhang et al., 2001a). Although direct evidence for modulation of descending controls by 5-HT_{2A} receptors does not appear to be available, cerebral populations of 5-HT_{2A} receptor are involved in the modulation of nociception, and 5-HT_{2A} sites in the RVM and PAG may intervene in the expression of MIA (Paul et al., 1989; Alhaider, 1991; Kiefel et al., 1992).

7.4.3.3. 5-HT_{2B} receptors. Very little information is available concerning 5-HT_{2B} receptors. mRNA encoding 5-HT_{2B} sites was extracted from whole rodent and human spinal cord, while a diffuse and well-dispersed network of immunoreactive 5-HT_{2B} fibres was visualised in the DH of the rat. In addition, a low level of mRNA encoding 5-HT_{2B} sites has been detected in rat DRG (Helton et al., 1994; Pierce et al., 1996a,b; Duxon et al., 1997; Millan, 1997; Wu et al., 2001d). In general, levels of 5-HT_{2B} sites throughout rodent and human CNS are markedly inferior to those of their 5-HT_{2A} and 5-HT_{2C} counterparts and their functional significance remains debatable (Duxon et al., 1997; Barnes and Sharp, 1999). Nevertheless, above comments suggest the existence of modest populations of DH and DRG neurones generating 5-HT_{2B} sites. The recent discovery of highly-selective ligands differentiating 5-HT_{2B} from 5-HT_{2C} sites should allow for functional evaluation of any potential role in the modulation of nociceptive processing (Barnes and Sharp, 1999; Cussac et al., 2002).

7.4.3.4. 5-HT_{2C} receptors. Binding studies initially revealed the presence of 5-HT_{2C} receptors in the DH (Pazos and Palacios, 1985; Pranzateli et al., 1992), observations corroborated by more recent investigations employing selective antibodies (Sharma et al., 1997). The possibility that 5-HT_{2C} receptors are produced by intrinsic DH neurones is supported by the presence of the corresponding mRNA throughout the DH-in superficial and deep laminae (possibly on PNs) and in lamina X (Molineaux et al., 1989; Pompeiano et al., 1994; Helton et al., 1994; Fonseca et al., 2001). An additional population of 5-HT_{2C} receptors in the rat DH may be derived from PAFs, inasmuch as mRNA encoding these sites has, in most cases, proven to be present in the DRG of this species-though not, apparently, of man (Pompeiano et al., 1994; Wright et al., 1995; Pierce et al., 1996a,b, 1997; Ma, 2001; Wu et al., 2001d). In light of the excitatory influence of 5-HT_{2C} receptors upon neuronal activity and, presumably, PAFs (Cardenas et al., 1997b, 1999; Millan, 1999), this distribution of 5-HT_{2C} sites is compatible with a pronociceptive role in the DH. Curiously, virtually no information is available concerning functional actions of 5-HT_{2C} receptors with the exception of a study employing highly-selective ligands which proposed that 5-HT_{2C} receptors potentiate the pronociceptive actions of 5-HT_{1A} receptor agonists in the DH (Bervoets et al., 1990; Millan et al., 1997). This finding mirrors observations obtained at cerebral 5-HT_{2C} sites in suggesting that they exert an important modulatory influence upon actions mediated by co-localised populations of 5-HT_{1A} receptors (Millan et al., 1992). More generally, they highlight the paucity of data concerning the interplay of specific classes of multiple 5-HT receptor in the modulation of nociceptive processing in the DH and elsewhere. Positioning of 5-HT_{2C} sites on ININs would, evidently, transform a potential pronociceptive into an antinociceptive role (Millan, 1997; Bardin et al., 2000b).

The prominence of mRNA for 5-HT_{2C} receptors in both the IML and VH suggests that their activation contributes to the facilitatory influence of descending serotonergic pathways upon sympathetic and motor outflow from these structures (McCall and Clement, 1995; Millan, 1995, 1997; Fonseca et al., 2001).

At the supraspinal level, mRNA encoding 5-HT_{2C} sites is well represented in the PAG, PBN, NTS and RVM (including the NRM) and is detectable at a high concentration in the locus coeruleus—on GABAergic ININs (Molineaux et al., 1989; Pompeiano et al., 1994; Wright et al., 1995; Fonseca et al., 2001; Lopez-Gimenez et al., 2001). Indeed, as mentioned earlier (Section 7.4.1), 5-HT_{2C} receptors exert a pronounced and indirect inhibitory influence upon supraspinal noradrenergic (and dopaminergic) transmission by recruitment of GABAergic ININs (Gobert et al., 2000; Millan et al., 2000b). It would, thus, be of interest to directly explore their modulation of descending adrenergic and dopaminergic projections to the DH (Millan et al., 2000b). Serotonergic$_{2C}$ receptors have been suggested to exert an excitatory influence upon those tuberomammillary histaminergic neurones which project to the spinal cord (Brown et al., 2001).

The recent description of highly-selective antagonists at 5-HT_{2C} receptors, and the generation of knock-out mice lacking 5-HT_{2C} receptors (Rueter et al., 2000; Cussac et al., 2002), should accelerate characterisation of their functional roles in the descending modulation of nociceptive processing in the DH.

7.4.4. 5-HT_3 receptors

7.4.4.1. Coupling and localisation. Ionotropic 5-HT_3 receptors may be distinguished from all other classes of 5-HT receptor in that they constitute multi-subunit, ligand-gated, cation-permeable, pentameric ion channels. Two subunits are known, 5-HT_{3A} and 5-HT_{3B}, but the contribution of homomeric 5-HT_{3A} and heteromeric 5-HT_{3A}/5-HT_{3B} receptors to specific populations of native sites remains to be clarified. Activation of 5-HT_3 receptors enhances PLC activity, reinforcing their facilitatory influence upon neuronal excitability (Boess and Martin, 1994; Barnes and Sharp, 1999; Brüss et al., 2000; Hanna et al., 2000; Van Hooft and Vijverberg, 2000; Brady et al., 2001; Morales et al., 2001b; Mott et al., 2001).

Studies employing highly-selective radioligands and specific antibodies have collectively demonstrated that 5-HT_3 receptors are concentrated in superficial layers of the DH, particularly in lamina I (Gehlert et al., 1991; Radja et al., 1991; Laporte et al., 1992, 1996; Kia et al., 1995; Millan, 1997; Morales et al., 1998a,b). The pronounced reduction in their level provoked by elimination of fine calibre PAF input to the spinal cord suggests that a significant proportion is located on the terminals of C fibres innervating the superficial DH (Cesselin et al., 1994; Millan, 1997; Morales et al., 2001b). This contention is underscored by the presence of mRNA encoding 5-HT_3 receptors in the DRG of rodents, man and other species (Kia et al., 1995; Laporte et al., 1996; Pierce et al., 1996a,b, 1997; Coggeshall and Carlton, 1997; Morales et al., 2001b; Wu et al., 2001d). The in situ generation of 5-HT_3 receptors by intrinsic neurons has also been established in studies revealing the presence of mRNA for 5-HT_3 receptors in the DH (Tecott et al., 1993; Kia et al., 1995; Fonseca et al., 2001). The mRNA is found both within the superficial zone as well as in deeper DH laminae, dendrites of which ramify into laminae I and II. At least a subpopulation of these deep DH neurones appears to represent GABAergic and opioidergic ININs (Section 7.4.4.3) (Morales et al., 1998a,b; Tsuchiya et al., 1999). However, it cannot be discounted that 5-HT_3 receptors are also expressed by PN (and EXINs).

7.4.4.2. Influence upon terminals of primary afferent fibres. 5-HT_3 receptors synthesised and assembled in DRG are delivered to peripheral terminals of cutaneous, visceral and other populations of nocisponsive PAF where they play a well-characterised excitatory role incriminated in the induction of inflammatory pain. The pronociceptive effects of 5-HT_3 sites are expressed in synergy with 5-HT_{2A} and 5-HT_4 sites (Robertson and Bevan, 1991; Meller and Gebhart, 1992; Cardenas et al., 1997b; Doak and Sawynok, 1997; Todorovic et al., 1997; Bevan, 1999; Millan, 1999; Smith et al., 1999; Morales et al., 2001b). In this light, it might be anticipated that 5-HT_3 receptors exercise pronociceptive actions at central terminals of PAFs, providing an explanation for electrophysiological and behavioural reports that activation of spinal populations of 5-HT_3 receptors increases nociception (Ali et al., 1996; Oyama et al., 1996; Millan, 1997; Garraway and Hochman, 2001a,b; Morales et al., 2001b). Indeed, it has been reported that 5-HT_3 receptors potentiate the stimulated release of SP in the DH (possibly by a NO-dependent mechanism). However, conflicting data have been documented in this regard, and certain studies have observed a decrease in liberation (Saria et al., 1990; Bourgoin et al., 1993; Scott and Fone, 1994; Yang et al., 1996a; Inoue et al., 1997; Hamon and Bourgoin, 1999; Hamon M, personal communication). If exerted directly (rather than via ININs), the latter effect may be related to "primary afferent-induced depolarisation" which can actually suppress release from PAF terminals (Lopez-Garcia and King, 1996; Millan, 1999; Rudomin and Schmidt, 1999). Indeed, 5-HT_3 agonists have been shown to elicit primary afferent-induced depolarisation at PAF terminals in a manner susceptible to reversal by selective 5-HT_3 antagonists (Khasabov et al., 1999; Peng et al., 2001). It should be pointed out that DRG may synthesise both 5-HT_{3A} and heteromeric 5-HT_{3A}/5-HT_{3B} receptors, the proportions of which are not necessarily identical at central versus peripheral terminals of PAFs (Morales et al., 2001b).

7.4.4.3. Recruitment of inhibitory interneurones in the induction of antinociception. The above-evoked induction of primary afferent depolarisation by 5-HT_3 receptor agonists does not involve intervention of GABAergic mechanisms-which are known to elicit this process (Lopez-Garcia and King, 1996; Millan, 1999; Rudomin and Schmidt, 1999; Peng et al., 2001). This observation is of significance inasmuch as recruitment of GABAergic ININs in the DH has been proposed to underlie numerous observations that 5-HT_3 receptors mediate antinociception (Glaum et al., 1990; Alhaider et al., 1991; Lin et al., 1994; Peng et al., 1996c; Yang et al., 1998a; Paul et al., 2001). More recently, Tsuchiya et al. (1999) provided evidence that 5-HT_3 receptors are also localised on a further class of antinociceptive ININ in the DH: that is, those containing ENK. This possibility coincides well with their innervation by descending serotonergic pathways (Basbaum and Fields, 1984; Lopez-Costa et al., 1994; Yaksh, 1999a) and with the attenuation of 5-HT_3 receptor-induced spinal antinociception by naloxone in certain—though not all—studies (Kellstein et al., 1988; Giordano, 1991; Yang et al., 1994b). Irrespective of the relative contributions of GABAergic, ENKergic and, perhaps, other classes of ININ, their engagement offers an appealing substrate for antinociceptive actions of 5-HT_3 receptor agonists at the spinal level (Millan, 1997; Bardin et al., 1997b, 2000b; Watkins et al., 1997a,b; Garraway and Hochman, 2001a,b) (Fig. 7).

Activation of segmental 5-HT_3 receptors has been implicated in the antinociception elicited by PAG stimulation, stress and spinal administration of calcitonin and paracetamol (Rodgers et al., 1991; Alloui et al., 1996; Peng et al., 1996c; Ormazabal et al., 1999). A reduction of inflammatory nociception has also been reported with 5-HT_3 agonists (Sasaki et al., 2001). In addition, analgesic properties of the atypical analgesic and 5-HT uptake inhibitor, tramadol, were impaired by concurrent administration of a 5-HT_3 antagonist in human subjects (De Witte et al., 2001). Finally, 5-HT_3 receptors may be involved in the antinociceptive properties of the general anesthetic, nitrous oxide (Mueller and Quock, 1992), while the volatile anaesthetics, halothane and isoflurane, directly potentiate 5-HT_3 receptor-induced cation currents, an action conceivably related to their influence upon somatosensory transmission (Zhang et al., 1997a).

7.4.4.4. Actions in regions other than the DH. Notwithstanding the paucity of binding sites for 5-HT_3 receptors

in the VH (Laporte et al., 1992, 1996; Millan, 1997), antibody studies have identified 5-HT_3 receptor-positive MNs, findings underpinned by studies reporting the presence of mRNA at a high level in the rat VH (Tecott et al., 1993; Kia et al., 1995; Morales et al., 1998a,b; Fonseca et al., 2001). This may explain observations of motor excitation upon the spinal administration of 5-HT_3 agonists (Fone et al., 1991).

In supraspinal structures, there is a high concentration of 5-HT_3 receptors in the NTS, located on the terminals of vagal afferents (Morales et al., 1998a,b). Their antagonism is implicated in the clinical, anti-emetic properties of 5-HT_3 antagonists (Barnes and Sharp, 1999; Ye et al., 2001). This population of excitatory 5-HT_3 receptors on the central projections of vagal afferents may facilitate their activation of NTS relay neurones transmitting nociceptive information to descending controls in the RVM (Section 3.2.4) (Ren et al., 1988, 1991). This possibility is supported by findings that 5-HT_3 receptors on peripheral terminals of vagal nerves participate in the induction of cardiac and visceral nociception (Meller and Gebhart, 1992; Millan, 1995, 1999). A high density of mRNA encoding 5-HT_3 sites was recently documented in the RVM itself raising the question of their influence upon descending pathways originating in this structure (Fonseca et al., 2001). On the other hand, monoaminergic descending pathways do not appear to possess 5-HT_3 receptors (Barnes and Sharp, 1999; Millan et al., 2000b; Fonseca et al., 2001).

7.4.5. 5-HT_4 receptors

The excitatory influence of 5-HT_4 receptors upon neuronal activity reflects their positive coupling to AC which, via stimulation of protein kinase A, leads to the inactivation (phosphorylation) of K^+-channels (Boess and Martin, 1994; Eglen et al., 1995; Barnes and Sharp, 1999).

Binding studies with selective ligands have established that 5-HT_4 receptors are concentrated in superficial regions of the DH, in all probability upon intrinsic neurones, though this requires verification (Waeber et al., 1993, 1994). Further, there is functional and anatomical evidence for their presence in the DRG and, inasmuch as their transport to cutaneous and visceral terminals has been demonstrated, it is likely that they also occur on central terminals of nocisponsive PAFs in the DH (Cardenas et al., 1997a; Doak and Sawynok, 1997; Espejo and Gil, 1998; Wu et al., 2001d).

5-HT_4 receptors located on the peripheral terminals of nocisponsive C fibres projecting to laminae I and II of the DH mediate potent excitatory, pronociceptive actions. There is evidence for a generalised role of cyclic adenosine monophosphate in the sensitisation of PAF terminals (Taiwo and Levine, 1991; Bevan, 1999; Levine and Reichling, 1999; Millan, 1999). Thus, an increase in cyclic adenosine monophosphate levels upon activation of 5-HT_4 receptors may—following protein kinase A—induced phosphorylation of tetrodotoxin-resistant Na^+-channels at least partially underlie the excitation of PAF terminals (Cardenas et al., 1997a,b; Doak and Sawynok, 1997; Espejo and Gil, 1998; Bevan, 1999; Millan, 1999). Smith et al. (1999) revealed that pronociceptive actions at 5-HT_4 receptors upon PAFs reinforce those mediated by 5-HT_3 sites. By analogy, then, it is likely that 5-HT_4 receptors (alone or in concert with 5-HT_3 sites) exert an excitatory, pronociceptive influence upon the central endings of fine calibre PAFs in superficial DH. This action may be complemented by a facilitatory influence upon PN activity. It would be of considerable interest to directly validate these hypotheses employing the many selective 5-HT_4 ligands now available (Barnes and Sharp, 1999).

At the supraspinal level, 5-HT_4 receptors are prominent in the PAG and their density is intermediate in the PBN and NTS, consistent with a possible interaction with descending pathways, although this remains to be directly examined (Jackeman et al., 1994; Waeber et al., 1994; Mengod et al., 1996). The presence of 5-HT_4 sites in the DRN, and their ability to enhance hippocampal 5-HT release, suggests that they augment serotonergic transmission. However, they are scarce in the NRM (and in the RVM in general) and in the locus coeruleus: to date, no evidence that they reinforce monoaminergic input to the DH is available (Jackeman et al., 1994; Waeber et al., 1994; Mengod et al., 1996; Barnes and Sharp, 1999). Indeed, the induction of antinociception by intracerebroventricular (i.c.v.) administration of 5-HT_4 agonists is expressed independently of monoaminergic mechanisms and may, interestingly, involve descending cholinergic pathways, in-line with the well-established facilitatory influence of 5-HT_4 receptors upon (ascending) cholinergic neurones (Barnes and Sharp, 1999).

7.4.6. 5-HT_5 receptors

Of the 5-HT_5 receptor family, little is known concerning 5-HT_{5B} sites (which may not be functional in man), but their 5-HT_{5A} counterparts are of potential interest as concerns descending controls (Rees et al., 1994). Thus, a recent, immunohistochemical study identified 5-HT_{5A}-positive neurones at a high concentration in the spinal trigeminal nucleus, although information for the spinal cord itself was not presented (Oliver et al., 2000). This study did not examine the precise localisation of 5-HT_{5A} receptors relative to PAFs, but a recent investigation of mRNA encoding 5-HT_{5A} receptors suggested their synthesis in the DRG, and production of 5-HT_{5A} sites by intrinsic DH neurones also appears probable (Pierce et al., 1996a,b; Barnes and Sharp, 1999; Wu et al., 2001d). Although older studies had indicated a preferential localisation of 5-HT_{5A} receptors on astrocytes, these findings appear to represent a lack of antibody selectivity, and 5-HT_{5A} receptors are indeed present on neurones (Grailhe et al., 1999; Oliver et al., 2000).

Initial difficulties in identifying transduction mechanisms for 5-HT_{5A} receptors have been surmounted and 5-HT_{5A} receptors couple, via G-proteins, to both K^+-currents

(facilitatory) and AC (inhibitory) (Francken et al., 2000; Thomas et al., 2000; Grailhe et al., 2001). This analogy to 5-HT_{1A} receptors suggests that, if localised upon ININs and PNs, 5-HT_{5A} receptors in the DH may mimic their pro and antinociceptive actions, respectively. Although selective ligands for 5-HT_{5A} receptors remain to be discovered, this hypothesis could be directly evaluated in transgenic mice lacking 5-HT_{5A} receptors (Mogil and Grisel, 1998; Grailhe et al., 1999).

Additional incentive to explore the potential significance of 5-HT_{5A} receptors in descending controls and nociceptive processing is provided by their predilection for structures giving rise to (and interacting with) descending pathways to the DH, including the hypothalamus (PVN, posterior periventricular, dorsomedial and arcuate nuclei), amygdala, PBN, NTS and RVM (Oliver et al., 2000; Kinsey et al., 2001). Moreover, their density is pronounced in the PAG. Their high concentration in monoaminergic cell clusters projecting to the spinal cord, notably the locus coeruleus and the NRM, suggests moreover, that they may modulate the activity of descending noradrenergic and serotonergic pathways (Oliver et al., 2000).

7.4.7. 5-HT_6 receptors

In distinction to 5-HT_{5A} receptors, 5-HT_6 receptors are positively coupled to AC, indicative of a facilitatory influence upon neuronal activity (Barnes and Sharp, 1999). The use of selective antibodies permitted demonstration of their existence in the spinal cord, but more refined analyses of their laminal organisation do not appear to have been undertaken (Gérard et al., 1997). Although in situ hybridisation failed to detect mRNA encoding 5-HT_6 sites, a more sensitive technique of quantitative polymerase chain reaction was successful, suggesting their production by intrinsic neurones (Ward et al., 1995; Gérard et al., 1996). This approach similarly revealed mRNA encoding 5-HT_6 sites in the DRG, although, utilising a similar approach, Pierce et al. (1996a,b) did not observe their presence, so the provision of 5-HT_6 receptor to the DH by PAF terminals remains to be confirmed. In contrast to 5-HT_{5A} sites, 5-HT_6 receptors do not appear to be present in monoaminergic cell bodies and they are not particularly enriched in cerebral structures innervating the DH (Gérard et al., 1997; Ward et al., 1995; Dawson et al., 2000; Kinsey et al., 2001). Selective ligands for 5-HT_6 sites have been described (Barnes and Sharp, 1999; Dawson et al., 2000) but do not, surprisingly, appear to have been utilised for evaluation of the role of segmental (or other populations of) 5-HT_6 receptors in nociceptive processing.

7.4.8. 5-HT_7 receptors

5-HT_7 receptors share the positive coupling of 5-HT_4 and 5-HT_6 receptors to AC (Boess and Martin, 1994; Heidmann et al., 1997; Vanhoenacker et al., 2000). The superficial DH is endowed with a modest level of 5-HT_7 receptors. They may be predominantly localised on the terminals of PAFs rather than on intrinsic neurones inasmuch as mRNA encoding 5-HT_7 receptors has been detected in the DRG but not, as yet, in the spinal cord (Gustafson et al., 1996; Pierce et al., 1996b, 1997; Terron et al., 2001; Wu et al., 2001d).

Surprisingly, there have been no attempts to directly examine the role of spinal populations of 5-HT_7 receptor in nociceptive processing employing selective agents (Roberts et al., 2001). Nevertheless, their ligand recognition profile is similar to that of 5-HT_{1A} receptors and certain actions of the 5-HT_{1A} agonist, 8-OH-DPAT, have been re-interpreted as those of a "surrogate" ligand of 5-HT_7 sites (Millan, 1995, 1997; Pierce et al., 1996a,b, 1997; Garraway and Hochman, 2001b). Thus, based on the premise that high concentrations of 8-OH-DPAT recognise 5-HT_7 receptors, its ability to stimulate AC in nocisponsive PAFs and to elicit nociception at their peripheral terminals has been attributed to activation of 5-HT_7 as opposed to 5-HT_{1A} receptors, the latter of which couple negatively to AC. Indeed, stimulation of AC and the consequent generation of cyclic adenosine monophosphate is known to excite peripheral PAF teminals (Taiwo and Levine, 1991; Levine et al., 1993; Pierce et al., 1996a,b, 1997; Bevan, 1999; Millan, 1999). Excitation of peripheral PAF terminals by 5-HT_7 receptors has, together with their vasorelaxation of cerebral blood vessels, led to the inference that they contribute to migraine headaches (Terron, 1998). Support for a putative pronociceptive, excitatory influence of 5-HT_7 receptors at afferent PAF terminals in the DH is afforded by a study of Aδ fibres in the DRG which demonstrated that 5-HT_7 receptors, probably via generation of cyclic adenosine monophosphate, elicit a "hyperpolarisation-activated cation current" (I_H). This results in an enhancement of transmitter release from small calibre PAFs, as well as an increase in the excitability and responsiveness of PAFs to noxious stimulation (Cardenas et al., 1999, 2001). Interestingly, similar effects were seen at large calibre (Aβ) DRG neurones, potentially implicating central PAF-localised 5-HT_7 sites in the mediation of mechanical allodynia (Cardenas et al., 1999). The likelihood that such actions of 5-HT_7 sites are expressed at PAF terminals in the DH is strenghthened by the demonstration that 5-HT_7 sites similarly elicit this I_H current in the sensory thalamus (Chapin and Andrade, 2001a,b). Very recently, concurring with these earlier comments, an electrophysiological study suggested a pronociceptive role for DH-localised 5-HT_7 receptors (Garraway and Hochman, 2001b).

At the supraspinal level, despite their presence in the thalamus, the density of 5-HT_7 sites and their mRNA is not impressive in regions giving rise to monosynaptic pathways to the DH, in the PAG and in monoaminergic cell clusters of the brainstem, providing no evidence for a particular role in the modulation of descending controls of nociception, an issue requiring direct assessment in functional studies (To et al., 1995; Gustafson et al., 1996; Heidmann et al., 1997, 1998; Stowe and Barnes, 1998; Kinsey et al., 2001; Roberts et al., 2001).

7.5. Interrelationship between descending serotonergic and noradrenergic pathways

A diversity of evidence indicates an intricate and reciprocal functional interrelationship between the operation of descending noradrenergic and serotonergic pathways, expressed at both segmental and supraspinal loci.

As mentioned earlier, α_1- and α_2-ARs exert a facilitatory and inhibitory influence, respectively, upon serotonergic transmission (Section 5)—although this effect is incompletely characterised at the segmental level in terms of the release of 5-HT (Rosin et al., 1993; Guyenet et al., 1994; Gobert et al., 1995; Nicholas et al., 1997; Barnes and Sharp, 1999; Millan et al., 2000b). Contrariwise, noradrenergic cell bodies are subject to marked modulation by serotonergic mechanisms, including an indirect, GABA-mediated facilitatory and inhibitory influence of 5-HT_{1A} and 5-HT_{2C} receptors, respectively, although, again, this influence has not been systematically examined for descending pathways (Sections 7.4.1.4 and 7.4.3.4) (Bobker and Williams, 1989; Rosin et al., 1993; Guyenet et al., 1994; Nicholas et al., 1997; Barnes and Sharp, 1999; Gobert et al., 2000; Millan et al., 2000a,b).

Within the DH, interactions between descending noradrenergic and serotonergic pathways are also of significance, including an inhibitory influence of NA upon the release of 5-HT mediated via α_{2A}-ARs localised on their terminals (Guyenet et al., 1994; Gobert et al., 1995; Sawynok and Reid, 1996; Millan, 1997). Several authors have hypothesised a functional interdependence between descending noradrenergic and serotonergic pathways in the co-operative expression of DI: for example, in the induction of SPA and MIA (Basbaum and Fields, 1984; Kellstein et al., 1988; Sawynok, 1989; Post and Archer, 1990; Bervoets and Millan, 1994; Zhang et al., 1995b; Sawynok and Reid, 1996; Millan, 1997; Nakagawa et al., 1990). This interrelationship is a function of the roles of specific subtypes of 5-HT and α-AR in the mediation of pro as compared to antinociceptive actions. For example, agonists at 5-HT_{1B} and, possibly, 5-HT_2 receptors, can synergise with α_2-AR agonists in the induction of antinociception (Section 5.9.6), whereas 5-HT_{1A} receptor agonists interfere with noradrenergic (α_2-AR-mediated) mechanisms of analgesia (DeLander and Hopkins, 1987a; Danzebrink and Gebhart, 1991a; Clatworthy et al., 1988; Millan, 1997).

Knowledge of functional interactions between serotonergic and noradrenergic mechanisms for the spinal control of nociceptive processing remains, nevertheless, fragmentary. This question should most appropriately be addressed within the perspective of the above-delineated framework of contrasting pro and antinociceptive properties of multiple classes of α-AR and 5-HT receptor. Clarification of interrelationships between their actions may afford important insights into the design of novel analgesics which concomitantly harness and attenuate monoaminergic mechanisms of DI and DF, respectively (Section 12.5).

8. Non-monoaminergic transmitters exclusively delivered to the spinal cord by descending pathways

8.1. Histamine

8.1.1. Multiple receptors and origins of descending histaminergic pathways

Histamine exerts its actions via four classes of receptor. Of these, H_1, H_2 and H_3 receptors are found in the CNS, and the latter functions both post-synaptically to histaminergic neurones and as an autoreceptor on their terminals (Hough, 1988, 2001). Both H_1 receptors (which couple positively to PLC and PhospolipaseA$_2$) as well as H_2 receptors (which couple positively to AC) are excitatory. H_3 receptors (which are negatively coupled to AC and Ca^{2+}-currents) are inhibitory, in line with their role as inhibitory autoreceptors. Whether H_4 receptors—which couple negatively to AC—occur in the CNS remains controversial (Leurs et al., 1995; Hough, 2001).

Cell bodies synthesizing histamine are largely restricted to the tuberomammillary nucleus of the hypothalamus, which projects strongly to the PAG, PBN, NTS and, albeit less prominently, the brainstem-including the RVM and locus coeruleus-as well as the spinal cord (Watanabe et al., 1984; Wahlestedt et al., 1985; Hough, 1988; Panula et al., 1989; Brown et al., 2001). Immunohistochemical studies have shown that histaminergic perikarya display colocalization with GABA, adenosine, GAL and opioids (Köhler et al., 1986; Ericson et al., 1991; Brown et al., 2001).

8.1.2. Role of histamine receptors in the DH

Both H_1 and H_2 receptors are found in the DH, as well as a modest level of H_3 receptors, all of which are preferentially localized in superficial laminae (Traifford et al., 1992; Vizuete et al., 1997; Bouthenet et al., 1988). The presumed expression of these sites by intrinsic DH neurones remains to be established and at least a sub-population of H_1 receptors is generated in the DRG: further, PAF injury leads to an up-regulation of H_1 receptors in the DRG (Ninkovic and Hunt, 1985; Kashiba et al., 1999, 2001). This observation is in line with the familiar excitatory influence of histamine (via actions at H_1 receptors) upon peripheral PAF terminals (Bevan, 1999; Millan, 1999; Parada et al., 2001; Raffa, 2001) and is suggestive of a pronociceptive role of H_1 sites on the central terminals of PAFs in the DH. In line with this possibility, it was suggested that the hyperalgesic actions of H_1 receptors in the spinal cord are mediated by NK_1 and NMDA receptors, presumably following release of SP and GLU from PAF terminals (Sakurada et al., 2002). The decrease in inflammatory nociception seen in H_1 receptor knock-out mice was attributed to a loss of the pronociceptive actions of histaminergic pathways in the DH (Yanai et al., 1998; Mobarakeh et al., 2000), and spinal administration of H_1 antagonists elicits antinociception (Olsen et al., 2002). Moreover, an elevation in histamine release in the spinal cord was shown to elicit nociception and to

attenuate the antinociceptive action of clonidine (Chiechio et al., 1997). Curiously, in contrast to these indications for pronociceptive properties of histamine H_1 receptors, i.t. administration of H_1 antagonists was reported to attenuate the spinal antinociceptive actions of morphine (Suh et al., 1999), an observation awaiting confirmation.

Post-synaptic H_3 receptors reduce NA release in the DH, presumably by a direct interaction with noradrenergic neurones (Celuch, 1995). This action also favours mechanisms for the enhancement of spinal nociception. On the other hand, H_3 receptors may inhibit release from nocisponsive PAF terminals in the DH (Ohkubo et al., 1995). The significance of H_2 sites remains unclear. Considerable study will, then be necessary to more precisely define the significance of descending histaminergic pathways and multiple classes of histamine receptor in the segmental control of nociceptive processing.

8.1.3. Modulation by cerebral histamine receptors of descending controls

Histamine$_1$ receptors are present in a high density in the PVN (on VP-containing neurones), in the NTS, and in the locus coeruleus and other noradrenergic and serotonergic nuclei of the brainstem (Martinez-Mir et al., 1990; Brown et al., 2001). The additional presence of H_2 receptors in the locus coeruleus and other monoaminergic nuclei raises the possibility that, together with H_1 sites, they may synergistically activate noradrenergic and serotonergic pathways (Haas, 1992; Traifford et al., 1992; Vizuete et al., 1997; Brown et al., 2001). Activation of descending monoaminergic tracts provides, thus, one potential substrate for the induction of antinociception by cerebral actions of histamine at H_1 and/or H_2 sites (Bhattacharya and Parmar, 1985; Malmberg et al., 1994; Lamberti et al., 1996). On the other hand, H_3 receptors in the locus coeruleus inhibit the activity of noradrenergic neurones (Pollard et al., 1993).

Though the precise contribution of supraspinal populations of H_1 as compared to H_2 receptors to the modulation of nociception by histamine remains unclear, H_2 receptors appear to mediate the antinociception evoked by its introduction into the PAG. This role of H_2 sites likely reflects activation of an excitatory link to brainstem nuclei mediating DI (Hough and Nalwalk, 1992a,b; Malmberg et al., 1994; Thoburn et al., 1994; Hough et al., 1997; Malmberg-Aiello et al., 1998). Correspondingly, a role of PAG-localized H_2 receptors has been implicated in the antinociception elicited by administration of μ-opioids into this structure, in line with: (1) the enhancement of central histamine release induced by systemic and PAG application of morphine (Gogas and Hough, 1988; Toh et al., 1989; Hough and Nalwalk, 1992a,b; Barke and Hough, 1993; Thoburn et al., 1994; Suh et al., 1999) and (2) its (indirect) depolarizing influence upon histaminergic neurones in the tuberomammillary nucleus (Ericsson et al., 1999). Thus, an action of histamine at H_2 sites may contribute to the induction of DI by cerebral μ-opioidergic mechanisms. Offering additional support for antinociceptive actions of supraspinal histaminergic networks, the increase in central concentrations of histamine provoked by treatment with H_3 autoreceptor antagonists and histamine precursors is associated with antinociception, whereas the reduction of histamine release elicited by H_3 receptor agonists and histamine depletors enhances nociception (Malmberg et al., 1994, 1997; Suh et al., 1999). (Although histamine antagonists have been reported to possess analgesic properties, they cannot be attributed to actions at defined classes of histamine receptor and the underlying mechanisms remain to be elucidated (Brown et al., 2001)).

Acute noxious and other forms of stressful stimuli by an, as yet, unclear mechanism enhance the activity of central histaminergic neurones: H_2 sites may be involved in the accompanying antinociception. However, it is not known whether long-term inflammatory or neuropathic states result in a sustained alteration in the activity of histaminergic neurones projecting to the PAG, brainstem and DH (Gogas and Hough, 1988; Itoh et al., 1988; Gogas et al., 1989; Toh et al., 1989; Nalwalk et al., 1995; Wong, 1995; Brown et al., 2001). Histaminergic perikarya are heavily innervated by monoaminergic, GABAergic, glutamatergic, cholinergic and other pathways. Notably, 5-HT$_{2C}$, NMDA and nicotinic receptors enhance, while GABA$_A$ and GABA$_B$ receptors inhibit, their activity (Brown et al., 2001). However, the relevance of such modulatory input to the role of descending histaminergic projections in the modulation of nociception remains unclear.

8.2. Vasopressin and oxytocin

8.2.1. Multiple receptors and origins of descending vasopressin- and oxytocin-containing pathways

While oxytocin (OT) exerts its actions via epynomously-named OT receptors, vasopressin (VP) activates three different classes of receptor, termed V_{1a}, V_{1b} and V_2, respectively (Burbach et al., 1995; Barberis et al., 1999). V_2 sites are found almost exclusively in the kidney and, in contrast to V_{1a} and OT sites, there is currently no evidence for expression of V_{1b} sites in the spinal cord (De Wied et al., 1993; Burbach et al., 1995; Hernando et al., 2001). V_{1a} and OT sites are, thus, likely to mediate the influence of VP and OT, respectively upon nociceptive processing in the DH. In each case, they are positively coupled to PLC, and their stimulation enhances intracellular levels of Ca^{2+} (Barberis et al., 1999).

Vasopressin- and OT-containing pathways project directly from the parvocellular and, to a lesser degree, magnocellular compartments of the hypothalamic PVN to the spinal cord (Swanson and Sawchenko, 1983; Millan et al., 1984a; Jo et al., 1998; Hallbeck and Blomqvist, 1999; Burbach et al., 2001; Hallbeck et al., 2001; Nylen et al., 2001). In analogy to monoaminergic and histaminergic pathways to the spinal cord, these projections constitute the exclusive source of DH pools of VP and OT (Millan et al., 1984a; De Wied et al., 1993; Hallbeck et al., 1996, 1999, 2001). Both VP- and

OT-containing fibres are abundant in the superficial zone of the DH and they also ramify in deeper DH laminae and lamina X (De Wied et al., 1993; Hallbeck et al., 1996, 1999, 2001).

8.2.2. Induction of spinal antinociception by VP and OT

This distribution pattern of VP- and OT-containing terminals suggests a role in the modulation of nociception. Indeed, despite certain conflicting data, the balance of evidence favours a role of both VP and OT in the mediation of antinociception in the DH (Millan et al., 1984b; Thurston et al., 1988; Arletti et al., 1993; De Wied et al., 1993; Lundeberg et al., 1994; Jo et al., 1998; Hallbeck et al., 2001). These studies indicated that V_1 sites mediate the induction of spinal antinociception by VP and, although formal evidence is awaited, on anatomical grounds, a role of V_{1a} receptors may be surmised (Section 8.2.1). OT receptors, on the other hand, mediate the actions of OT. Inasmuch as V_{1a} and OT receptors exert an excitatory influence upon neuronal activity, it may be deduced that the populations mediating segmental antinociception (DI) are localized on ININs. Direct support for this contention has been provided by Jo et al. (1998) who demonstrated that OT recruits GABAergic ININs in the DH via: (1) mobilization of intracellular Ca^{2+} (following induction of PLC) and (2) activation of Na^{+}-currents.

The recent discovery of DYN and ENK in a subset of VP- and OT-containing tracts projecting from the PVN to the spinal cord raises the possibility that they participate in the modulation of spinal nociceptive processing by this nucleus. Further, VP and OT may interact with these opioid peptides in the expression of their antinociceptive properties in the DH (Hallbeck et al., 2001). Similarly, NO has been detected in neurones travelling from the PVN to the spinal cord and it is, at least partially, colocalized with VP and OT (Hallbeck et al., 2001; Nylen et al., 2001).

The nature of physiological stimuli activating descending VP- and OT-containing pathways awaits detailed elucidation, although they are essentially refractory to many manipulations engaging magnocellular tracts running to the posterior hypophysis (Millan et al., 1984a; De Wied et al., 1993; Burbach et al., 2001). Both acute and chronic noxious stimulation modify levels of VP and OT in the hypothalamus, medulla and DH consistent with a role of descending pathways in the modulation of spinal nociceptive processing (Hamamura et al., 1984; Millan et al., 1985a,b; Onaka et al., 2001). In line with this contention, Truesdell and Bodnar (1987) suggested that VP plays a role in the induction of antinociception by stress. VP- and OT-containing neurones in the hypothalamus are subject to a modulatory noradrenergic, serotonergic and dopaminergic input, though its influence upon pathways descending to the spinal cord is unclear (Onaka et al., 2001).

Oxytocin-containing neurones target parasympathetic neurones controlling pelvic and uterine function and localized in lumbosacral segments of the spinal cord. Further, both VP- and OT-expressing pathways innervate the IML, consistent with functional studies suggesting a role in the control of autonomic function (Hallbeck et al., 2001; Puder and Papka, 2001). Whether excitatory actions of VP and OT in the IML are pertinent to painful states sustained by sympathetic outflow remains to be established.

8.2.3. Supraspinal actions of VP and OT in the modulation of descending controls

Several cerebral populations of VP-containing neurones are potentially involved in the modulation of nociceptive processing by VP. First, collaterals of PVN-derived, caudally-projecting pathways expressing VP penetrate the medulla including both the RVM and its more lateral component: at least in neighbouring regions of the medulla, VP has been shown to exert an excitatory influence upon intrinsic neurones (Shafton et al., 1998; Hallbeck et al., 1999; Nylen et al., 2001; Yang et al., 2001b). Second, a further cluster of VP-containing neurones emanating from the bed nucleus of the stria terminalis similarly projects to the RVM and medullary noradrenergic nuclei (Hallbeck et al., 1999). Thus, VP-containing neurones target brainstem regions giving rise to descending controls. Third, both the PBN and the PAG possess minor populations of neurones positive for mRNA encoding VP, although evidence that they innervate the brainstem or spinal cord is lacking (Hallbeck et al., 1999). Fourth, VP evokes antinociception upon i.c.v. administration. One locus of action may be the amygdala which engages mechanisms of DI via a relay in the PAG (Section 3.3) (Berkowitz and Sherman, 1982; De Wied et al., 1983; Lu et al., 1997; Ahn et al., 2001).

9. Transmitters contained in descending pathways and predominantly in intrinsic dorsal horn neurones

9.1. Acetylcholine

9.1.1. Multiple receptors and origins of cholinergic neurones in the dorsal horn

Cholinergic mechanisms for the modulation of nociception are particularly intriguing (Table 2) inasmuch as ACh may be involved: (1) in the activation of non-cholinergic descending pathways mediating DI; (2) in the mediation of DI following its own release from descending pathways and (3) in the induction of antinociception following release from ININs in the DH. Further, ACh modulates nociception by a complex pattern of effects mediated via multiple classes of muscarinic and nicotinic receptor (Coggeshall and Carlton, 1997; Eisenach, 1999; Decker and Meyer, 1999).

Currently, five classes of muscarinic receptor are recognized, although M_5 sites remain incompletely characterized and the discussion herein focusses on M_1–M_4 receptors. Coupling of multiple muscarinic receptors to intracellular transduction mechanisms is complex and tissue-dependent. Excitatory M_1, M_3 and M_5 sites are positively coupled via Gq/11 to PLC and AC, while Gi/o-coupled M_2 and M_4

Table 2
Overview of the functional roles of transmitters which display multiple pro- and antinociceptive actions

Transmitter	Receptor(s)	Sites(s) of action	Effect (indirect)	Neuronal target(s)	Influence
Histamine	H_1	DH	STIM	PAF	Pronociceptive
Histamine	H_2	PAG	STIM	Excitatory output to RVM	Antinociceptive
Acetylcholine	Nicotinic	DH	STIM	NA/5-HT terminals	Antinociceptive
Acetylcholine	Nicotinic	DH	STIM	PAF	Pronociceptive
Acetylcholine	Nicotinic	NRM/A_7 nucleus	STIM/(STIM)	5-HT/NA perikarya	Antinociceptive
GABA	$GABA_{A/B}$	DH	INH	PN, PAF	Antinociceptive
GABA	$GABA_{A/B}$	NRM/A_7 nucleus, RVM	INH	5-HT/NA perikarya, OFF cells	Pronociceptive
GABA	$GABA_{A/B}$	NRM/A_7 nucleus, RVM	(STIM)	5-HT/NA perikarya, OFF cells	Antinociceptive
GABA	$GABA_{A/B}$	RVM	INH	ON cells	Antinociceptive
GABA	$GABA_{A/B}$	PAG	INH	Excitatory output to RVM and A_7 nucleus	Pronociceptive
Neuropeptide FF	FF_2	DH	INH	PAF	Antinociceptive
Neuropeptide FF	FF_2	DH	(STIM)?	Opioidergic ININs?	Antinociceptive
Neuropeptide VF	FF_1	PAG, AMYG, NTS	INH	Excitatory output to RVM	Pronociceptive
Neurotensin	NT_1	DH	STIM/(INH)	ININ/PAF, PN?	Antinociceptive
Neurotensin	NT_2	PAG	STIM	Excitatory output to RVM	Antinociceptive
Neurotensin	NT_2	A_7 nucleus/RVM	STIM	NA/ACh perikarya, OFF cells?	Antinociceptive
Neurotensin	NT_1?	RVM	STIM	ON cells?	Pronociceptive
Galanin	GAL_1	DH	INH	PN, PAF	Antinociceptive
Galanin	GAL_2	DH	STIM	PN, PAF	Pronociceptive
Galanin	GAL_1/GAL_2?	PAG	(STIM)/STIM	Excitatory output to RVM	Antinociceptive
Galanin	GAL_1	NRM, A_7 nucleus	INH	5-HT/NA perikarya	Pronociceptive
Substance P	$NK_{1(2,3)}$	DH	STIM	PN	Pronociceptive
Substance P	NK_1?	A_7 nucleus	STIM	NA perikarya	Antinociceptive
Glutamate	NMDA/AMPA/MTB	DH	STIM	PN	Pronociceptive
Glutamate	NMDA	RVM	STIM	ON cells?	Pronociceptive
Glutamate	NMDA	A_7 nucleus	(INH)	NA perikarya	Pronociceptive
Glutamate	NMDA	PAG/RVM	STIM	Excitatory output to RVM-NA/OFF cells	Antinociceptive
Glutamate	NMDA	NRM/A_7 nucleus	STIM	5-HT/NA perikarya	Antinociceptive
Glutamate	AMPA	RVM	STIM	OFF cells?	Antinociceptive

The Table provides a summary of the principle pro and antinociceptive actions of those transmitters which exert multiple, opposing influences upon nociception at the spinal and/or supraspinal level. The list is not exhaustive (see text for details). For simplicity, it is assumed that activation of centripetal serotonergic pathways is associated, like their descending noradrenergic counterparts, with the induction of antinociception. STIM, stimulation; INH, inhibition; NT, neurotensin; GAL, galanin; NK, neurokinin; NMDA, *N*-methyl-D-aspartate; AMPA, α-amino-2,3-dihydro-5-methyl-3-oxo-4-isoxazolepropanoic acid; MTB, metabotropic; DH, dorsal horn; RVM, rostroventromedial medulla; PAG, periaqueductal grey; ARC (HYPOTH), arcuate nucleus of hypothalamus; PAF, primary afferent fibre; PN, projection neurone; NA, noradrenaline; 5-HT, serotonin; ACh, acetylcholine; DP, descending pathway; NRM, nucleus raphe magnus; DRN, dorsal raphe nucleus; VTA, ventrotegmental area; AMYG, amygdala and NTS, nucleus tractus solirarius.

receptors are inhibitory, reflecting their suppression of AC activity and Ca^{2+}-currents and, for M_2 sites at least, activation of K^+-channels (Cautfield and Birdsall, 1998; Levine et al., 1999). Pentameric, ionotropic (cation-permeable), excitatory nicotinic receptors are constructed from at least 17 different receptor subunits with subtypes named in accordance with their precise composition. Numerous combinations of subunits have been conjectured, of which the $\alpha_4\beta_2$ variant predominates throughout the CNS. Many other subtypes of nicotinic receptor also occur in the brain, DH and DRG (Jones et al., 1999; Lukas et al., 1999; Cordero-Erausquin and Changeux, 2001; Genzen et al., 2001; Khan et al., 2001).

While a percentage of spinal pools of ACh is derived from supraspinal structures, such as the NRM and various medullary-pontine nuclei, the prevailing view is that intrinsic neurones are the predominant source of ACh in the DH (Bowker et al., 1983; Jones et al., 1986; Gillberg et al., 1990; Ribeiro-da-Silva and Cuello, 1990; Todd and Spike, 1993; Fang and Proudfit, 1996; Baba et al., 1998; Cordero-Erausquin and Changeux, 2001). Cholinergic perikarya are concentrated in laminae III/IV, and arborize both in deep and in superficial laminae. They receive input from unmyelinated (fine calibre) and low threshold (large calibre) PAFs and, in a reciprocal fashion, cholinergic terminals are pre-synaptic to each of these classes of PAF (Gillberg et al., 1990; Ribeiro-da-Silva and Cuello, 1990; Todd and Spike, 1993). In addition, cholinergic terminals contact a substantial population of intrinsic DH neurones, including PNs. A considerable number of DH-localized ININs display colocalization of ACh with GABA, which may act cooperatively in the induction of antinociception Sections 9.2 (Todd and Spike, 1993; Mui et al., 1997; Baba et al., 1998; Hwang et al., 2001).

The above-summarized configuration of cholinergic terminals in the DH evidently permits the modulation of nociceptive processing by actions expressed both at intrinsic DH neurones and upon the terminals of nocisponsive PAFs (Decker and Meyer, 1999; Eisenach, 1999; Li and Zhuo, 2001). It is also consistent with extensive evidence for the mediation of antinociception by segmental cholinergic mechanisms, and with their role of the induction of DI in response to supraspinal application of morphine and stimulation of the RVM (Zhuo and Gebhart, 1990b; Fang and Proudfit, 1996; Decker and Meyer, 1999; Eisenach, 1999; Shannon et al., 2001).

9.1.2. Muscarinic receptors

Cholinergic (primarily muscarinic) mechanisms in the DH have been implicated in the induction of antinociception by spinal administration of α_2-AR agonists (Section 5.8.2). This mechanism operates under conditions of neuropathic pain due to PAF injury and may ultimately reflect generation of NO by ACh (Wotta and El-Fakahany, 1997; Eisenach, 1999; Xu et al., 2000; Hama et al., 2001). Although the underlying mechanisms are not clear, these observations are compatible with the ability of cholinesterase inhibitors to potentiate the induction of spinal antinociception by α_2-AR agonists (Section 5.9.1) (Naguib and Yaksh, 1994; Abram and O'Connor, 1995; Hood et al., 1996; Eisenach, 1999). Similarly to spinal actions of α_2-AR agonists, activation of supraspinal μ-opioid receptors by morphine enhances ACh release in the DH, while MIA is potentiated by cholinergic agonists and cholinesterase inhibitors. This interaction may reflect, then the role of descending noradrenergic pathways in mediating the cerebral actions of μ-opioid agonists (Section 5.3) (Naguib and Yaksh, 1994; Abram and O'Connor, 1995; Fang and Proudfit, 1996; Dougherty and Staats, 1999; Eisenach, 1999; Yaksh, 1999a; Gage et al., 2001).

Antinociceptive effects of ACh in the DH predominantly involve muscarinic mechanisms, in line with the presence of muscarinic receptors on both PAF terminals (M_2, M_3 and, possibly, on functional criteria, M_4) and on intrinsic DH neurones (M_2–M_4) (Coggeshall and Carlton, 1997; Höglund and Baghdoyan, 1997; Yung and Lo, 1997; Haberberger et al., 2000). However, the pharmacology of spinal muscarinic antinociception is in a state of flux. Thus, in contrast to older studies which asserted a major role of M_1 sites, it has more recently been contended that M_2, M_4 and, perhaps, M_3 receptors are critically involved in the induction of analgesia (Bartolini et al., 1992; Naguib and Yaksh, 1997; Shannon et al., 1997, 2001; Sheardown et al., 1997; Ellis et al., 1999; Gomeza et al., 1999; Hwang et al., 1999; Honda et al., 2000; Xu et al., 2000; Ma et al., 2001a).

It is important to mention the pronounced cardiovascular and motor effects of spinal (and systemic) administration of muscarinic agonists which reflect the heavy innervation by cholinergic fibres of preganglionic neurones and MNs in the IML and VH, respectively (Lothe et al., 1994; Li et al., 1995; Feldman et al., 1996; Yung and Lo, 1997; Dougherty and Staats, 1999). Clarification of the precise roles of specific muscarinic receptor subtypes in the segmental induction of antinociception as compared to the induction of motor and cardiovascular side-effects appears essential prior to their exploitation as targets for novel analgesic agents (Gainetdinov and Caron, 1999; Gomeza et al., 1999; Levine et al., 1999).

It is also important to take account of supraspinal muscarinic mechanisms modulating nociception. Thus, cholinergic neurones in the RVM (M_2 receptors), in the lateral hypothalamus and in the PAG can trigger antinociception via activation of noradrenergic channels of DI and, subsequently, the engagement of α_2-ARs in the DH (Zhuo and Gebhart, 1991b; Iwamoto and Marion, 1993, 1994; Guimaraes and Prado, 1999; Nuseir et al., 1999; Holden and Naleway, 2001; Ma et al., 2001a). Moreover, activation of descending cholinergic neurones originating in the RVM may elicit DI and antinociception (Section 7.3.2). It should be mentioned that a role for M_2 receptors in peripheral antinociception has been proposed (Buerkle et al., 1997).

9.1.3. Nicotinic receptors

In analogy to muscarinic receptors, activation of nicotinic receptors may contribute to the antinociceptive actions of α_2-AR agonists in the DH (Xu et al., 2000). Indeed, like muscarinic agonists, nicotinic agonists synergize with α_2-AR agonists in the expression of analgesic properties in the DH (Hama et al., 2001). On the other hand, Khan et al. (2001) proposed that nicotine evokes antinociception in the DH by direct activation of the terminals of noradrenergic neurones. These authors posited a role of $\alpha_4\beta_2$ nicotinic receptors in this interaction. This proposition is of interest in view of a study by Damaj et al. (1997) who calculated that the potency of structurally-heterogeneous cholinergic agonists for the induction of spinal antinociception correlated well to their affinities for $\alpha_4\beta_2$ nicotinic receptors. Further, $\alpha_4\beta_2$ nicotinic receptors have been implicated in the induction of glycine release in superficial DH, providing a further mechanism of spinal antinociception (Kiyosmua et al., 2001).

The preceding observations imply a reciprocal and mutual facilitatory interrelationship of nicotinic receptor- and α_2-AR-mediated mechanisms of antinociception in the DH. An additional level of complexity has been provided by studies suggesting that nicotinic receptors also elicit antinociception via an interaction with serotonergic terminals in the DH (Cordero-Erausquin and Changeux, 2001). The subclass(es) of nicotinic receptor(s) mediating this effect require(s) delineation. Moreover, a poorly-understood component of nicotine-induced antinociception may reflect an interaction with PAF terminals leading to reduced release of SP and desensitization of vanilloid (VR_1) receptors (Puttfarcken et al., 1997; Genzen et al., 2001; Zhang et al., 2001a).

Irrespective of their identity, then, multiple subtypes of nicotinic receptor, acting via contrasting neuronal substrates, are implicated in the spinal induction of antinociception

(Damaj et al., 1998; Marubio et al., 1999; Cordero-Erausquin and Changeux, 2001; Genzen et al., 2001; Khan et al., 2001; Kiyosawa et al., 2002).

Interestingly, the $\alpha_4\beta_2$ class of nicotinic receptor has been implicated in supraspinal antinociceptive actions of nicotine mediated via direct activation of descending serotonergic soma in the NRM (Iwamoto, 1991; Bitner et al., 1998; Hunt et al., 1998; Marubio et al., 1999; Decker and Meyer, 1999; Ma et al., 2001a). That is to say, a subtype different to that which enhances segmental release of 5-HT via actions at the terminals of descending serotonergic pathways (Cordero-Erausquin and Changeux, 2001). A further component of the supraspinal antinociceptive actions of nicotine apparent upon its introduction into the RVM involves the (indirect) engagement of descending noradrenergic pathways emanating from the A_7 nucleus of the brainstem (Section 5.3) (Decker and Meyer, 1999; Nuseir et al., 1999). Nicotine receptors in the nucleus accumbens, probably in interaction with mesolimbic dopaminergic pathways, were recently suggested to participate in the expression of MIA (Schmidt et al., 2001).

Despite increasing interest in antinociceptive actions of nicotinic receptors expressed in interaction with descending controls (Damaj et al., 1998; Decker and Meyer, 1999; Lawand et al., 1999), evidence for pronociceptive actions of nicotine in the DH and periphery should be noted. These actions are effected via excitation of central and peripheral terminals of PAFs and likely involve multiple sub-classes of receptor (including the $\alpha_3\beta_4$ form) differing from those inducing central antinociception (Flores et al., 1996; Khan et al., 1996; Buerkle et al., 1997; Decker and Meyer, 1999; Jinks and Carstens, 1999; Genzen et al., 2001; Hama and Menzaghi, 2001; Khan et al., 2001; Miao et al., 2001).

9.1.4. Dissociation of analgesic versus other actions

To summarize, there is currently intense interest in cholinergic mechanisms of antinociception. Muscarinic actions in the DH downstream of noradrenergic mechanisms of DI, and nicotinic mechanisms in the brainstem upstream of serotonergic mechanisms of DI, deserve special mention in the present context. The exploitation of cholinergic avenues for pain relief presupposes a more thorough characterization of the functional roles of individual subtypes of muscarinic and nicotinic receptor. By their discrete manipulation, it may be possible to achieve an acceptable therapeutic window between doses expressing analgesic versus disruptive cardiovascular, motor and other side-effects (Gillberg et al., 1990; Eisenach, 1999). In addition, for nicotinic agonists, it will be essential to circumvent potential problems of addiction and tolerance and, with appropriately-selective ligands, to separate actions at receptor subtypes mediating antinociception from those enhancing nociception. In each of these respects, the utilization of cholinergic agonists as adjuncts to μ-opioid and α_2-AR agonists may prove fruitful for the induction of analgesia (Section 5.9.1). The relative contribution of descending cholinergic pathways and cholinergic ININs in the DH to the induction of antinociception remains to be determined.

9.2. GABA and glycine

9.2.1. GABAergic neurones in the spinal cord: $GABA_A$ and $GABA_B$ receptors

In the preceding section, it was pointed out that ACh is present in supraspinal networks regulating descending controls, in descending pathways themselves and in intrinsic DH neurones. GABA similarly displays such a triple localization and the role of this key inhibitory neurotransmitter in the modulation of nociceptive processing is, accordingly, both crucial and complex.

GABA exerts its actions via two classes of receptor. $GABA_A$ receptors, like $5\text{-}HT_3$ and nicotinic receptors, comprise pentameric ion channels which are assembled from-at least 18-different subunits. However, they may be distinguished from the former by their permeability to anions (chloride) underlying an inhibitory influence upon cellular excitability (Barnard, 1996, 2000). They possess several modulatory (facilitatory) sites, notably to volatile and intravenous anesthetics such as isoflurane and propofol, respectively (Sieghart, 1995; Krasowski et al., 1998; Vahle-Hinz et al., 2001). $GABA_B$ receptors are heterodimers which are coupled via Gi/o to an enhancement of K^+-currents, suppression of Ca^{2+}-currents and, generally, inhibition of AC: their engagement reduces neuronal activity (Kerr and Ong, 1995; White et al., 1998; Bowery and Enna, 2000; Bouvier, 2001; Marsh et al., 2001; Schuler et al., 2001; Charles et al., 2001; Yang et al., 2001a).

$GABA_A$ and $GABA_B$ sites are both enriched in the DH, particularly in superficial laminae, wherein they are localized on (and inhibit) the terminals of small and large diameter PAFs: in addition, they occur on (and inhibit) intrinsic DH neurones, including PNs (Coggeshall and Carlton, 1997; Margeta-Mitrovic et al., 1999; Millan, 1999; Charles et al., 2001; Yang et al., 2001a).

Via actions at both $GABA_A$ and $GABA_B$ receptors, GABAergic ININs play a critical and well-established role in antinociceptive processes, both in the spinal cord and in the trigeminal nucleus. They express this role tonically (under "resting" conditions) and, in particular, in response to acute and chronic noxious stimulation (Pieribone et al., 1994; Sorkin et al., 1998; Weng et al., 1998; Millan, 1999; Couve et al., 2000; Bertrand et al., 2001; Patel et al., 2001; Loomis et al., 2001; Schuler et al., 2001; Takemura et al., 2001; Von Heijne et al., 2001; Wang et al., 2001a). In distinction, the potential contribution of GABA released from descending pathways to mechanisms of antinociception in the DH remains unclear. Although the degree of colocalization is contentious (Stamp and Semba, 1995; Antal et al., 1996; Stornetta and Guyenet, 1999), a proportion of NRM-derived serotonergic neurones innervating superficial DH laminae and the IML synthesize and release GABA (Sections 7.1.2 and 7.3) (Maxwell et al., 1996). This

suggests that "serotonergic" pathways may reduce nociceptive transmission (elicit DI) not only by excitatory actions of 5-HT at GABAergic ININs in the DH but also by direct GABAergic inhibition of PNs (Lin et al., 1994, 1996b; Peng et al., 1996a, 2001; Li and Willis, 1999). GABA is also colocalized with NA in descending noradrenergic neurons (Iijima et al., 1992), while virtually all histaminergic neurones of the tuberomammillary nucleus (Section 8.1) contain GABA (Ericson et al., 1991; Onodera et al., 1994), providing further potential supraspinal sources of GABA for the expression of DI in the DH.

9.2.2. Glycinergic neurones

In analogy to the extensive co-occurrence of GABA and a further inhibitory amino acid, glycine, in ININs, a population of GABAergic pathways descending from the RVM also contains glycine, which presumably participates in the inhibition of DH neurones upon its release from descending pathways (Section 7.3) (Coggeshall and Carlton, 1997; Cui et al., 1999; Raiteri et al., 2001).

Like $GABA_A$ receptors, glycine receptors form intrinsic, pentameric, chloride-permeable ion channels inhibitory to neuronal activity (Rajendra et al., 1997). Glycine receptors are often colocalized with $GABA_A$ sites in the DH, in line with the co-existence of glycine and GABA in descending pathways and ININs. Likewise mimicking GABAergic receptors, glycinergic sites are localized on PNs, in particular in deep laminae—though evidence for glycinergic sites on PAF terminals remains inconclusive (Todd and Spike, 1993; Coggeshall and Carlton, 1995; Raiteri et al., 2001). This overlapping organization of GABA/GABAergic receptors and glycine/glycinergic receptors accords well with functional reports that they fulfill a cooperative, synergistic role in suppressing the transmission of nociceptive information in the DH (Millan, 1999; Milne et al., 2001; Loomis et al., 2001).

Likewise in analogy to $GABA_A$ receptors, the activity of glycine receptors can be suppressed by their phosphorylation following activation of protein kinase A (via AC) or C (via PLC). Thus, excitatory transmitters mediating DF and coupled to AC or PLC excite and sensitize PNs both directly and by interfering with their inhibition by GABAergic and glycinergic ININs (Porter et al., 1990; Lin et al., 1994, 1996b; Millan, 1999; Albarran et al., 2001). (As noted in Section 10, PAF-derived pronociceptive transmitters, such as SP and glutamate, likewise exercise such a dual, excitatory influence upon PNs).

9.2.3. GABAergic input to spinal regions other than the DH

Non-monoaminergic neurones originating in medullary structures such as the parapyramidal area provide a descending GABAergic input specifically to sympathetic neurones of the IML (Stornetta and Guyenet, 1999), from which one may infer that descending GABAergic neurones (and GABAergic ININs) modulate sympathetic outflow. This may be of importance not only for the control of autonomic function but also for the modulation of nociception in painful states due to PAF injury which are: (1) exacerbated by sympathetic hyperactivity and (2) accompanied by the disappearance (and/or functional incapacitation) of GABAergic ININs in the DH (Millan, 1999).

9.2.4. Supraspinal GABAergic modulation of descending pathways

At the supraspinal level, the sheer abundance and ubiquity of GABAergic neurones suggests a multiplicity of roles in the control of nociception (Table 2). In analogy to the DH, the crucial significance of inhibitory GABAergic neurones in suppressing excessive (and irreversible) excitation of nociceptive circuits in the thalamus and cortex under conditions of chronic pain cannot be overemphasized (Millan, 1999; Miletic and Miletic, 2001).

However, not all actions of GABA favour antinociception. Indeed, GABAergic neurones exert an inhibitory influence, both directly and indirectly, upon several pathways mediating DI. First, PAG microinjection of $GABA_A$ antagonists evokes analgesia by disinhibiting pathways excitatory to mechanisms of DI originating in the RVM and A_7 noradrenergic nucleus (Section 3.3) (Beitz et al., 1987; Depaulis et al., 1987; Wiklund et al., 1988; Reichling and Basbaum, 1990a,b; Fields et al., 1991; Roychowdhury and Fields, 1996; Budal et al., 1998; Fields and Basbaum, 1999; Yaksh, 1999a; Koyama et al., 2000). Second, GABAergic ININs in the RVM preferentially inhibit the activity of OFF as compared to ON cells, thereby favouring mechanisms of DF over those of DI (Section 3.2.4) (Heinricher and Tortorici, 1994; Thomas et al., 1995; Bajic et al., 2001; Gilbert and Franklin, 2001b). Third, they also exert a direct, inhibitory influence upon perikarya in the brainstem giving rise to descending noradrenergic and descending serotonergic pathways (Reichling and Basbaum, 1990a; Gilbert and Franklin, 2001b; Wang et al., 2001b; Wirtshafter and Sheppard, 2001). For example, virtually all monoaminergic cell groups are subject to inhibition by local GABAergic and glycinergic neurones (Fields and Basbaum, 1999; Margeta-Mitrovic et al., 1999; Bajic et al., 2001; Somogy and Llewellyn-Smith, 2001; Varga et al., 2001). Notably, as described earlier (Section 7.3.3), those "primary" (serotonergic) neurones in the NRM which mediate DI are subject to direct inhibition by GABAergic "secondary" cells: inhibition of these GABAergic units contributes to μ- and δ-opioidergic mechanisms of antinociception evoked from this structure (Jones et al., 1991; Pan et al., 1997; Margeta-Mitrovic et al., 1999; Vaughan et al., 1999; Li and Wang, 2001). Both $GABA_A$ and, possibly, $GABA_B$ receptors are involved in this inhibition of serotonergic neurones. Accordingly, pro and antinociceptive actions of GABAergic agonists and antagonists, respectively have been reported upon their application into the RVM (Heinricher and Tortorici, 1994; Thomas et al., 1995; Hama et al., 1997; Hammond et al., 1998; Gilbert and Franklin, 2001b).

On the other hand, illustrative of the complex and multifarious role of GABAergic neurones, they attenuate the release of other inhibitory afferents to primary (serotonergic) neurones via actions at $GABA_B$ receptors. This action may underlie the antinociceptive actions of $GABA_B$ agonists, such as baclofen, upon introduction in the RVM (Hammond et al., 1998; Margeta-Mitrovic et al., 1999). Direct inhibition of ON cells by GABAergic mechanisms is also implicated.

A bidirectional influence of GABA in the A_7 nucleus upon nociception has also been proposed in that GABAergic mechanisms both enhance (indirectly) and brake (directly) noradrenergic mechanisms of DI originating therein (Section 5.3) (Nuseir and Proudfit, 2000; Bajic et al., 2001).

Such opposite pro- and antinociceptive actions of GABAergic mechanisms within the RVM (Table 2) parallel: (1) similar bidirectional actions of κ-opioids agonists (Section 9.3.3) and neurotensin (NT) (Section 9.6) upon their administration into the RVM and (2) the induction of DI or DF by stimulation of the RVM at different intensities (Zhuo and Gebhart, 1990a,b; Urban and Gebhart, 1993; Urban et al., 1999a; Ackley et al., 2001).

Clearly, then it is not meaningful to attribute a unitary pro or antinociceptive role to the complex pattern of influence exerted by discrete populations of supraspinal GABAergic neurones upon descending controls.

9.3. Opioid peptides

9.3.1. Multiple opioid peptides and multiple μ-, δ- and κ-opioid receptors

Rather unusually, for μ-, δ- and κ-opioid receptors in each case, several endogenous ligands have been identified, and there is no immediately obvious pattern of correspondence between multiple opioid peptides and multiple opioid receptors (Table 3).

Opioid peptides are processed from distinct precursor proteins which give rise to several families of sequences known to be independently localized and to fulfill contrasting functional roles in the modulation of nociceptive processing (Khachaturian et al., 1985; Millan, 1986, 1990; Herz et al., 1993; Kieffer, 1995; Mansour et al., 1995; Satoh and Minami, 1995; Dickenson and Besson, 1997; Yaksh, 1999a). Pre-pro-enkephalin is cleaved into the pentapeptides, Met- and Leu-ENK, together with several longer species of dubious physiological relevance (Section 9.3.2). Pro-opiomelanocortin (POMC) is processed into β-EP and several melanocortins (MC) (Section 9.3.5), while pre-pro-dynorphin is spliced into $DYN_{1–17}$ (DYN) and a suite of other peptides displaying comparable characteristics (Section 9.3.3). Of the various processing products, discussion herein is restricted to ENKs (as a "single" entity),

Table 3
Overview of the diverse influence of multiple opioidergic mechanisms upon nociception and descending controls

Precursor	Product(s)	Receptor(s)	Site(s) of action	Neuronal origin(s)	Influence
Pre-pro-ENK	Met- and Leu-ENK	δ	DH	ININ, DP	Antinociceptive
	Met- and Leu-ENK	δ	PAG, amygdala	Local	Antinociceptive
	Met- and Leu-ENK	δ	RVM, A_7 nucleus	PAG/local	Antinociceptive
Pre-pro-DYN	DYN	κ	DH	ININ, DP	Antinociceptive
	DYN	NMDA, other	DH	ININ, DP	Pronociceptive
	DYN	κ	Amygdala, PAG, RVM	Local	Antinociceptive
	DYN	κ	RVM	Local	Pronociceptive
Pre-pro-endomorphin	Endomorphin 2 and 1	μ	DH	PAF	Antinociceptive
	Endomorphin 2 and 1	δ/κ	DH (via ENK/DYN)	PAF	Antinociceptive
	Endomorphin 1 and 2	μ	PAG, amygdala	Local? ARC (HYPOTH)?	Antinociceptive
Pre-POMC	β-EP	μ	DH	ININ, DP	Antinociceptive
	β-EP	μ	Amygdala, PAG	ARC (HYPOTH)	Antinociceptive
	MSH, ACTH	MC_4	DH	ININ, DP	Pronociceptive
	MSH, ACTH	MC_1, MC_4?	PAG	ARC (HYPOTH)	Pronociceptive
Pre-pro-OFQ	OFQ, OFG	ORL_1	DH	ININ, DP?	Antinociceptive
	OFQ, $OFQ_{13–17}$	ORL_1, other	DH	ININ, DP?	Pronociceptive
	OFQ, OFG	ORL_1	Amygdala, RVM	Local	Antinociceptive
	OFQ	ORL_1	PAG, RVM	Local	Pronociceptive
	Nocistatin	?	DH	ININ, DP?	Antinociceptive (Blockade of OFQ)
	Nocistatin	?	PAG, RVM	Local	Antinociceptive (Blockade of OFQ)

The Table provides a summary of the principle pro and antinociceptive actions of various families of opioid peptide. The list is not exhaustive, e.g. many cerebral structures can sustain μ-opioid-elicited antinociception (see text for details). ENK, enkephalin; DYN, dynorphin; POMC, pro-opiomelanocortin; β-EP, β-endomorphin; MSH, melanocyte stimulating hormone; ACTH, adrenocorticotrophic hormone; OFQ, orphaninFQ; OFG, orphaninFG; MC, melanocortin; ORL, opioid receptor like; NMDA, *N*-methyl-D-aspartate; DH, dorsal horn; PAG, periaqueductal grey; ARC (HYPOTH), acuate nucleus of hypothalamus; RVM, rostroventral medulla; ININ, inhibitory interneurone; DP, descending pathway and PAF, primary afferent fibre.

β-EP, MCs and dynorphin (DYN). In addition, two more recently discovered endogenous opioids, endomorphins 1 and 2 (Section 9.3.4), are discussed (Zadina et al., 1997).

Like endomorphins, both β-EP and ENK exercise actions via μ-receptors. In addition, δ-opioid receptors intervene in the effects of ENKs and, possibly, β-EP. On the other hand, κ-opioid receptors mediate the actions of DYN and its relatives (Millan, 1990; Kieffer, 1995; Satoh and Minami, 1995; Dickenson and Besson, 1997; Zadina et al., 1997; Yaksh, 1999a). μ-, δ- and κ-opioid receptors display a homogeneous pattern of coupling to transduction mechanisms: all are negatively coupled to AC and enhance and suppress K^+- and Ca^{2+}-currents, respectively, actions responsible for their marked inhibitory influence upon neuronal excitability (Kieffer, 1995; Satoh and Minami, 1995; Connor and Christie, 1999; Yaksh, 1999a; Sanchez-Blazquez et al., 2001).

It should be briefly pointed out that, in the DH and elsewhere, there is evidence for colocalization of various classes of opioid receptor on single neurones (Kieffer, 1995; Coggeshall and Carlton, 1997). This is of pertinence to recent observations of functional interactions amongst opioid receptors, including the constitution of μ/δ and κ/δ heterodimers which present binding and coupling characteristics distinct from the equivalent monomers (Section 13) (Jordan and Devi, 1999; Georges et al., 2000; Bouvier, 2001; Marshall, 2001). It remains to be determined whether such complexes are of genuine physiological significance and whether they may account for certain reports of "subtypes" of μ-, δ- or κ-opioid receptor (Kieffer, 1999).

9.3.2. Enkephalin

ENKergic neurones resemble GABAergic ININs (Section 9.2) in exerting an important inhibitory role in many supraspinal circuits controlling the activity of descending pathways, in contributing to the expression of DI in the DH, and in their occurrence in descending pathways themselves (Table 3). The general significance of supraspinal and DH populations of ENK-containing neurones in the response to noxious stimuli and the mediation of antinociception has been widely discussed (Fields and Basbaum, 1978, 1994, 1999; Millan, 1982, 1986; Kaplan and Fields, 1991; Herz et al., 1993; Kieffer, 1995; Yaksh, 1999a) and does not require reiteration here.

However, it is important to accentuate that: (1) PAG populations of ENKergic neurones activate (via inhibition of GABAergic- or glycinergic-ININs) excitatory output to brainstem mechanisms eliciting DI and (2) ENKergic neurone in the brainstem (indirectly) enhance the activity of OFF cells, serotonergic, noradrenergic and other categories of descending pathway mediating antinociception (Dickenson et al., 1988; Fields et al., 1991; Williams et al., 1995; Millan, 1997; Pan et al., 1997; Fields and Basbaum, 1999; Hirakawa et al., 1999; Hurley and Hammond, 2001; Jeong et al., 2001b; Wu et al., 2001a,b).

As discussed earlier (Section 7.4.4.3), the involvement of segmental ENKergic ININs in transducing the influence of descending serotonergic (and other) mechanisms upon nociceptive processing should also be mentioned.

Finally, it is justified to emphasize the presence of ENK in various descending pathways targetting the DH, including VP/OT-containing fibres from the PVN (Section 8.2), noradrenergic neurones from the locus coeruleus (Section 5.2) and serotonergic tracts from the NRM (Section 7.1.2) (Menétrey and Basbaum, 1987; Todd and Spike, 1993; Proudfit and Yeomans, 1995; Millan, 1997). It is difficult to differentiate the role of ENK in descending pathways from the more substantial pool of ENK in ININs. Nevertheless, a component of spinal opioidergic antinociception may well reflect release of ENK from various classes of centrifugal pathway (Section 7.3.2).

9.3.3. Dynorphin: pro and antinociceptive actions

The 17 amino acid opioid peptide, DYN, is processed from pre-pro-DYN, and, together with several related peptides also derived from this precursor, principally interacts with κ-opioid receptors (Section 9.3.1). DYN is present in a substantial population of ININs in the DH, and it is also found in descending pathways (Khachaturian et al., 1985; Millan, 1986, 1990; Wu and Wessendorf, 1992; Vanderah et al., 1996b, 2001b; Hökfelt et al., 2000). Within the latter, DYN is partially co-localized with monoamines and additional sources of DYN input to the DH may be derived from the perifornical hypothalamus (Cechetto and Saper, 1988) and the PVN (Section 3.2.1). DYN may be distinguished from ENKs and β-EP in that: (1) it participates in both pro and antinociceptive processes at spinal and supraspinal loci and (2) it exerts its actions via opioid and non-opioid mechanisms.

In the spinal cord, upon exposure to both acute and chronic pain, actions of DYN at κ-receptors contribute to antinociceptive processes (Millan, 1986, 1990, 1993; Stiller and Schaible, 1993; Herrero and Cervero, 1996; Ossipov et al., 1996; Simonin et al., 1998; Hiramatsu et al., 2001; Wang et al., 2001c). However, DYN and metabolic fragments thereof also elicit pronociceptive actions in the DH (Dubner and Max, 1992; Vanderah et al., 1996b; Laughlin et al., 1997; Ruda et al., 1999, 2001a,b; Wang et al., (2001c) via mechanisms independent of κ- (and other classes of) opioid receptor. Enhanced nociception likely involves: (1) a facilitation in the activity of NMDA receptors resulting in an increase in NO synthesis and Ca^{2+}-levels by direct allosteric actions at glycine B or other modulatory sites (Lai et al., 1998; Millan, 1999; Tang et al., 1999; Laughlin et al., 2001); (2) an enhancement of glutamate and SP release from PAF terminals (Arcaya et al., 1999; Laughlin et al., 2001; Wang et al., 2001c); (3) a non-opioid, non-NMDA receptor mediated elevation in intracellular Ca^{2+}-levels (Tang et al., 2000); (4) recruitment of CCK (Rady et al., 1999) and/or (5) an interaction with glial cells (Laughlin et al., 2001; Liu et al., 2001c). These actions of DYN act oppositely to those mediated via κ-receptors in aggravating chronic painful states (Dubner and Ruda, 1992; Malan

et al., 2000; Vanderah et al., 2001b; Wang et al., 2001c) which are associated with an upregulation of DYN gene expression in the DH (Millan, 1986, 1990, 1993; Dubner and Ruda, 1992; Bian et al., 1999; Malan et al., 2000).

An increase in the spinal release of DYN may interfere with the supraspinal induction of DI by μ-opioids and account for paradoxical observations that opioids elicit DF and pain, most notably upon long-term treatment which is associated with "tolerance" to analgesic properties (Stillman et al., 1987; Mao et al., 1995; He and Lee, 1997; Larcher et al., 1998; Célérier et al., 2001; Vanderah et al., 2001a,b, 2000). As mentioned earlier, pronociceptive actions of DYN may be mediated by NMDA receptors (Section 10.2) which have similarly been implicated both in the pronociceptive actions of opioids and in the development of tolerance to their analgesic properties (Mao et al., 1995; Larcher et al., 1998; McNally, 1999; Yaksh, 1999a; Célérier et al., 2001; Vanderah et al., 2001b). A role of spinal pools of DYN in mediating the hyperalgesia elicited by stimulation of vagal afferents has also been postulated (Section 4.3) (Gebhart and Randich, 1992), similarly in line with the implication of spinal populations of NMDA receptors in the induction of DF (Sections 4.3 and 10.2). It is unclear whether DYN released from descending pathways or from ININs is implicated in these pronociceptive actions.

DYN is present in several supraspinal circuits which impinge upon and modulate descending pathways (Khachaturian et al., 1985; Millan, 1990). κ-Opioid receptor-mediated actions of DYN in the PAG and amygdala can, in analogy to β-EP and ENK (which act at μ- and δ-receptors) elicit antinociception via mechanisms of DI (Millan, 1986, 1990; Czlonkowski et al., 1987; Hiramatsu et al., 2001). In the RVM, activation of κ-receptors by DYN may also indirectly recruit serotonergic mechanisms of DI (Section 7.3.3) (Ackley et al., 2001). However, in this structure, DYN also acts via κ-receptors to directly interfere with the engagement of serotonergic pathways mediating DI by μ-opioids (Pan et al., 1997). DYN may, thus, be appended to the incremental list of transmitters, such as GABA and NT, which exert a bidirectional influence upon descending pathways via contrasting neuronal circuits (Table 3). There is currently no evidence for supraspinal, pronociceptive actions of DYN mediated independently of κ-opioid receptors.

To summarize, antinociceptive actions of DYN are expressed both supraspinally (reinforcement of DI) and spinally via κ-opioid receptors, whereas its pronociceptive actions (accentuation of DF) are exerted supraspinally via κ-opioid receptors, and spinally independently of opioidergic mechanisms. Amongst opioid peptides, then DYN plays a unique pattern of interaction with descending pathways mediating DI and DF.

9.3.4. Endomorphins

The tetrapeptides, endomorphins 1 and 2, both possess exceptionally high affinity and selectivity for μ-opioid receptors. They (fibre networks) display a preferential localization in several supraspinal regions such as the PBN, NTS, locus coeruleus, PAG and amygdala which play an important role in the modulation of descending controls though cell bodies have only, as yet, been detected in the hypothalamus and NTS (Goldberg et al., 1998; Martin-Schild et al., 1999; Horvath, 2000). Levels of endomorphin 2 are elevated in the PAG under conditions of neuropathic pain (Sun et al., 2001a). In the spinal cord, while endomorphin 1 is present in only modest amounts, there is an intense network of endomorphin 2 fibres in the DH, particularly in superficial laminae (Schreff et al., 1998; Martin-Schild et al., 1999). The prevalence of endomorphin$_2$ in these superficial layers reflects the provision of a substantial proportion from fine calibre nocisponsive PAFs (Pierce et al., 1998). In contrast to the PAG, a reduction in spinal cord levels of endomorphin 2 has been seen upon damage to PAFs, though any participation in the accompanying hyperalgesia remains to be demonstrated (Smith et al., 2001).

Not surprisingly, i.c.v. and i.t. administration of endomorphins elicits antinociception, primarily via μ-receptors. However, it has been suggested that they possess partial rather than full agonist properties at μ-sites in the PAG and DH and it is not, as yet, clear whether endomorphins 1 and 2 act via identical or distinctive mechanisms (Horvath, 2000; Mizoguchi et al., 2001; Ohsawa et al., 2001b; Wu et al., 2001b). Spinal release of DYN and ENKs, acting at κ- and δ-opioid receptors, respectively may also contribute to segmental (and supraspinal) antinociception elicited by endomorphin 2, though it is not obvious as to how it recruits (disinhibits) ENKergic and DYNergic ININs: perhaps, via inhibition of GABAergic ININs (Mizoguchi et al., 1999; Wu et al., 1999; Sakurada et al., 2000, 2001; Ohsawa et al., 2001a,b).

As yet, virtually no information is available concerning potential interactions of endomorphins with descending controls, with the exception of a report that its supraspinal antinociceptive actions are subject to inhibition by CCK (Section 9.5) (Kamei et al., 2001), and that α_2-AR antagonists attenuate induction of antinociception by the i.t. injection of endomorphin 1 (Hao et al., 2000). This question is of particular interest since spinal pools of endomorphins largely originate in PAFs, distinguishing them from all other opioid peptides in the DH.

9.3.5. β-endorphin and melanocortins

9.3.5.1. β-endorphin. Proteolytic cleavage of the precursor protein, POMC, yields the 31 amino acid peptide, β-EP, which is concentrated in cell bodies of the hypothalamic arcuate nucleus. These neurones provide an intense innervation of the PAG (Khachaturian et al., 1983, 1985; Millan, 1986; Mansour et al., 1995; Fields and Basbaum, 1999; Yaksh, 1999a). Activation of β-EP terminals in this structure plays a major role in the initiation of SPA and DI via the engagement of μ-opioid receptors (Basbaum and Fields, 1984; Millan, 1986; Millan et al., 1986, 1987a,b;

Bach and Yaksh, 1995; Fields and Basbaum, 1999; Wang et al., 2001b). β-EP-containing pathways projecting from the arcuate nucleus to the PAG also participate in the induction of antinociception by, for example, noxious and non-noxious stress (Millan, 1986, 1993; Rubistein et al., 1996) and moderate the nociception which accompanies tissue inflammation (Porro et al., 1988, 1999; Facchinetti et al., 1992; Siuciak et al., 1995; Zangen et al., 1998; Wu et al., 2001a). These roles of β-EP (Table 3) ressemble those of descending noradrenergic pathways (Section 5.4) which contribute to mechanisms of DI triggered by actions of β-EP in the PAG (Millan, 1997; Porro et al., 1999). The amygdala comprises a further locus for expression of analgesic actions of β-EP derived from the arcuate nucleus, probably via a PAG relay to the RVM (Section 3.3) (Pavlovic et al., 1996; Helmstetter et al., 1998).

An additional (minor) group of β-EP-containing cell bodies has been discovered in the NTS (Tsou et al., 1986; Bronstein et al., 1992). As mentioned in Section 3.2.3, the NTS projects directly to the spinal cord and β-endorphinergic neurones originating therein may also innervate the DH (Khachaturian et al., 1985; Tsou et al., 1986; Van der Kraan et al., 1999), although it has not been formally demonstrated that their activation contributes to the antinociception initiated upon stimulation of the NTS (Tsou et al., 1986; Aicher and Randich, 1990). Finally, a small cluster of β-EP-positive neurones is located within the DH itself (Khachaturian et al., 1985; Tsou et al., 1986; Gutstein et al., 1992; Van der Kraan et al., 1999), and a further, minor, population has been detected in DRG. Compared to local ENKergic ININs in the DH, virtually nothing is known of the functional role of these units, but they probably interact with descending pathways and fulfill an antinociceptive role via μ-opioid receptors.

9.3.5.2. Melanocortins: spinal and supraspinal pronociceptive actions. Post-translational processing of POMC generates several other biologically-active neuropeptides collectively termed MCs and including α-, β- and γ-melanocyte stimulating hormone, as well as adrenocorticotrophin releasing hormone (Mansour et al., 1985; Adan and Gispen, 1997, 2000; Wikberg, 1999). In contrast to μ-, δ- and κ-opioid receptors, all five subtypes of MC receptor couple positively to AC (Mountjoy et al., 1992; Kieffer, 1995; Adan and Gispen, 1997, 2000; Wikberg, 1999; Abdel-Malek, 2001). This observation hints at opposite and potentially interactive modulation of neuronal activity by MCs versus opioids. This contention is supported by functional studies which generally, though not invariably, reveal divergent actions of β-EP (and other opioid receptor agonists) as compared to ligands at MC receptors (Adan and Gispen, 1997, 2000; Huszar et al., 1997; René et al., 1998). The role of MCs in the modulation of nociceptive processing in the DH may emerge to be even more complex inasmuch as an endogenous antagonist (or inverse agonist) of MC_4 receptors has been discovered, Agouti-Related Protein. This is produced by a population of neurones independent from those generating POMC which track the distribution of the latter throughout the brain, including the PAG, PBN, PVN, NTS and locus coeruleus-though not, apparently, the spinal cord (Bagnol et al., 1999; Haskell-Luevano et al., 1999; Haskell-Luevano and Monck, 2001; Nijenhuis et al., 2001).

The following comments focus on MC_4 receptors, since they are enriched in cerebral regions involved in the modulation of nociceptive processing (see subsequent sections), and since they are the only type of MC receptor as yet to be found in the spinal cord. MC_4 receptors are concentrated in superficial layers and lamina X, as well as in deep laminae and the IML (Mountjoy et al., 1992, 1994; Van der Kraan et al., 1999; Vrinten et al., 2000). mRNA studies indicate expression of MC_4 sites by intrinsic DH neurones, rather than PAFs. As mentioned earlier (Section 9.3.5.1), there is evidence that POMC-derived peptides in the spinal cord are derived from intrinsic neurones, supraspinal sources (the arcuate nucleus and, perhaps, the NTS), while a small pool may also be transported into the DH from the DRG (Tsou et al., 1986; Bronstein et al., 1992; Gutstein et al., 1992; Cechetto and Saper, 1998; Van der Kraan et al., 1999). The contribution of various sources of MCs to actions at MC_4 receptors remains to be clarified. In any case, an early study of Belcher et al. (1982) indicated that adrenocorticotrophin releasing hormone attenuates spinal MIA, presumably via an action at MC_4 receptors in the DH. Further, in a model of PAF injury which is accompanied by an increase in the density of MC_4-receptors in the spinal cord, Vrinten et al. (2000, 2001) revealed that MC_4 agonists and antagonists respectively amplify and block allodynia upon their i.t. administration. This constitutes powerful evidence for pronociceptive actions of MC_4 receptors in the spinal cord: that is, in opposition to actions of β-EP and other opioid peptides. Obviously, one component of the facilitatory influence of MC_4 receptors upon nociceptive processing is expressed in the DH. In addition, an excitatory influence of MC_4 receptors upon preganglionic neurones in the IML may participate in their pronociceptive actions under conditions of PAF injury (Cechetto and Saper, 1988; Dunbar and Lu, 2000).

Intriguingly, MCs may not be the only pronociceptive peptide to be derived from POMC-containing neurones innervating the spinal cord. Thus, these neurones also generate a peptide named cocaine and amphetamine related transcript, administration of which into the spinal cord elicits hyperalgesia (Koylu et al., 1997; Kuhar and Dall Vechia, 1999; Ohsawa et al., 2000; Vrinten et al., 2000).

Functional interactions amongst various, functionally-heterogeneous POMC-derived peptides involved in the modulation of nociceptive processing are not confined to the DH. In this regard, older studies generally reported hyperalgesia and an attenuation of MIA upon i.c.v. or intra-PAG application of α-melanocyte stimulating hormone and adrenocorticotropin releasing hormone (Gispen et al., 1976; Walker et al., 1980; Sandman and Kastin, 1998; Smock and Fields, 1981; Contreras and Takemori, 1984). The high concentration of MC_4 receptors in the

PAG may well mediate these effects, but a role of MC_1 receptors cannot be excluded (Roselli-Rehfuss et al., 1993; Xia et al., 1995; Adan and Gispen, 1997, 2000; Wikberg, 1999). The observation that morphine down-regulates MC_4 receptor levels in the PAG further underlines the potential importance of interactions between μ-opioids and MC_4 receptors therein to the modulation of descending controls and nociceptive processing (Alvaro et al., 1996). Since MC_4 receptors in the brain are also enriched in the PVN, NTS, PBN and RVM, they are strategically located for the modulation of descending transmission (Mountjoy et al., 1994). As concerns a possible interaction of MCs with descending monoaminergic pathways, their presence in both the NRM and noradrenergic brainstem nuclei is also of note. Further, it has been shown that β-EP and MCs exert an opposite influence upon the activity of locus coeruleus neurones, an interaction likely involving MC_4 sites (René et al., 1998). It would be of interest to determine whether direct excitation of descending noradrenergic pathways and descending serotonergic pathways by MCs may elicit antinociception, in contrast to their pronociceptive actions mediated via spinal and PAG populations of MC_4 receptor.

Finally, antinociceptive effects of γ_2-melanocyte stimulating hormone were recently reported upon its i.c.v. administration, apparently independently of both MC and opioid receptors, and involving a GABAergic mechanism (Klusa et al., 2001).

9.3.5.3. Contrasting pro and antinociceptive roles of POMC-derived opioid peptides. The preceding observations add yet a further element of complexity to the spinal and supraspinal role of POMC-related peptides in the modulation of descending controls and nociceptive processing. It is probable that the coming years will witness further therapeutically-relevant insights into the varied role of POMC-derived peptides in the modulation of nociception. What is already manifestly clear is that, like noradrenergic and serotonergic pathways to the spinal cord, it is simplistic to consider opioidergic neurons (descending pathways and intrinsic DH neurones) as fulfilling a purely antinociceptive role (Table 3). DYN exerts both pro and antinociceptive properties, while the antinociceptive actions of β-EP are opposed by pronociceptive actions of several co-released, peptides, notably MCs. As discussed in the following section, a final member of the opioid peptide family, nociceptin, also appears to express both pro and antinociceptive properties.

9.3.6. OrphaninFQ (nociceptin)

9.3.6.1. Receptor coupling and localization of orphaninFQ. The 17 amino acid, "orphan" opioid, orphaninFQ (OFQ) or nociceptin is proteolytically cleaved from a pre-pro-OFQ precursor. It expresses its actions via a opioid-receptor-like-1 (ORL_1) receptor, also called, in accordance with recent nomenclature, the "NOP" receptor (Henderson and McKnight, 1997; Civelli et al., 1998; Darland et al., 1998; Yamamoto et al., 1999; Calo et al., 2000; Grisel and Mogil, 2000; Mogil and Pasternak, 2001). These sites, though inaccessible to opioid peptides and the "universal" opioid antagonist, naloxone, show marked homology to multiple (μ, δ and κ) opioid receptors. They also share their major mode of signal transduction: inhibition and potentiation of Ca^{2+}- and K^+-currents, respectively, and inhibition of AC (Meunier et al., 1995; Meunier, 1997; Calo et al., 2000; Borgland et al., 2001). Further, like opioid peptides and μ-, δ- and κ-opioid receptors (Mansour et al., 1995), OFQ and ORL_1 receptors are broadly distributed in CNS structures involved in the processing of nociception (Riedl et al., 1996; Neal et al., 1999a,b; Slowe et al., 2001). However, OFQ fulfills a role distinctive to and independent of the actions of ENK, DYN, β-EP and endomorphins (Monteillet-Agius et al., 1998; Köster et al., 1999; Neal et al., 1999a,b; Calo et al., 2000; Grisel and Mogil, 2000; Houtany et al., 2000; Mogil and Pasternak, 2001).

9.3.6.2. Spinal actions of OFQ. OFQ is highly expressed by ININs in the DH, principally in laminae II and X, although a few deep laminae III/VI also display mRNA encoding OFQ. Likewise, OFQ-containing fibres are enriched in superficial laminae and lamina X, with less intense networks of fibres in deeper laminae of the DH. PAFs provide little OFQ to the DH, as judged by their low expression of mRNA encoding OFQ (Riedl et al., 1996; Neal et al., 1999a,b) though their central terminals, like intrinsic DH neurones (most clearly in lamina II), bear ORL_1 receptors (Neal et al., 1999a,b; Xie et al., 1999a; Calo et al., 2000). The high density of OFQ-positive fibres and ORL_1 receptors in the IML (preganglionic sympathetic nucleus) and ventral horn should be also noted. While the issue does not appear to have been investigated, it is possible that OFQ is provided to the DH by descending pathways. Thus, numerous structures which monosynaptically project to the DH (Sections 3.2.1, 3.2.3, 3.2.4, 5.2 and 7.1.1) possess high levels of mRNA encoding OFQ: the PVN, the NTS, the RVM and both the NRM as well as A_5 and A_6 (locus coeruleus) cell clusters. The potential colocalization of OFQ with 5-HT and/or with NA would be of interest to evaluate (Neal et al., 1999a,b).

Several studies have indicated pronociceptive actions of OFQ (at low doses) in the DH, possibly reflecting an interaction with: (1) SP and glutamate released from PAFs; (2) prostaglandins and/or (3) glycinergic ININs (Minami et al., 1997; Inoue et al., 1999; Calo et al., 2000; Zeilhofer et al., 2000; Ruscheweyh and Sandkühler, 2001). However, the precise mechanistic bases for these effects remain unclear and most behavioural work supports an antinociceptive role of (high doses of) OFQ in the DH, expressed against both inflammatory and neuropathic pain, and in synergy with μ-opioids (Stanfa et al., 1996; Inoue et al., 1999; Yamamoto et al., 1999, 2000, 2001; Calo et al., 2000; Carpenter et al., 2000; Corradini et al., 2001; Lu et al., 2001; Mogil and Pasternak, 2001; Ruscheweyh and Sandkühler, 2001). This conjecture is underpinned by studies showing that OFQ

inhibits the excitation of laminae II neurones elicited by nociceptive input from PAFs, probably by a pre-synaptic reduction of the release of glutamate, in line with the inhibitory and facilitatory influence of ORL_1 receptors upon Ca^{2+}- and K^+-currents, respectively (Stanfa and Dickenson, 1994; Borgland et al., 2001; Zeilhofer et al., 2000; Ahmadi et al., 2001). Post-synaptic inhibition of PNs may also participate in the antinociceptive properties of OFQ (Wang et al., 1999b). Though modulation of DYN release has been implicated in the spinal actions of OFQ, it is not clear how this is brought about (Gupta et al., 2001). These findings strongly suggest a role of DH-localized pools of OFQ in the expression of DI, a hypothesis requiring direct experimental evaluation. With respect to the contrasting pro and antinociceptive actions of OFQ at the segmental level, it has been suggested that, in addition to dose-dependent effects, gender and hormonal factors may play a role in determining its influence upon nociception (Flores et al., 2001; Gupta et al., 2001; Mogil and Pasternak, 2001).

9.3.6.3. Supraspinal actions of OFQ. At the suprapinal level, the actions of OFQ are different to the DH inasmuch as it exerts a broad and generalized inhibitory influence upon antinociceptive processes, including diverse mechanisms of DI and their inception (Henderson and McKnight, 1997; Civelli et al., 1998; Darland et al., 1998; Yamamoto et al., 1999; Calo et al., 2000; Grisel and Mogil, 2000; Mogil and Pasternak, 2001). Such pronociceptive actions of OFQ are revealed in its suppression of (opioid and non-opioid) stress-induced antinociception and of the analgesia elicited via various classes of opioid receptor: these actions are expressed at sites both in the RVM and in the PAG (Heinricher et al., 1997; Morgan et al., 1997; King et al., 1998; Yaun et al., 1999; Grisel and Mogil, 2000; Letchworth et al., 2000; Bytner et al., 2001; Di Giannuario et al., 2001; Kest et al., 2001; Rizzi et al., 2000, 2001; Yang et al., 2001c,d). In the latter structure, PAG injury triggers an increase in levels of OFQ (Sun et al., 2001a). Pronociceptive actions of OFQ are abrogated in knock-out mice lacking ORL_1 receptors and they are also blocked by antisense probes and selective antagonists directed against ORL_1 sites, agents which themselves elicit antinociception and enhance supraspinal MIA (Noda et al., 1998; Calo et al., 2000; Canaletti and Ferri, 2000; Bytner et al., 2001; Di Giannuario et al., 2001; Mogil and Pasternak, 2001; Rizzi et al., 2001).

Inasmuch as OFQ mimicks the inhibitory influence of morphine upon neuronal firing, its attenuation of MIA is unlikely to be mediated by cells expressing both ORL_1 and μ-opioid receptors, an argument underscored by anatomical studies (Heinricher et al., 1997; Monteillet-Agius et al., 1998; Calo et al., 2000; Slowe et al., 2001). There are several, possible explanations for its pronociceptive actions: (1) OFQ prevents the opioid-induced increase in PAG output which triggers DI from brainstem nuclei; (2) ORL_1 receptors are found on serotonergic and noradrenergic nuclei of the brainstem. Thus, OFQ may directly inhibit noradrenergic and serotonergic mechanisms of DI. Studies of NA and 5-HT release in forebrain structures provide functional support for such an inhibitory influence of OFQ upon noradrenergic and serotonergic transmission, although the influence of supraspinal pools of OFQ upon the spinal release of NA and 5-HT has not, as yet, been reported (Sbrenna et al., 2000; Schlicker and Movari, 2000) and (3) in line with the latter comments, OFQ directly inhibits those primary (serotonergic) and OFF cells in the RVM which are (indirectly) excited by opioids and mediate DI (Sections 7.3.2) (Heinricher et al., 1997; Pan et al., 2000; Mogil and Pasternak, 2001; Vaughan et al., 2001; Yang et al., 2001c,d).

Recently, Rady et al. (2001) provided a possible basis for the inhibition of spinal μ-opioid antinociception by supraspinal OFQ. They proposed that supraspinal actions of OFQ activate a mechanism of DF which releases or recruits pronociceptive, spinal pools of PGE_2 and EP_1 receptors (Millan, 1999).

These have been a few reports that, under certain conditions, OFQ can actually elicit antinociception by supraspinal actions (Yamamoto et al., 1999, 2001; Calo et al., 2000; Yang et al., 2001c,d). Indeed, providing a further example of a transmitter capable of exerting a bidirectional influence upon nociceptive processing by actions in the RVM, Pan et al. (2000) suggested that an inhibitory influence of OFQ upon secondary (GABAergic) cells may elicit antinociception upon discontinuation of chronic exposure to μ-opioid agonists, while (Vaughan et al., 2001) recently showed that OFQ reduces GABA release in the RVM via a pre-synaptic mechanism. Furthermore, in analogy to μ- and κ-opioid receptor agonists, microinjection of OFQ into the amygdala elicits antinociception via a PAG link to mechanisms of DI integrated in the brainstem (Shane et al., 2001; Sun et al., 2001b).

9.3.6.4. Nocistatin. In addition to actions of OFQ at ORL_1 receptors, it has been hypothesized that, via an independent mechanism possibly involving SP release, its C-terminal (13–17) fragment may enhance spinal nociception (Inoue et al., 2001). Moreover, the precursor protein which gives rise to OFQ incorporates several pairs of basic amino acids, processing of which can yield two further peptides known to modify nociception (Nothacker et al., 1996): (1) OrphaninFQ2, a 17 amino acid sequence downstream from OFQ which elicited antinociception both spinally and supraspinally in a study by (Rossi et al., 1998) though these findings require corroboration (Mogil and Pasternak, 2001) and (2) the 30 amino acid peptide, nocistatin (NST). The latter does not recognize ORL_1 receptors and acts via its own site, the relationship of which to ORL_1 receptors remains under investigation (Okuda-Ashitaka et al., 1998; Hiramatsu and Inoue, 1999; Nakano et al., 2000; Okuda-Ashitaka and Ito, 2000; Zeilhofer et al., 2000; Ahmadi et al., 2001; Sun et al., 2001b). NST can attenuate several, pronociceptive actions of OFQ, including: (1) induction of hyperalgesia and allodynia; (2) attenuation of MIA; (3) aggravation of

inflammatory pain by i.t. application of low doses of OFQ (Minami et al., 1998; Zhao et al., 1999a; Okuda-Ashitaka et al., 1998; Nakano et al., 2000; Okuda-Ashitaka and Ito, 2000) and (4) at least supraspinally, modulation of glutamate currents (Nicol et al., 1998). Further, antibodies neutralizing NST potentiate OFQ-induced allodynia, while NST itself elicits antinociception against inflammatory pain by a spinal action (Yamamoto et al., 1999; Nakano et al., 2000). Despite this coherent pattern of data suggesting that NST blocks the hyperalgesic actions of OFQ, the underlying mechanisms remain to be elucidated. Further, in distinction to the above-mentioned observation that NST interferes with the spinal, pronociceptive actions of low doses of OFQ, the analgesic actions effects of higher doses of OFQ are not susceptible to blockade by NST (Nakano et al., 2000; Okuda-Ashitaka and Ito, 2000; Zeilhofer et al., 2000). Moreover, NST was reported to itself increase nociception by pre-synaptic suppression of GABA and glycine release from ININs in the DH (Xu et al., 1999a; Zeilhofer et al., 2000). Providing additional support of contrasting roles of NST as compared to OFQ in the modulation of nociceptive processing, i.c.v. administration of NST suppressed inflammatory hyperalgesia whereas pronociceptive actions of OFQ were observed under these conditions (Nakagawa et al., 1999; Calo et al., 2000).

9.3.7. Complex pro and antinociceptive roles of opioid peptides

Thus, much remains to be learned of the precise roles of, and interrelationship between, NST and OFQ in the control of nociceptive processing at spinal and supraspinal sites (Table 3). In any case, the essentially pronociceptive actions of OFQ/ORL_1 receptors at the supraspinal level are diametrically opposed to the essentially antinociceptive actions of opioid peptides mediated via μ-, δ- and κ-opioid receptors. Moreover, the (generally) opposite and interactive influence of OFQ and NST, which are derived from the same precursor protein, upon nociception mimics the differential roles of β-EP versus MCs, both of which are derived from POMC. These observations underline the notion that the pivotal role of opioidergic networks in the modulation of descending controls and nociceptive processing is far more complex than imagined only a few years ago (Table 3).

9.4. NeuropeptideFF and other FMRFamide-related peptides

9.4.1. Localization of neuropeptideFF-like peptides

In analogy to OFQ, various peptides (including the octapeptides, neuropeptideFF (NPFF) and the 18 amino acid "NPAF") related to the molluscan, cardioexcitatory peptide, "FMRFamide", modulate nociception: they exert antinociceptive versus pronociceptive/anti-opioid actions at segmental versus supraspinal sites, respectively (Panula et al., 1996, 1999; Roumy and Zajac, 1998). Further, like OFQ, their actions appear to be expressed in interaction with descending controls.

Studies of mRNA encoding the precursor for NPFF, and of NPFF-like immunoreactivity, demonstrated two major groups of supraspinal neurone which synthesize NPFF-like peptides: (1) in the ventromedial and dorsomedial hypothalamus and (2) in the NTS (Kivipelto et al., 1989; Lee et al., 1993; Cesselin, 1995; Panula et al., 1996, 1999; Vilim et al., 1999). The former provides an intense input to the PAG, and also projects to the NTS and amygdala (Aarnisalo and Panula, 1995; Panula et al., 1996, 1999; Vilim et al., 1999). The NTS itself was shown to provide NPFF-positive fibres to the PBN and to the RVM (Aarnisalo and Panula, 1995; Panula et al., 1999). Although there is currently no direct evidence that the hypothalamus and NTS provide NPFF and related peptides to the DH, NPFF-like peptides were observed in a subset of noradrenergic pathways innervating the spinal cord. In addition, the PVN and the supraoptic nucleus are potential sources of NPFF-like peptide containing neurones projecting to the dorsal horn (Liu et al., 2001b). There may, then be a modest cerebral contribution to the high density of NPFF-expressing neurones in the superficial DH (Ferrarese et al., 1986; Kivipelto and Panula, 1991a,b; Kivipelto et al., 1992; Aarnisalo and Panula, 1995; Panula et al., 1999) for which the predominant source is intrinsic neurones. A few PAFs synthesizing NPFF also occur in the DRG (Allard et al., 1999). There is an abundance of NPFF-immunoreactive fibres in the superficial DH, and fibres are also present in deeper laminae, lamina X, sympathetic/parasympathetic nuclei and the VH (Allard et al., 1991; Panula et al., 1996; Roumy and Zajac, 1998; Vilim et al., 1999). NPFF binding sites are concentrated in superficial layers and lamina X, although they are also present more deeply. A subpopulation appears to be localized on PAF terminals (Dupouy and Zajac, 1995; Gouardères et al., 1997; Roumy and Zajac, 1998; Panula et al., 1999; Bonini et al., 2000; Kotani et al., 2001; Liu et al., 2001b).

9.4.2. Spinal, antinociceptive actions of NPFF

Peripheral inflammation leads to an elevation in the levels and gene expression of NPFF in the DH. This change is associated with a potentiation in the antinociception elicited by electrical stimulation of the RVM, an observation interpreted as reflecting an enhanced contribution of spinal pools of NPFF to DI (Kontinen et al., 1997; Pertovaara et al., 1998; Vilim et al., 1999). Although PAF injury does not, in distinction, elevate levels of NPFF in the DH, i.t. administration of NPFF (and stabilized analogues) inhibits neuropathic hyperalgesia and allodynia, actions involving recruitment of local opioid receptors and expressed super-additively with morphine (Kontinen and Kalso, 1995; Gouardères et al., 1996; Courteix et al., 1999; Panula et al., 1999; Vilim et al., 1999; Xu et al., 1999c; Wei et al., 2001b). These findings are consistent with observations obtained under other conditions that i.t. administration of NPFF elicits antinociception alone and-in general-potentiates the spinal analgesic actions of opioids. The antinociceptive properties of NPFF may represent either: (1) an indirect opioidergic

mechanism involving recruitment of ENK and δ-opioids receptors or (2) synergistic, cellular actions of NPFF shared with opioids, such as an inhibitory influence upon AC, or upon Ca^{2+}-currents in PAF terminals (Gouardères et al., 1993, 1996; Roumy and Zajac, 1996; Ballet et al., 1999; Panula et al., 1999). However, transduction mechanisms underlying actions of NPFF in the CNS remain under discussion (Section 9.4.4). Interestingly, morphine has been shown to release NPFF in the spinal cord (Devillers et al., 1995) suggesting a reciprocal influence of μ-opioid receptors upon NPFF-containing neurones. The influence of NPFF upon spinal antinociceptive actions of α_2-AR agonists currently remains indeterminate with contradictory reports of either attenuation or potentiation (Kontinen and Kalso, 1995; Roumy and Zajac, 1998; Panula et al., 1999).

9.4.3. Supraspinal, pronociceptive actions of NPFF-like peptides

At the supraspinal level, in accordance with their reputation as anti-opioid peptides, NPFF and related peptides attenuate antinociceptive actions of morphine, as well as the antinociception elicited by stress which likely involves an opioidergic component: in distinction, antibodies generated against NPFF-like sequences potentiate the analgesic actions of opioids (Kavaliers, 1990; Oberling et al., 1993; Altier and Stewart, 1997; Roumy and Zajac, 1998; Panula et al., 1999; Liu et al., 2001b). Such actions are expressed not only upon i.c.v. administration but also upon introduction of peptides into several discrete regions, including the ventrotegmental area, the parafasicular thalamus and the dorsal raphe nucleus. In line with a role of the latter structure, the inhibition of opioidergic antinociception by NPFF may reflect modulation of serotonergic transmission (Dupouy and Zajac, 1997; Roumy and Zajac, 1998), although the mechanisms involved are less well characterized than equivalent actions of OFQ (Section 9.3). Complicating interpretation of these data, there are indications that NPFF itself can elicit analgesia via actions exerted independently of opioidergic networks, and likewise involving the dorsal raphe nucleus and serotonergic mechanisms (Oberling et al., 1993; Roumy and Zajac, 1998; Wei et al., 1998, 2001b; Panula et al., 1999; Pertovaara et al., 2001; Liu et al., 2001b).

9.4.4. Receptorial mechanisms involved in the actions of NPFF-like peptides

Although NPFF and other FMRF-amide-related peptides clearly play an important role in the modulation of nociception, interacting with descending pathways at both segmental and cerebral loci, there remain many questions, in particular as concerns: (1) the precise roles of individual peptides, and structure–activity relationships for expression of their actions; (2) cellular transduction mechanisms modulating nociception and (3) neuronal pathways mediating their actions. Resolution of such issues will be facilitated by the recent cloning of two receptors for NPFF: FF_1 and FF_2. Althought it appears that both are inhibitory to AC and that, when appropriate G proteins are variable, they can modulate $[Ca^{2+}]$ levels, coupling mechanisms remain under exploration (Roumy and Zajac, 1996; Bonini et al., 2000; Elahourbagy et al., 2000; Hinuma et al., 2000; Kotani et al., 2001; Liu et al., 2001b; Mazarguil et al., 2001; Zajac, 2001). The preponderance of FF_2 receptors in DRG, spinal cord and trigeminal medulla—as well as in the thalamus and NTS of the rat—suggest a prominent role in the earlier-discussed segmental modulation of nociception (Roumy and Zajac, 1996; Bonini et al., 2000; Kotani et al., 2001; Liu et al., 2001b). However, there are preliminary data indicating that in human spinal cord, mRNA encoding FF_1 sites is more abundant than mRNA for FF_2 sites, underscoring the potential importance of species differences (Bonini et al., 2000). In distinction to FF_2 sites, FF_1 receptors appear to be enriched in the hypothalamus, amygdala, PAG, monoaminergic nuclei of the medulla and the dorsomedial/ventromedial hypothalamus: the latter location suggests that they might act as autoreceptors (Bonini et al., 2000; Liu et al., 2001b).

In addition to NPFF and related sequences derived from a common precursor, novel peptides cleaved from a "second" precursor have recently been recently cloned (Panula et al., 1999; Bonini et al., 2000; Elahourbagy et al., 2000; Hinuma et al., 2000; Bonnard et al., 2001; Liu et al., 2001b; Ukena and Tsutsui, 2001; Zajac, 2001). The distribution of the octopeptide, NPVF (FRP-3), derived from this novel gene was recently compared to that of NPFF itself (Hinuma et al., 2000; Liu et al., 2001b). Interestingly, NPFF is primarily expressed in the PVN and supraoptic nucleus of the hypothalamus, NTS and superficial DH (Vilim et al., 1999; Liu et al., 2001b). NPVF was confined to the ventromedial/dorsomedial hypothalamus. Since its projection targets (PAG, NTS and amygdala) contain FF_1 sites which are more sensitive to NPVF and NPFF, it may be deduced that actions of NPVF at cerebral FF_1 sites inhibit MIA. In addition, NPVF/FF_1 receptors in limbic structures may well be involved in the affective dimension of pain. On the other hand, actions of NPFF at spinal FF_2 sites elicit antinociception.

The availability of cloned receptors should accelerate identification of selective, non-peptidergic ligands at FF_1 and FF_2 receptors, the use of which will permit improved comprehension of the complex role of NPFF and related peptides in the modulation of nociception.

9.5. Choleckystokinin

9.5.1. Receptor coupling and localization of CCK

A further neuropeptide which plays an important role in the spinal and supraspinal control of nociception and which interacts both with descending controls and with opioids, is the sulphated octapeptide, CCK (Crawley and Corwin, 1994; Han, 1995; Benedetti, 1997). However, in contrast to OFQ (Section 9.3.6) and NPFF (Section 9.4), which primarily exert their anti-opioid actions in supraspinal structures, CCK exerts a more generalized, pronociceptive, anti-opioid role at

all levels of the neuroaxis (Wiertelak et al., 1992; Cesselin, 1995; Dickenson, 1997; Benedetti, 1997).

Two classes of receptor mediate the actions of CCK: CCK_1 (CCK_A) receptors are positively coupled via Gq/11 to the activation of PLC, AC and Phospholipase A_2, while CCK_2 receptors are likewise positively coupled to PLC and Phospholipase A_2 via Gq/11 (Han, 1995; Wang et al., 1995; Benedetti, 1997; Noble and Roques, 1999; Pommier et al., 1999).

Under "normal" circumstances, the extensive arborization of CCK-positive fibres in the DH is derived principally from intrinsic neurones (mostly in laminae II/III), together with a modest contribution from descending pathways, including cell bodies localized in the RVM and the PAG-in the latter case, colocalized with SP (Skirboll et al., 1983; Maciewicz et al., 1984; Mantyh and Hunt, 1984; Todd and Spike, 1993; Benedetti, 1997; Dickenson, 1997; Noble and Roques, 1999). However, as outlined in the following sections, under conditions of PAF injury, there is a marked induction of mRNA encoding CCK in PAFs which deliver CCK to the DH via their central terminals (Hökfelt et al., 1994; Antunes-Bras et al., 1999; Millan, 1999).

CCK displays a pattern of distribution in nervous tissue remarkably similar to that of opioid peptides and, at all levels of the neuroaxis, from the periphery via the DH to supraspinal centres, principally via engagement of CCK_2 receptors, CCK counters the antinociceptive properties of μ-opioid receptor agonists in rodents (Crawley and Corwin, 1994; Han, 1995; Skinner et al., 1997; Noble and Roques, 1999). The anti-analgesic actions of CCK are exerted under a diversity of conditions, including neuropathic pain, inflammatory pain and stress (Wiertelak et al., 1992, 1997; Benedetti, 1997; Benedetti and Amanzio, 1997; Perrot et al., 1998; Schäfer et al., 1998; Millan, 1999; McNally, 1999; Noble and Roques, 1999; Kovelowski et al., 2000). Blockade of the actions of CCK potentiates the acute antinociceptive properties of morphine, and may also retard the development of tolerance upon its repeated administration (McNally, 1999).

9.5.2. Spinal, pronociceptive actions of CCK

Of particular pertinence to the present article are actions of CCK expressed in the DH and brainstem in interaction with descending controls. Following PAF injury, there is a pronounced elevation in levels of mRNA encoding in the DRG, suggesting that actions of CCK derived from damaged PAFs may interfere with DH-integrated, opioidergic mechanisms of antinociception under conditions of neuropathic pain (Hökfelt et al., 1994; Suh et al., 1996a; Vanderah et al., 1994, 1996a; Antunes-Bras et al., 1999; Millan, 1999; Noble and Roques, 1999; Kamei and Zushida, 2001). Indeed, μ-opioids such as morphine are relatively inefficacious in treating the mechanical allodynia which typifies neuropathic painful states (Section 2.2). Nevertheless, evidence for an elevation in the central release of CCK remains inconsistent (Gustafsson et al., 1998; Xu et al., 2001a).

Consistent with a role in the expression of DF, pronociceptive (anti-analgesic) actions of CCK in the DH have been revealed under a broad range of conditions: illness, PAF injury and inflammation, in interaction with μ- and δ-opioids, enkephalinases and GABAergic agonists, in response to spinal administration of DYN and supraspinal application of NT (Faris et al., 1983; Wiertelak et al., 1992; Ossipov et al., 1994; Valverde et al., 1994; Vanderah et al., 1994; Nichols et al., 1995; Yamamoto and Nozaki-Taguchi, 1996; Urban et al., 1996a,b; Dickenson, 1997; Idänpään-Heikkilä et al., 1997; Holmes et al., 1999; McNally, 1999; Rady et al., 1999; Rezayat et al., 1999). Currently, the relative contributions of CCK derived from descending pathways as compared to intrinsic neurones and—following their injury—PAFs to pronociceptive actions is unclear. Further, the circuitry underlying anti-analgesic effects of CCK in the DH also remains be clarified: actions at PNs (and EX-INs) bearing both CCK_2 and μ-opioid receptors may be of greater importance than modulation by CCK of release from nocisponsive PAFs, though it should be noted that PAF injury up-regulates CCK_2 receptors in the DRG (McNally, 1999; Urban et al., 1996a,b).

Interference with the actions of opioids reflects the opposite influence of excitatory CCK_2 and inhibitory μ-opioid receptors upon Ca^{2+}-currents and intracellular Ca^{2+} concentrations. More specifically, CCK may incapacitate μ-opioid receptors by triggering their phosphorylation via the induction of PLC and protein kinase C (Schäfer et al., 1998; McNally, 1999; Millan, 1999). This process would offer an intriguing analogy to the phosphorylation (inactivation) of GABAergic and glycine receptors on PNs upon induction of PLC and AC by excitatory transmitters released from PAFs or descending pathways (Sections 9.2 and 10.1). Although opioids modulate the segmental release of CCK, their precise influence remains unclear: recent studies indicated a facilitation mediated by δ-opioid receptors (Benoliel et al., 1994; Gustafsson et al., 2001).

It has been reported that, in contrast to opioids, CCK does not modify the spinal antinociception elicted by α_2-AR agonists (Zhou et al., 1993a; Sullivan et al., 1994; Han, 1995; Gustafsson et al., 1999).

9.5.3. Supraspinal, pronociceptive actions of CCK

The overlapping distribution of ENK- and CCK-containing neurones in the PAG, RVM and other cerebral structures provides a potential substrate for analogous, pronociceptive actions of CCK at the supraspinal level, including interference with the initation of DI by opioids (Noble et al., 1993; Vanderah et al., 1994; Skinner et al., 1997; Wiesenfeld-Hallin et al., 1999; Lapeyre et al., 2001). Indeed, i.c.v. administration of CCK attenuates the antinociceptive effects of stress and of microinjection of μ-opioids into the RVM (Suh et al., 1996a; Wiesenfeld-Hallin et al., 1999). Indicative of the activation of medullary pools of CCK by PAF injury, application of CCK_2 antagonists into the RVM reverses the accompanying allodynia and restores

the blunted antinociceptive effect of PAG administration of morphine, while i.c.v. administration of CCK reduces the analgesic actions of centrally-administered μ-opioids in a further model of neuropathic pain, diabetic mice (Wiesenfeld-Hallin et al., 1999; Kovelowski et al., 2000; Kamei et al., 2001; Kamei and Zushida, 2001). Heinricher et al. (2001a) have postulated that CCK prevents the activation of RVM-localized OFF cells (Section 3.2.4) by morphine, possibly via a pre-synaptic mechanism since CCK does not itself alter their activity.

9.5.4. Clinical studies

These observations provide a compelling body of data for a generalized pronociceptive (anti-analgesic) role of CCK expressed in particular: (1) under conditions of neuropathic pain and in interaction with opioids; (2) via CCK_2 receptors at both spinal and supraspinal loci and (3) in interaction with descending pathways. As such, these data underscore arguments advanced earlier (Sections 4.3 and 4.4) that mechanisms of DF involving CCK contribute to the induction and maintenance of chronic painful states due to tissue or PAF injury. Blockade of CCK_2 receptors would appear to be an appealing target for the interruption of DF and alleviation of pain, at least in association with opioids. Clinical studies have, indeed, shown that the non-selective $CCK_{1/2}$ antagonist, proglumide, enhances the analgesic actions of morphine in patients (Price et al., 1985; Lavigne et al., 1989). Further, placebo analgesia, which involves an opioidergic component, is likewise enhanced by proglumide (Benedetti, 1996, 1997).

Nevertheless, while the majority of studies have focussed on a role of CCK_2 receptors, the role of CCK_1 sites in the modulation of nociception is unclear (Noble et al., 1993; Cesselin, 1995; Benedetti, 1997; Noble and Roques, 1999; McNally, 1999). This is of importance since neuroanatomical studies indicate that CCK_1 receptors may predominate over their CCK_2 counterparts in the spinal cord of man (Han, 1995; Benedetti, 1997; Hill et al., 1988). Finally, dependent upon the dose administered, certain studies have documented antinociceptive actions of CCK in the DH, albeit mediated via an as yet unelucidated mechanism (Han, 1995; Dickenson, 1997; McNally, 1999).

9.6. Neurotensin

In contrast to CCK, participation of the tridecapeptide, NT, in pronociceptive mechanisms involving DF appears to be restricted to supraspinal structures and, specifically, the RVM, a region receiving NT-containing afferents from the PAG and several other brain regions (Table 3) (Beitz, 1982b; Beitz et al., 1983, 1987; Wang et al., 1995; Urban et al., 1996a,b; Watkins et al., 1998). Exemplifying the complexity of descending controls and of difficulties confronted in their exploration-NT can engage pathways of both DI and DF in the RVM dependent upon the dose administered supraspinally (Fang et al., 1987; Behbehani, 1992a; Urban and Smith, 1993; Urban et al., 1996a,b; Smith et al., 1997; Garzon et al., 1999; Urban and Gebhart, 1999). These actions are, not unsurprisingly, mediated by anatomically-distinct pathways which recruit contrasting mechanisms in the DH: probably cholinergic and noradrenergic for DI, whereas mechanisms mediating DF probably involve a role of CCK (Urban and Smith, 1993; Urban et al., 1996a,b; Holmes et al., 1999; Urban and Gebhart, 1999). In line with a pronociceptive role of NT, its application into the RVM attenuates opioidergic antinociception elicited from the PAG, while inactivation of RVM-localized NT receptors with specific antagonists attenuates the hyperalgesia associated with peripheral inflammation (Urban et al., 1996a, 1999a,b), a stimulus which enhances gene expression and release of NT in the PAG (Williams and Beitz, 1993; Williams et al., 1995). PAF injury likewise enhances NT gene expression in the PAG, although it is not established whether NT-engaged mechanisms of DF contribute to the hyperalgesia and allodynia associated with PAF damage (Williams et al., 1995). In any case, these observations underpin remarks made earlier concerning the deleterious role of DF in the maintenence of long-term, clinical painful states (Section 4.4). Interestingly, within the PAG itself, administration of NT elicits antinociception (Behbehani, 1992b).

Currently, 3 subtypes of Gq/11-coupled NT receptor have been cloned (Vincent et al., 1999). NT_1 sites couple strongly and positively to PLC and AC, NT_2 sites show less pronounced activation of PLC while transduction mechanisms for NT_3 receptors remain unclear (Vincent et al., 1999). The NT_2 site may be the most important for the mediation of supraspinal antinociception. Although the identity of the subtype with acts pronociceptively does not appear to have been definitively established, NT_1 sites may be implicated (Dubuc et al., 1994, 1999; Gully et al., 1997; Smith et al., 1997; Urban et al., 1999a,c; Urban and Gebhart, 1999; Vincent et al., 1999).

In the spinal cord, NT is principally derived from intrinsic neurones, and receptors are localized both on PAF terminals and on intrinsic DH neurones. Following, PAF injury, levels of NT in the DH, and the density of NT receptors in the DRG are down-regulated, possibly contributing to the accompanying nociception (Zhang et al., 1995a; Xu et al., 2001c). NT mediates antinociception at the spinal level via actions both at intrinsic DH neurones (ININs) and upon PAF terminals (Yaksh et al., 1982). It is not clear how excitatory NT receptors (vide supra) reduce release from nocisponsive PAFs. It is also currently unclear whether spinal populations of NT receptors are recruited by mechanisms of DI.

9.7. Galanin

9.7.1. Receptor coupling and localization of GAL

The 29 amino acid neuropeptide, GAL, exerts its actions via at least three (GAL_1, GAL_2 and GAL_3) receptors, of which GAL_1 and GAL_3 receptors are negatively coupled

to AC, while GAL_2 receptors are positively coupled to PLC (Branchek et al., 2000; Wynick et al., 2001). GAL exerts, thus, like numerous transmitters discussed herein, contrasting actions via excitatory and inhibitory subtypes of receptor. This, at least partially, accounts for the exceptionally-complex and varied role of GAL in the modulation of nociception at both spinal and supraspinal levels of the neuroaxis as a function of the "normal" state, PAF injury or peripheral inflammation (Table 3) (Hökfelt et al., 1994; Hua et al., 1998; Millan, 1999; Branchek et al., 2000; Kerr et al., 2001; Liu et al., 2001a; Wynick et al., 2001; Yu et al., 2001).

GAL-immunoreactive bodies are found in both the NTS and the PBN, structures providing direct pathways to the DH (Sections 3.2.2 and 3.3) (Merchenthaler et al., 1993; O'Donnell et al., 1999; Pérez et al., 2001; Steiner et al., 2001), although there is currently no evidence that GAL is contained in these descending neurones. A very conspicuous cluster of GAL-containing neurones is located in the locus coeruleus and virtually all noradrenergic perikaya therein contain GAL (Skofitsch and Jacobowitz, 1985; Holets et al., 1988; Merchenthaler et al., 1993; Melander et al., 1986; Miller et al., 1999; Simpson et al., 1999; Pérez et al., 2001; Steiner et al., 2001). A_5 and A_7 noradrenergic cell groups (Section 5.2), serotonergic raphe nuclei (Section 7.1.2) (Xu et al., 1998; Miller et al., 1999; Pérez et al., 2001) and histaminergic nuclei of the tuberomammillary nucleus (Section 8.1) (Köhler et al., 1986), all of which provide descending pathways to the spinal cord, also possess GAL-containing neurones.

9.7.2. Spinal actions of GAL

Clearly, GAL released from monoaminergic and other classes of descending pathway may play an important role in the modulation of spinal nociceptive processing. However, this is difficult to discern in view of two additional pools of GAL in the DH. First, there is a substantial population of intrinsic DH neurones which synthesize GAL, localized mostly in superficial territories and lamina X and showing substantial colocalization with GABA (Merchenthaler et al., 1993; Simmons et al., 1995; Pérez et al., 2001; Wynick et al., 2001). Second, although PAF input of GAL to the DH is normally minimal, it may be substantially increased following PAF injury (Hökfelt et al., 1994; Xu et al., 1996b; Colvin et al., 1997; Zhang et al., 1998c; Millan, 1999; Luo, 2000). On the other hand, under conditions of inflammatory pain, GAL is upregulated in intrinsic neurones but not in PAFs.

Analysis and understanding of the role of GAL released from terminals of descending pathways is further complicated by the complex, state-dependent pattern of excitatory and inhibitory actions which it exerts through multiple GAL receptor types on PAF terminals and (at least for GAL_1 and GAL_2 receptors) on intrinsic DH neurones (Pooga et al., 1998; Millan, 1999; O'Donnell et al., 1999; Branchek et al., 2000; Kerr et al., 2000; Waters and Krause, 2000; Blackeman et al., 2001; Liu et al., 2001a). Of these diverse actions, it is probable that inhibitory, antinociceptive actions of GAL exerted via GAL_1 sites are of particular significance, whereas activation of GAL_2 sites may enhance nociception.

It seems possible, then that the concomitant release of GAL, NA and 5-HT cooperatively mediate DI in the DH, a supposition in line with interactions between actions of GAL and co-released 5-HT in cerebral tissues (Branchek et al., 2000; Diaz-Cabiale et al., 2000). Intruigingly, in this light, it has been suggested that GAL (possibly derived from ININs) may participate in the expression of noradrenergic, serotonergic and opioidergic mechanisms of DI in the DH (Reimann et al., 1994; Selve et al., 1996). However, these findings were dependent upon the precise experimental paradigm employed and require corroboration. Further, Reimann and Schneider (1993) showed that GAL inhibits release of NA in the DH. Whether this observation reflects a negative feedback action of GAL derived from descending pathways themselves, or a role of GAL originating in intrinsic DH neurones or PAF terminals, is unclear.

9.7.3. Supraspinal actions of GAL

GAL also modulates descending controls via supraspinal loci of action. Thus, probably via the reinforcement of opioidergic mechanisms, introduction of GAL into the PAG elicits antinociception (Przewlocka et al., 1995; Wang et al., 1999a, 2000). This observation coincides with the high density of GAL_1 and GAL_2 sites in the PAG (O'Donnell et al., 1999). There is also a pronounced concentration of mRNA encoding GAL_1 and GAL_2 receptors in brainstem monoaminergic nuclei suggesting direct modulation of descending controls by GAL (O'Donnell et al., 1999). In analogy to actions at noradrenergic terminals in the DH, following its release from noradrenergic terminals themselves, GAL exerts an inhibitory influence upon the activity of noradrenergic neurones in the locus coeruleus: this action may reflect the stimulation of GAL_1 autoreceptors (Seutin et al., 1989; O'Donnell et al., 1999; Xu et al., 2001b,c). There is likewise evidence that local release of GAL suppresses the activity of serotonergic perikarya (Xu et al., 1998). These findings suggest that, in distinction to its effects in the PAG, inhibitory actions of GAL upon monoaminergic pathways descending to the DH may restrain mechanisms of DI.

10. Transmitters contained in descending pathways and predominantly in primary afferent fibres

10.1. Substance P

A familiar feature of the DH is the massive provision of SP (and neurokinin (NK) A)-containing, fine calibre PAFs to superficial laminae of the DH which, via acti-

vation of NK_1- and, possibly, NK_2- and NK_3-receptors play an important role in nociceptive transmission (Cao et al., 1995; Seguin et al., 1995; Mantyh et al., 1995; DeFelipe et al., 1998; Millan, 1999; Yaksh, 1999a; Laird et al., 2000; Martinez-Caro and Laird, 2000; Ribeiro-da-silva and Hökfelt, 2000; Kamp et al., 2001; Todd et al., 2000; Trafton et al., 2001).

The excitatory influence of NK_1 receptors upon neuronal activity reflects their positive coupling via Gq/11 to PLC and Ca^{2+}-currents in contrast to their negative coupling to K^+-currents (Maggi and Schwartz, 1997; Wajima et al., 2000). Activation of PLC excites and sensitizes PNs both directly and by abrogating tonic, inhibitory actions at GABAergic and glycine receptors (Section 9.2.1) (Porter et al., 1990; Lin et al., 1994, 1996b; Millan, 1999; Albarran et al., 2001). Further, activation of PKCγ and PKC βII isoforms via PLC interferes with the inhibitory influence of μ-opioids upon PNs and accelerates their sensitization by prolonged nociceptive input (Narita et al., 1996, 2001; Malmberg et al., 1997; Martin et al., 1999c, 2001; Millan, 1999; Igwe and Chronwall, 2001; Ma and Quirion, 2001; Wen et al., 2001). These actions mimic those of CCK, which similarly exerts its excitatory actions at PNs via PLC (Section 9.5.2).

In addition to a few SP-containing neurones in the DH itself, a proportion of spinal cord pools of SP is derived via descending pathways from supraspinal regions. For example, SP has been detected in CCK-containing neurones emanating from the PAG (Sections 3.4 and 9.5) (Skirboll et al., 1983). Further, a sub-population of serotonergic fibres originating in the NRM and projecting to deep DH laminae also contains SP—although serotonergic neurones projecting from the raphe obscurus and raphe pallidus to the IML and VH show more pronounced co-localization with SP (Section 7.1.2) (Ruda et al., 1986; Wu and Wessendorf, 1992; Maxwell et al., 1996; Hökfelt et al., 2000). Extrapolating from functional observations obtained with pathways containing both 5-HT and SP and which project: (1) to the IML and (2) to forebrain regions from the dorsal raphe nucleus, SP and 5-HT likely interact in the DH in the modulation of nociceptive processing (Yang and Helke, 1995; Sergeyev et al., 1999).

It is possible that SP liberated from descending tracts in the DH participates in the induction of hyperalgesia accompanying inflammation and illness (Wiertelak et al., 1997; Watkins and Maier, 1999b). However, it should not automatically be assumed that descending pools of SP act pro-nociceptively. For example, release of SP from descending serotonergic fibres onto NK_1 receptor-bearing ININs should (in analogy to $5\text{-}HT_3$ receptors) (Section 7.4.4.3) elicit antinociception. This would contrast to pronociceptive actions of SP at PNs upon its liberation from descending pathways or PAF terminals.

In this light, it is of interest to note that excitatory SP-containing projections from the PAG and lateral hypothalamus to the A_7 nucleus trigger noradrenergic mechanisms of DI (Section 5.3) (Bajic et al., 2001; Holden and Naleway, 2001).

10.2. Glutamate

10.2.1. Ionotropic receptors

In analogy to SP, glutamate is a major transmitter of nociceptive information from PAFs to the DH, wherein it exerts its excitatory, sensitizing actions upon both PNs and EXINs via ionotropic, heteromeric, cation-permeable α-amino-2,3-dihydro-5-methyl-3-oxo-4-isoxazolepropanoic acid (AMPA), kainate and, predominantly, NMDA receptors in synergy with SP and CGRP (Seguin and Millan, 1994; Baranauskas and Nistri, 1998; Bleakman and Lodge, 1998; Dingeldine et al., 1999; Li et al., 1999d; Millan, 1999; Muraze et al., 1999; Lerma et al., 2001; Martin et al., 2001; Minami et al., 2001a; Wen et al., 2001; Zhou et al., 2001). Likewise in analogy to SP, glutamate has been identified in descending pathways, and a subset of serotonergic and noradrenergic neurones innervating the DH and IML contain glutamate (Ruda et al., 1986; Morrison et al., 1991; Nicholas et al., 1992; Wu et al., 1993). Interestingly, DH-localized NMDA receptors are involved in mechanisms of DF elicited by illness, and it has been suggested that this reflects a role of glutamate released from descending pathways rather than PAFs (Watkins et al., 1994; Wiertelak et al., 1997). Nonetheless, as pointed out for SP earlier (Section 10.1), it would be naive to assign a unitary pronociceptive role to glutamate in descending pathways. In this light, further, it is important to mention that GLU, via actions at ionotropic receptors, exerts an excitatory influence upon GABAergic and glycinergic ININs in the DH: their engagement could, in theory, be involved in mechanisms of DI (Millan, 1999; Kerchner et al., 2001).

Nevertheless, NMDA receptors activated by glutamate released from nocisponsive PAFs fulfill a crucial role in the sensitization of DH (PN, EXIN) neurones which underlies long-term, painful states. They act via multiple intracellular mechanisms including, in analogy to NK_1 receptors (Section 10.1), the activation of PLC (Baranauskas and Nistri, 1998; Doubell et al., 1999; Mao, 1999; Martin et al., 1999c, 2001; Millan, 1999; Muraze et al., 1999; Yaksh, 1999a; Guo and Huang, 2001). In supraspinal regions involved in nociceptive processing, such as the thalamus and cortex, NMDA receptors also participate in mechanisms of sensitization and neuronal excitation (Millan, 1999; Wei F. et al., 2001a). It is, thus, of interest that, under conditions of peripheral inflammation, RVM-localized NMDA receptors contribute to mechanisms generating DF (Urban et al., 1999b). Furthermore, this role may be confined to NDMA receptors inasmuch as blockade of ionotropic AMPA receptors in the RVM amplifies hyperalgesia. This finding implies that AMPA receptors, in contrast to NMDA receptors, may enhance induction of DI from this region (Urban et al., 1999b; Urban and Gebhart, 1999). Paralleling these findings, NMDA receptors have been proposed to enhance

mechanisms of DF elicited from the RVM under conditions of neuropathic pain (Wei and Pertovaara, 1999; Terayama et al., 2000). Such effects may reflect the excitation by NMDA receptors of ON cells triggering DF, possibly upon release of glutamate from local neuronal circuits (Heinricher et al., 2001a,b). NMDA receptors may also be excitatory to GABAergic ININs controlling the activity of descending noradrenergic pathways (Paquet and Smith, 2000; Sakamura et al., 2000).

Conversely, there is evidence that glutamatergic pathways projecting to the RVM from the PAG contribute to the induction of DI (Section 3.4) inasmuch as administration of glumatergic antagonists into the RVM blunts antinociception evoked by electrical stimulation of the PAG (Aimone and Gebhart, 1986; Spinelli et al., 1996). Such antinociceptive actions of NMDA receptors may involve activation of OFF cells mediating DI (Cheng et al., 1986; Osborne et al., 1996). Heinricher et al. (1999, 2001b) suggested that this mechanism intervenes in the induction of DI by application of morphine into the PAG. A role of glutamatergic pathways in the induction of antinociception by projections from hypothalamic nuclei to the RVM and PAG has also been proposed (Aimone and Gebhart, 1986; Jiang and Behbehani, 2001) (Section 3.2). Correspondingly, there is evidence from micro-injection studies that NMDA receptor activation can elicit antinociception from sites in the PAG (Berrino et al., 2001; Palazzo et al., 2001). Glutamatergic neurones are a major source of excitatory input to monoaminergic cell bodies in the brainstem from which pathways mediating DI travel to the DH (Section 3.4) (Fields and Basbaum, 1999; Yaksh, 1999a; Somogy and Llewellyn-Smith, 2001).

These contrasting actions of NMDA receptors in the RVM serve to illustrate that, as for many transmitters discussed herein, glutamate may exert an opposite influence upon descending controls and nociceptive processing as a function of the precise pool of (NMDA) receptors involved and the neuronal circuits engaged (Table 2). In view of the ubiquity of glutamatergic pathways and the diversity of roles fulfilled by multiple ionotropic and metabotropic (Section 10.2.2) receptors, their complex role in the modulation of mechanisms of DI and DF at the spinal and supraspinal level will require careful clarification.

10.2.2. Metabotropic receptors

In addition to ionotropic receptors, glutamate acts via several classes of metabotropic receptor (Conn and Pin, 1997; Anwyl, 1999). Of these group I mGluR1 and mGluR5 receptors, which are positively coupled via Gq/11 to PLC, play a cooperative role with NMDA receptors in exciting and sensitizing PNs. On the other hand, group II and III mGlu receptors, which are negatively coupled to AC, may attenuate the excitation of PNs and mediate antinociception (Young et al., 1998; Millan, 1999; Neugebauer et al., 1999; Yaksh, 1999a; Fundytus et al., 2001; Hofmann et al., 2001; Karim et al., 2001). It is generally assumed that mGluR sites, which may be localized both on PAF terminals and on intrinsic DH neurones, are activated by glutamate released from PAF terminals. However, the possibility that they are engaged by glutamate derived from descending pathways justifies consideration. In view of increasing evidence for the importance of mGluR receptors in the modulation of nociceptive processing (both centrally and peripherally), evaluation of their interactions with descending controls at spinal and supraspinal loci such as the PAG (Millan, 1999; Maione et al., 2000; Berrino et al., 2001; Hofmann et al., 2001; Palazzo et al., 2001) would be of considerable interest.

10.2.3. Nitric oxide

NO is derived from the degradation of L-citrulline by an action of NO synthase (Millan, 1999; Weisinger, 2001). Both neuronal and non-neuronal pools of NO play a complex and diverse role in the modulation of nociceptive processing at various levels of the neuroaxis (Gao and Qiao, 1988; Millan, 1999; Luo and Cizkova, 2000; Milne et al., 2001; Sousa and Prado, 2001; Wen et al., 2001; Wu et al., 2001c). For example, NO interacts with noradrenergic and cholinergic mechanisms of DI (Section 5.8.2).

On the other hand, an important role of NO in mediating the sensitization of DH neurones by NMDA and, possibly, mGluR1/5, receptors has been proposed: the ability of NO to trigger (via cGMP) protein kinase G-mediated phosphorylation of $GABA_A$ receptors may be of importance in this respect (Lin et al., 1999a,b,c; Millan, 1999; Yaksh, 1999a; Luo and Cizkova, 2000; Bie and Zhao, 2001; Wu et al., 2001c). As pointed out above, PN pools of NO may be activated by glutamate released from descending pathways rather than PAFs. Descending pathways themselves are potential sources of NO in the DH. Irrespective of its origins, it has been suggested that spinal pools of NO participate in glutamatergic mechanisms of DF triggered by illness and inflammation (Section 9.3). Further, as concerns interactions with descending controls, NO may weaken the influence of DI upon DH neurones, at least partially by the above-mentioned interference with GABAergic and glycinergic inhibitory tone upon PNs (Wiertelak et al., 1997; Lin et al., 1999a,b,c; Watkins and Maier, 1999b).

Parallelling these observations at the segmental level, NO has been implicated in the NMDA receptor-mediated initiation of mechanisms of DF in the RVM (Urban et al., 1999b; Heinricher et al., 2001b). On the other hand, Iwamoto and Marion (1994) suggested that NO intervenes in the induction of DI by muscarinic receptors in the RVM, in analogy to the purported role of NO in cholinergic mechanism of spinal antinociception (Section 5.8.2).

In view of its multiple sources, diverse mechanisms of induction (glutamatergic and other) and both pro and antinociceptive actions, considerable work will be required to elucidate the multivarious role of NO in the modulation and expression of descending controls.

11. "Transmitters" not generated in specific classes of neuronal pathway

11.1. Cannabinoids

11.1.1. Generation of cannabinoids: actions at CB_1 receptors

Of the two classes of cannabinoid receptor to date characterized, CB_1 and CB_2, only the former appears to be localized in the CNS (Pertwee, 1997). Although there is increasing evidence for promiscuous (pleiotropic) coupling of CB_1 receptors via various classes of G-protein to intracellular transduction mechanisms (Pertwee, 1997, 2001; Abadji et al., 1999; Ameri, 1999) they are well-established to negatively couple via Gi/o to AC and to enhance and suppress K^+- and Ca^{2+}-currents, respectively. The potential existence of subtypes of CB_1 receptor is currently under debate (Onaivi et al., 1996; Pertwee, 1997, 2001; Welch et al., 1998; Breivogel et al., 2001; Hajos et al., 2001). However, should central actions of cannabinoids emerge to be genuinely mediated by a single receptor class, this would provide a remarkable distinction to all other modulators of descending controls considered in this review. Cannabinoids themselves may also be distinguished from other "classical" transmitters discussed earlier.

At least two endogenous cannabinoid ligands for CB_1 receptors have been identified: anandamide and 2-arachidonylglycerol. Both are generated from membrane phospholipids (by actions of phospholipase D and C, respectively) and are subject to rapid depolarization (Ca^{2+})- and receptor-induced (non-vesicular) release and synthesis. They are immediately cleared by a Na^+- and energy-dependent, selective, saturable reuptake mechanism into neurones and glial cells and are rapidly degraded by a microsomal enzyme, fatty acid amide hydrolase (Di Marzo et al., 1998; Ameri, 1999; Glass and Northup, 1999; Piomelli et al., 2000; Cravatt et al., 2001; Giuffrida et al., 2001). Cannabinoids exert actions both conventionally (anterograde) and retrogradely whereby (in analogy to neurotrophins and NO (McMahon and Bennett, 1999; Millan, 1999)) their release from depolarized post-synaptic neurones results in a reduction in transmitter release from pre-synaptic terminals (Maejima et al., 2001; Ohno-Shosaku et al., 2001; Weisinger, 2001).

The discovery that CB_1 receptors may be constitutively active, and that prototypical "neutral" antagonists behave as inverse agonists (Pan et al., 1998b; Abadji et al., 1999), is of significance in the light of ongoing controversy as to whether CB_1 receptors play a tonic role in the modulation of nociception. Rather than blockade of the actions of spontaneously-released cannabinoids, if "antagonists" indeed act as inverse agonists they may exert intrinsic, pronociceptive effects opposite to those of cannabinoid agonists (Pertwee, 2001).

A substantial literature has accrued concerning the influence of cannabinoids upon pain, incorporating antinociceptive actions exerted peripherally (CB_1 and CB_2 receptors) (Calignano et al., 1998; Richardson et al., 1998c; Hohmann and Herkenham, 1999; Fox et al., 2001; Malan et al., 2001), segmentally (Chapman, 1998a,b, Chapman, 1999; Richardson et al., 1998a,b; Mason et al., 1999; Johanek et al., 2001) and (in several brain regions) supraspinally (Hohmann et al., 1999; Martin et al., 1999a; Walker et al., 1999) against both inflammatory and neuropathic pain (Ameri, 1999; Li et al., 1999a; Piomelli et al., 2000; Bridges et al., 2001; Pertwee, 2001). Transgenic mice lacking fatty acid amide hydrolase display a marked increase in central levels of anandamide in parallel with analgesia (Cravatt et al., 2001).

11.1.2. Spinal induction of antinociception by cannabinoids

CB_1 receptors are synthesized both by intrinsic DH neurones and by cell bodies in the DRG, from which they are transported to their central (and peripheral) terminals in superficial laminal (Tsou et al., 1998; Hohmann and Herkenham, 1999; Ong and Mackie, 1999; Ahluwalia et al., 2000; Farquhar-Smith et al., 2000; Ross et al., 2001). Correspondingly, cannabinoids elicit spinal antinociception under conditions of peripheral inflammation and PAF injury (Richardson et al., 1998a,b; Fox et al., 2001; Johanek et al., 2001) both in suppressing the release of SP, CGRP and other pronociceptive transmitters from PAF terminals (Richardson et al., 1998a,b; Kelly and Chapman, 2001; Millns et al., 2001; Morisset et al., 2001; Ross et al., 2001) and by post-synaptically inhibiting activation of PNs by nocisponsive fine calibre PAFs (Chapman, 1999; Farquhar-Smith et al., 2000; Abood et al., 2001). Protection of DH neurones against glutamatergic neurotoxicity would be of importance in countering long-term neurodegenerative changes associated with PAF injury (Millan, 1999; Abood et al., 2001). Actions of cannabinoids are exerted directly at PAF terminals and PNs. Based on studies of DYN release and the actions of κ-opioid receptor antagonists, it has been speculated that a further component of the spinal antinociceptive actions of cannabinoids reflects (indirect) recruitment of DYNergic ININs (Smith et al., 1994b; Corchero et al., 1997; Mason et al., 1999). In a recent study, of which the functional significance remains to be ascertained, an inhibitory influence of cannabinoids upon GABAergic and glycinergic transmission in the DH was observed: this action would counter antinociceptive properties expressed at PNs and PAFs (Jennings et al., 2001) and suggests analogies to other mediators (Figs. 4–6, Table 3) eliciting pro and antinociceptive actions at discrete CNS loci.

Several reports suggest that segmental populations of CB_1 receptor tonically exert antinociceptive properties, but not all observations are consistent with this hypothesis (Richardson et al., 1998a,b; Chapman, 1999; Ledent et al., 1999; Beaulieu et al., 2000; Bridges et al., 2001; Pertwee, 2001). Notwithstanding such discrepant findings, there is evidence that the activity of cannabinoids at spinal CB_1 receptors is augmented under conditions of long-term inflammatory or neuropathic pain (Martin et al., 1999d; Herzberg et al., 1997; Strangman et al., 1998), consistent with their interference

with the sensitization of wide-dynamic range neurones by persistent nociceptive input (Strangman and Walker, 1999). Factors responsible for their induction remain to be determined and, in this regard, descending pathways likely fulfill an important role. Curiously, however, there is currently no information concerning the influence of descending pathways mediating DI and/or DF upon activity at spinal CB_1 receptors (Jennings et al., 2001).

It should be noted that anandamide can interact with vanilloid (VR_1 subtype) receptors—at least at high concentrations. Accordingly, stimulation of VR_1 receptors on the central and peripheral terminals of C fibres may contribute to its influence upon nociception (Caterina et al., 2000; Di Marzo et al., 2000; De Petrocellis et al., 2001; Gauldie et al., 2001; Morisset et al., 2001; Tognetto et al., 2001). Further, possible interactions of anandamide with serotonergic (5-HT_{2A}) and muscarinic (M_1 and M_4) receptors may also influence nociception (Kimura et al., 1998; Christopoulos and Wilson, 2001).

11.1.3. Supraspinal induction of descending inhibition by cannabinoids

11.1.3.1. Multiple sites of action. The PAG is rich in CB_1 receptors (Tsou et al., 1998) and cannabinoids elicit robust antinociceptive effects upon introduction into its dorsolateral quadrant, in distinction to morphine which most effectively triggers antinociception from its ventral subdivision (Martin et al., 1999a; Walker et al., 1999; Palazzo et al., 2001). Thus, neuroanatomical substrates for PAG-elicited analgesia by cannabinoids differ to opioids, in line with the general independence of cannabinoid-induced analgesia from μ-opioid receptors (Ledent et al., 1999; Pertwee, 2001)-though long-term treatment with cannabinoids amplifies the gene expression of ENKs in the PAG (Manzanares et al., 1998). The complementary nature of cannabinoid- and μ-opioidergic mechanisms of antinociception elicited from the PAG (and elsewhere) is underscored by their synergistic induction of analgesia (Welch et al., 1995; Reche et al., 1996). One important communality with μ-opioids is the ability of cannabinoids to diminish GABAergic synaptic transmission in the PAG, albeit—in contrast to morphine—via pre-synaptic rather than post-synaptic actions (Han et al., 1999; Vaughan et al., 2000; Wang et al., 2001b). This disengagement of GABAergic ININs relieves excitatory pathways projecting to neurones initiating mechanisms of DI in the brainstem (Sections 3.4 and 9.2.4). It is probable that glutamatergic efferents from the PAG are involved in this regard (Section 10.2), and a role of excitatory amino acids (NMDA and metabotropic receptors) in the antinociceptive actions of cannabinoids in the PAG has been proposed. However, the precise relationship between cannabinoids and glutamatergic circuits in the PAG remains unclear (Vaughan et al., 2000; Berrino et al., 2001; Palazzo et al., 2001; Robbe et al., 2001).

Walker et al. (1999) have shown that electrical stimulation of the PAG concomitantly elicits a local increase in dialysis levels of anandamide and an antinociception susceptible to blockade by selective CB_1 antagonists, indicative that endogenous cannabinoids participate in mechanisms of analgesia (DI) generated from this structure. In support of this argument, inflammatory pain similarly provokes the release of anandamide in the PAG (Walker et al., 1999). Cannabinoids in the PAG may, thus, play a role in the activation of mechanisms of DI countering sustained painful states (Herzberg et al., 1997; Li et al., 1999a; Walker et al., 1999; Palazzo et al., 2001). However, the degree of tonic influence of supraspinal populations of CB_1 receptors upon nociception under resting conditions remains controversial (Meng et al., 1998; Strangman et al., 1998; Ledent et al., 1999; Bridges et al., 2001; Pertwee, 2001). Like μ-opioid receptor-induced antinociception in primates, antinociception elicited by systemic application of a CB_1 agonist was attenuated by lesions of the (central nucleus of the) amygdala (Manning et al., 2001). However, it is unclear whether this structure represents a locus of antinociceptive action of CB_1 agonists, or is engaged downstream of the PAG.

Microinjection of cannabinoids into the RVM elicits antinociception via recruitment of DI (Tsou et al., 1998; Martin et al., 1998, 1999a; Monhemius et al., 2001). Therein, there is also evidence that cannabinoids (pre-synaptically) suppress GABAergic transmission (Vaughan et al., 1999). This action disinhibits neurones mediating DI. Indeed, Meng et al. (1998) showed that cannabinoids indirectly activate OFF cells in the RVM (Section 3.2.4), indicative of their induction of (non-monoaminergic) mechanisms of DI from this region. In addition to suppression of GABAergic transmission, the ability of cannabinoids to inhibit ON cells (Section 3.2.4), likely participates in their stimulation of OFF neurones. Interference with the activity of ON cells itself may favour antinociception in reducing DF. It has been hypothesized that recruitment of CB_1 receptors in the RVM plays a key role in the reinforcement of DI engendered by chronic inflammatory and neuropathic pain (Section 4.4) (Li et al., 1998; Azami et al., 2001; Monhemius et al., 2001).

The NTS possesses a high density of CB_1 receptors, activation of which is involved in the anti-emetic properties of cannabinoids (Tsou et al., 1998). It is conceivable that CB_1 receptors in the NTS modulate the passage of vagal nociceptive information to brainstem nuclei mediating DI and DF.

11.1.3.2. Involvement of monoaminergic mechanisms. The induction of antinociception (DI) by systemic injection of cannabinoids is blocked by i.t. administration of α_2-AR antagonists, whereas blockade of spinal 5-HT receptors or elimination of spinal serotonergic transmission is ineffective (Lichtman and Martin, 1991). Although the respective roles of descending noradrenergic versus serotonergic pathways in the actions of cannabinoids in defined cerebral structures would benefit from re-examination with α-AR and 5-HT receptor subtype-selective agents, a role of segmental noradrenergic mechanisms in the expression of supraspinal cannabinoid-induced antinociception is coherent with:

(1) the key role of A_7-derived centrifugal fibres in the mediation of other modes of analgesia elicited from the PAG and RVM (Section 5.3) and (2) the induction of antinociception by direct administration of cannabinoids into the A_5 noradrenergic nucleus-the A_7 nucleus remains to be investigated (Martin et al., 1999a). Furthermore, the recent demonstration that dopamine D_2 antagonists blunt the antinociceptive properties of systemically-applied cannabinoids was purported to reflect the engagement of descending dopaminergic pathways (Section 6.4) (Carta et al., 1999). This is an intriguing possibility inasmuch as cannabinoids are known to activate ascending dopaminergic pathways (Ameri, 1999; Piomelli et al., 2000; Robbe et al., 2001).

11.2. Adenosine

11.2.1. Generation of adenosine: actions at multiple adenosine receptors

In analogy to cannabinoids, adenosine is not restricted to specific classes of neuronal pathway and it can be ubiquitously generated throughout the CNS by all neuronal and non-neuronal cells which exploit ATP as an energy source. Resting levels of adenosine are maintained at a low level. In the DH, one well-defined pool of adenosine involved in the modulation of nociceptive processing is derived from PAF terminals (Sawynok, 1998). Adenosine and the cellular machinery requisite for its clearance and degradation are also localized in several supraspinal structures, such as the PAG and brainstem, involved in the modulation of descending controls (Braas et al., 1986; Geiger and Nagy, 1986). Comparatively little functional information is available concerning a potential role of cerebral adenosinergic mechanisms in the modulation of descending pathways, so the following comments concentrate principally on the segmental role of adenosine in the induction of antinociception in interaction with descending pathways (Sawynok and Sweeney, 1989; Sawynok et al., 1998; Sawynok, 1998, 1999; Segerdahl and Sollevi, 1998; Dickenson et al., 2000).

Within cells, adenosine formation is intimately linked to the production of ATP and intracellular energy balance. It is intracellulary formed by: (1) the hydrolysis of 5′-adenosine monophosphate by ecto-5′-nucleotidase and (2) the transformation of 5-adenosyl homocysteine by 5′-adenosylhomocysteine hydrolase (Salter et al., 1993; Linden, 1994; Geiger et al., 1997; Lattini and Pedata, 2001; Patterson et al., 2001). Extracellular pools of adenosine are derived either from: (1) its (non-vesicular) release via a reversible nucleoside carrier (sometimes referred to as "facilitated diffusion"); (2) from the conversion of ATP-which is released conventionally from neurones and glial cells-via adenosine diphosphate, then 5′-adenosine monophosphate to adenosine and (3) less rapidly, from the conversion of cAMP, likewise via 5′-adenosine monophosphate (Salter et al., 1993; Linden, 1994; Geiger et al., 1997; Poelchen et al., 2001). Adenosine is taken up in neurons and glial cells by multiple classes of specialized, Na^+-dependent, bi-directional, nucleoside transporters. It is then metabolized by adenosine deaminase into inosine which is ultimately recycled into ATP. Adenosine kinase converts adenosine into adenosine monophosphate (Salter et al., 1993; Linden, 1994; Geiger et al., 1997; Lattini and Pedata, 2001; Patterson et al., 2001). Like adenosine itself, ecto-5-nucleotidase, adenosine deaminase and adenosine kinase are concentrated in the DH, in particular in superficial laminae. This pattern of localization reflects the importance of nocisponsive PAF terminals as a source of DH pools of adenosine, while descending pathways and, presumably, intrinsic neurones also contribute to pools of adenosine therein (Nagy and Daddona, 1985; Braas et al., 1986; Salter et al., 1993; Poelchen et al., 2001).

Four distinct receptors for adenosine have been cloned: A_1, A_{2A}, A_{2B} and A_3 (Ralevic and Burnstock, 1998; Olah and Stiles, 2000). CNS-localized A_1 receptors interact via Gi/o with AC (inhibition), K^+- (facilitation) and Ca^{2+}-currents (potentiation). A_3 receptors also attenuate AC activity via Gi but are not discussed further here since a central role in the modulation of nociceptive processing has not been documented. Contrariwise, A_{2A} and A_{2B} receptors couple positively to AC via Gs. The latter have been detected in the spinal cord, but there are no data specifically relevant to a potential role in nociceptive processing so they are not evoked further the following sections. The opposite patterns of coupling of A_1 versus A_{2A} sites to AC and, accordingly, their differential modification of cellular excitability, suggest that they modify nociceptive processing by contrasting neuronal mechanisms (see subsequent sections).

11.2.2. Modulation of spinal nociceptive processing by adenosine

11.2.2.1. Antinociceptive actions mediated by A_1 receptors. While present throughout the DH, A_1 sites are concentrated in superficial laminae wherein they are primary localized upon intrinsic neurones: PAF terminals also bear A_1 receptors (Geiger et al., 1984; Choca et al., 1988; Salter et al., 1993). Correspondingly, stimulation of A_1 receptors by administration of adenosine itself, A_1 agonists and inhibitors of adenosine deaminase and kinase, diminishes nociceptive transmission by: (1) directly inhibiting (hyperpolarizing) PNs (Doi et al., 1987; DeLander and Whal, 1988; Salter et al., 1993; Li and Perl, 1994; Patel et al., 2001) and (2) interrupting the release of SP and other transmitters from fine calibre PAFs (Sawdeloli et al., 1993; Santicioli et al., 1993; Sjölund et al., 1997; Carruthers et al., 2001). The latter effect accords with evidence for antinociceptive actions of A_1 receptors at peripheral PAF terminals in rodents (Sawynok, 1998; Millan, 1999—but see Hu and Li, 1997; Bevan, 1999; Dowd et al., 1998). These observations underpin evidence that activation of spinal A_1 receptors abrogates sensitization of wide-dynamic range neurones by prolonged noxious stimulation due to tissue inflammation of PAF injury (Reeve and Dickenson, 1995; Sumida et al., 1998; Suzuki et al.,

2001) and elicits antinociception against both inflammatory and neuropathic pain (Lee and Yaksh, 1996; Cui et al., 1997, 1998; Poon and Sawynok, 1998; Sawynok, 1998; Kowaluk et al., 1999; Johansson et al., 2001; Von Heijne et al., 2001). Initial clinical experience is encouraging as regards potential antinociceptive properties of spinally-administered adenosine and A_1 agonists (Rane et al., 1998; Segerdahl and Sollevi, 1998; Belfrage et al., 1999; Collins et al., 2001).

It has been suggested that a component of μ-opioid-mediated spinal antinociception involves carrier-mediated "liberation" of adenosine from nocisponsive PAFs (Sweeney et al., 1989, 1993; Salter et al., 1993; Cahill et al., 1995). Engagement of A_1 receptors cooperatively (additively) elicits antinociception both with μ-, δ- and κ-opioid receptor agonists (DeLander and Keil, 1994; Cahill et al., 1995; Reeve and Dickenson, 1995; Lavand'homme and Eisenach, 1999).

Certain studies showing hyperalgesic actions of A_1 receptor antagonists suggest that they may tonically control nociceptive processing in the DH, and adenosine production is enhanced under conditions of long-term pain (Sawynok and Sweeney, 1989; Keil and DeLander, 1996; Kowaluk et al., 1999). Stimulation of NMDA receptors may contribute to this increased generation of adenosine in PNs and, reflecting a negative feedback mechanism, adenosine reduces the release of glutamate from PAFs and interferes with its sensitization of PNs via NMDA receptors (Reeve and Dickenson, 1995; De Mendonça and Ribeiro, 1997; Sumida et al., 1998; Yaksh, 1999a; Dickenson et al., 2000; Suzuki et al., 2001). In addition, as indicated in Section 11.2.2.3, pathways mediating DI may recruit DH adenosinergic mechanisms under conditions of long-term exposure to noxious stimulation.

In addition to actions in the DH, suppression of sympathetic outflow may contribute to the reduction of neuropathic pain by A_1 receptors agonists, although actions in the IML perturb autonomic function (Lee and Yaksh, 1996; Deuchars et al., 2001). While stimulation of VH-localized A_1 receptors results in motor weakness, such effects are seen at relatively high doses and do not appear to compromize interpretation of the influence of A_1 agonists upon nociceptive processing in algesiometric paradigms (Nakamura et al., 1997; Sawynok, 1998).

11.2.2.2. A potential role of A_{2A} receptors. In analogy to A_1 sites, A_{2A} receptors are enriched in the DH as compared to its ventral counterpart and they similarly display a preferential localization on intrinsic neurones (Choca et al., 1988). However, in light of the excitatory influence of A_{2A} receptors upon neuronal excitability as compared to inhibitory A_1 sites, if they similarly elicit antinociception, contrasting mechanisms must be involved. In fact, data remain inconsistent as regards the potential role of A_{2A} receptors in the induction of antinociception (DeLander and Hopkins, 1987b; Aran and Proudfit, 1990a,b; DeLander and Keil, 1994; Reeve and Dickenson, 1995; Lee and Yaksh, 1996; Poon and Sawynok, 1998; Sawynok, 1998; Patel et al., 2001), and mice lacking A_{2A} receptors actually show hypoalgesia (Ledent et al., 1997). Moreover, A_{2A} receptors mediate pronociceptive actions at peripheral PAF terminals (Sawynok, 1998; Bevan, 1999; Millan, 1999), questioning potential antinociceptive actions at their central projections. In any case, in view of the excitatory properties of A_{2A} receptors—in analogy to 5-HT_3 receptors (Section 7.4.3), it is necessary to interpose an ININ between them and PNs and PAFs in order to account for potential antinociceptive actions in the DH. Alternatively, in analogy to cerebral structures (Okada et al., 2001), A_{2A} receptors may directly enhance release from descending monoaminergic or cholinergic pathways mediating antinociception.

Activation of A_{2A} receptors fulfills a more prominent role than A_1 sites in the induction of motor dysfunction, presumably by direct stimulation of MNs (Lee and Yaksh, 1996).

11.2.2.3. Interaction of adenosine with mechanisms of descending inhibition. There is evidence that supraspinal application of morphine enhances extracellular levels of adenosine in the spinal cord (Sweeney et al., 1990, 1991; Kaplan and Leite-Morris, 1997) and a generalized blockade of adenosine receptors attenuates the induction of antinociception by its supraspinal administration, either i.c.v. or into the PAG (DeLander and Hopkins, 1986; DeLander and Whal, 1988; Sawynok et al., 1991a). Counterintuitively, it was suggested that A_1 receptors are not involved in this interaction, although they contribute to the induction of antinociception by supraspinal administrations of β-EP (Suh et al., 1997). In distinction, A_{2A} receptors were suggested to be involved in the induction of antinociception by cerebral actions of both morphine and β-EP (Suh et al., 1997). These observations require corroboration.

In view of the key role of descending noradrenergic pathways in the mediation of supraspinal MIA (Section 5.3), an interaction of adenosine with noradrenergic mechanism of antinociception in the DH is of particular interest. In fact, data are ambiguous as to whether NA enhances extracellular levels of adenosine in the spinal cord. Furthermore, while certain studies have contended that adenosine participates in the induction of antinociception by spinal administration of NA, conflicting data have also been documented (DeLander and Hopkins, 1987a,b; Sweeney et al., 1987, 1990, 1991; Sawynok and Sweeney, 1989; Yang et al., 1994a, 1998b). Nevertheless, in line with a contribution of adenosine to noradrenergic mechanisms of antinociception in the DH, the antinociceptive effects of locus coeruleus stimulation were attenuated by i.t. administration of adenosine antagonists (Zhao et al., 1999b). Reciprocally, it has been argued that induction of antinociception by segmental actions of adenosine requires functionally-intact descending noradrenergic pathways (Sawynok et al., 1991b). Irrespective of the precise interrelationships amongst noradenergic and adenosinergic modes of spinal antinociception, which require clarification, adenosine agonists and NA synergistically elicit antinociception upon their cojoint administration

(Section 5.9.7) (DeLander and Hopkins, 1987b; Aran and Proudfit, 1990a,b).

Descending serotonergic pathways also contribute to the induction of MIA from cerebral sites (Section 7.3.3) and the i.c.v. administration of morphine was shown to enhance extracellular levels of adenosine in the spinal cord via a serotonergic mechanism (Sweeney et al., 1990, 1991; Kaplan and Leite-Morris, 1997). Correspondingly, 5-HT itself enhances the release of adenosine from a population of fine calibre C fibre afferents (Sweeney et al., 1988). This finding may be related to the inhibitory influence of non-selective adenosine antagonists upon the induction of antinociception by spinal administration of 5-HT and certain "5-HT_1" but not "5-HT_2" or 5-HT_3-receptor agonists (DeLander and Hopkins, 1987a,b; Sawynok and Reid, 1991, 1996).

Finally, a role of adenosine in the induction of antinociception by the spinal application of DA was proposed by Yang et al. (1996b).

11.2.3. Supraspinal modulation of descending controls by adenosine

Several supraspinal structures involved in the initiation and/or modulation of descending pathways possess substantial levels of adenosine and adenosine deaminase, including the hypothalamus, PAG, RVM and other brainstem regions (Nagy and Daddona, 1985; Braas et al., 1986; Geiger and Nagy, 1986). This pattern of localization is consistent with a role in the modulation of descending controls. While adenosine is known to interact with ascending monoaminergic and cholinergic pathways (Okada et al., 2001), virtually no information is available as regards its potential supraspinal influence upon descending monoaminergic pathways. However, its i.c.v. administration has been reported to elicit antinociception (Herrick-Davis et al., 1989) and-like opioids and cannabinoids-adenosine inhibits synaptic transmission in the PAG (Bagley et al., 1999).

Paradoxically, antinociception has likewise been observed upon the systemic and i.c.v. administration of A_1 antagonists (Sawynok and Reid, 1996; Ghelardini et al., 1997), and this effect is abolished by depletion of central pools of 5-HT. The underlying mechanisms—and the apparent dependence upon serotonergic pathways—require elucidation. Disinhibition of cholinergic transmission may be involved inasmuch as the induction of antinociception by A_1 antagonists was blocked by muscarinic antagonists (Ghelardini et al., 1997).

12. Therapeutic exploitation of descending controls for improved pain relief

12.1. General considerations

In the therapeutic exploitation of descending controls for improved pain relief, the ultimate objective would be to develop an orally-active formulation of a drug with the following characteristics: (1) effective in all patients against inflammatory and/or neuropathic pain of disparate pathologies; (2) active over a well-defined dose-range; (3) selectively suppressing nociceptive as compared to non-nociceptive input; (4) with an appropriate duration of action; (5) devoid of problems of tolerance and dependence and (6) yielding robust analgesia at doses substantially lower than those eliciting undesirable side-effects.

Such a panacea has yet to be described and may even be unobtainable. The treatment of pain by drugs will, nevertheless, remain of central importance for the foreseeable future. In addition to their oral utilization, it is important to consider the possibility of their cerebral and spinal administration. Prospects for the former route are bleak (Section 12.2), but they are far more positive for the latter, and it is instructive to discuss advantages and disadvantages of the spinal route of drug delivery for the alleviation of pain (Section 12.3) (Eisenach et al., 1996; Dougherty and Staats, 1999; Williams et al., 1999; Yaksh, 1999b,c).

Complementary to pharmacological strategies of analgesia targetting specific receptors—of which a wealth of potential targets are now known (Figs. 3 and 4)—Fig. 8 illustrates several alternative concepts for manipulation of mechanisms of DI and DF. These may be categorized in essentially two (interrelated) ways. First, mechanistically: (1) targets pre-synaptic to (upstream of) descending pathways; (2) descending pathways themselves and (3) targets post-synaptic to (downstream of) descending pathways. Second, topographically: cerebral as compared to segmental loci, a fundamental distinction inasmuch as the latter offer the possibility of direct intervention at the spinal level by epidural and i.t. administration protocols.

12.2. Supraspinal strategies for exploitation of descending controls

12.2.1. Reinforcement of descending inhibition, attenuation of descending facilitation

As concerns the enhancement of DI, the majority of interactions indicated in Fig. 4 apply to descending noradrenergic (Section 5) and serotonergic (Section 7) pathways, or to the activity of defined classes of cell in the RVM (Section 3.2.4) (Fields et al., 1991; Millan, 1997; Fields and Basbaum, 1999; Mason, 1999; Yaksh, 1999a). The influence of supraspinal modulatory mechanisms upon transmitters colocalized with 5-HT and/or NA in descending pathways is likely to be comparable. Little information is available concerning afferent mechanisms which control the activity of other classes of descending pathway. As regards DF, the constellation of modulatory influences depicted in Fig. 4 is almost certainly incomplete inasmuch as DF has only belatedly received the attention afforded to its counterpart, DI. In theory, several complementary strategies operative at the supraspinal level may permit the reinforcement of DI and/or the attentuation of DF (Fig. 8).

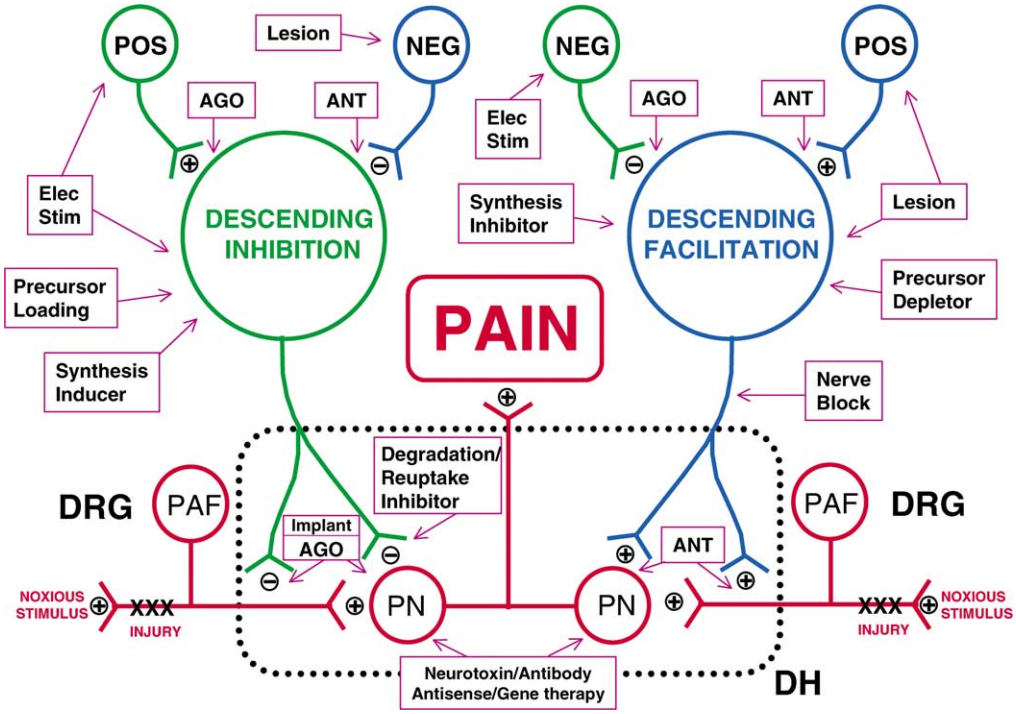

Fig. 8. Summary of approaches which may potentially be exploited clinically in the manipulation of descending controls for pain relief. As described in the text, not all strategies illustrated can currently be undertaken in patients. Many approaches have been best characterized for serotonergic and noradrenergic mechanisms of descending inhibition but they are also, in principle, applicable to other transmitters. Neurotoxin, antibody and antisense/gene therapy strategies are intended to selectively suppress expression of those receptors on PN which enhance transmission of nociceptive information. Abbreviations as follows: DRG, dorsal root ganglion; PAF, primary afferent fibre; DH, dorsal horn; ANT, antagonist; AGO, agonist; POS, positive modulator; NEG, negative modulator and elect stim, electrical stimulation. For further details, see text.

12.2.2. Therapeutic approaches

First, one might advocate the local administration of agonists or antagonists as appropriate into defined cerebral structures. However, even if a drug displayed an acceptable pharmacological, pharmacokinetic and safety profile permitting its use by such an approach, with the exception of isolated cases of otherwise-intractable pain, it is unlikely that cerebral microinjection procedures would be preferred to standard procedures of systemic drug administration. While opioids and/or other drug classes have not been microinjected into discrete cerebral structures in man, i.c.v. administration of morphine and β-EP has been shown to alleviate pain in clinical studies (Yaksh, 1999a).

Second, electrical stimulation of a variety of brain structures elicits antinociception via recruitment of supraspinal mechanisms (Fig. 2) which ultimately lead to a reinforcement of DI: actions of, for example, cannabinoids (Section 11.1.3) and β-EP (Section 9.3.5) in the PAG have been implicated (Akil et al., 1976; Besson et al., 1978; Fields et al., 1991; Millan et al., 1996; Fields and Basbaum, 1999). Opioidergic mechanisms have also been implicated in reports of SPA in man. In addition to the PAG, pain relief in patients has been documented from a variety of regions including the anterior hypothalamus and cortex (Morgan et al., 1989a,b; Richardson, 1990; Yaksh, 1999a). However, in view of its technical complexity, brain-stimulation for activation of pathways mediating DI will probably remain of marginal significance to clinical pain relief.

Third, methods for the modification of 5-HT and NA availability have been described in the psychiatric literature (Van Der Does, 2001). Provision of metabolic precursors (loading) to increase the synthesis of NA and 5-HT has been shown to enhance the induction of opioidergic analgesia in man (Richardson, 1990). Histamine precursors have likewise been shown to elicit antinociception in experimental studies (Section 8.1) (Hough, 1988, 2001; Brown et al., 2001). Thus, systemically-active agents capable of accelerating or inhibiting synthesis of transmitters inducing/mediating DI or DF, respectively, would be of potential interest. Transmitters afferent to descending pathways mediating DI or DF might also be targetted. Thus, this approach incorporates both “supraspinal” and “spinal” strategies. The reversible modification of transmitter production might be preferable to the destruction of structures inducing or mediating DF (Section 12.3.3.2) in light of clinical observations of unpredictable and undesirable side-effects upon: (1) surgical interruption of ascending channels of nociceptive information (spinal and thalamic) and (2) sympathectomy (Gybels and Sweet, 1989; Millan, 1999).

12.3. Spinal strategies for exploitation of descending controls

12.3.1. Benefits and drawbacks of spinal drug delivery

12.3.1.1. Pharmacokinetics. The over-riding goal of spinal drug delivery is just that: to selectively access segmental targets without affecting other regions, thereby avoiding potentially detrimental side-effects and maximizing analgesic efficacy. This principle of spatially-delimited, regional analgesia implies prevention of drug access not only to peripheral tissues but also to the brain, and even to regions of the spinal cord distant from the injection catheter. Correspondingly, the pharmacokinetic profile of a spinally-administered drug is a critical issue (Eisenach et al., 1996; Dougherty and Staats, 1999; Yaksh, 1999b,c; Menigaux et al., 2001). A certain degree of liphophilicity sufficient to permit tissue penetration (to the DH and, for sympathetic pain, to the IML) is essential. However, it should not be so pronounced as to favour drug absorption and redistribution via the systemic circulation to supraspinal centres or peripheral tissues. Indeed, for highly lipophilic drugs, there is little or no advantage in terms of potency and efficacy between epidural administration and an i.v. bolus, questioning the utility of "spinal" administration (Eisenach et al., 1996; Menigaux et al., 2001). A further difficulty is rostral diffusion via the CSF to higher centres. For example, by actions in the medulla, μ-opioids and α_2-AR agonists can elicit delayed respiratory depression and hypotension/sedation, respectively, even upon spinal administration. Nevertheless, for certain agents, such as the α_2-AR agonist, clonidine, despite eventual dispersion to other sites, potency is superior for epidural versus i.v. administration and a spinal locus of analgesic action has been rigorously confirmed (Eisenach et al., 1996, 1998). In particular for drugs of high lipophilicity, i.t. (subdural) administration—analgous to experimental studies—is an important option to help confine drug actions to the spinal cord, to improve potency and to augment the therapeutic window (Eisenach et al., 1996, 1998, 2000). However, the necessity for this more demanding technique can prove restrictive in the evaluation and therapeutic use of drugs. It should also be recalled that gains in therapeutic window due to avoidance of supraspinal and peripheral side-effects may be offset by cardiovascular and motor perturbation due to actions at spinal populations of preganglionic neurones and MNs, respectively (Section 2.5) (Eisenach et al., 1996; Millan, 1997; Dougherty and Staats, 1999; Yaksh, 1999b; Goodarzi and Narasimhan, 2001).

Several novel delivery strategies, such as the use of polymers and liposomes to stabilize and prolong drug actions, and the use of computer-controlled infusion protocols to optimize infusion rates, may facilitate the use of analgesic agents upon their spinal administration (Masters et al., 1993; Eisenach et al., 1995b, 1996; Dougherty and Staats, 1999; Yaksh, 1999a,b,c).

Thus, while spinal administration may permit major gains in terms of potency, efficacy, rapidity, regionality of action and therapeutic window (as well as permitting drug associations), all these potential advantages require careful experimental and clinical evaluation, taking into account the pharmacokinetic profiles of drugs upon their epidural and/or intrathecal administration (Yaksh, 1999b,c).

12.3.1.2. Safety and general utility. The importance of pharmacokinetic studies by the spinal route was emphasized above. There is similarly a need to thoroughly examine the safety profile of drugs in terms of their general toxicity, incorporating their local influence upon spinal vasculature and function, as judged by behavioural, histopathological and clinical criteria (Yaksh, 1999b,c).

Regional analgesia is appropriate for certain conditions in which pain is localized and can be attributed to an identified mechanism, such as obstetric pain, post-operative pain from specific organs and certain types of chronic pain due to injury or disease. It is less well adapted to diffuse (and long-term) pains, such as rheumatoid arthritis. Further, several common forms of cranial pain (headache and dental pain) integrated in the trigeminal nucleus are not amenable to spinal delivery strategies. Thus, there are limitations to the utilization of spinal analgesia. Moreover, spinal drug administration is a very different affair to the oral consumption of a drug such as aspirin. This (for patient and practioner alike) specialized and challenging technique constitutes an insurmountable obstacle to its universal utilization for pain relief. What may be necessary and desirable in a hospital environment is simply irrealistic in daily settings.

Thus, though conceptually attractive, and presenting numerous, potential advantages, drug development employing spinal routes of administration is complex, invasive and technically-demanding. Further, in contrast to more conventional oral treatments, there are important restrictions as concerns the number and type of patient which can be treated as well as specific problems, such as the risk of infection. Regrettably, in the present economic and legislative climate, these reflections do little to encourage the pursuit of drugs exclusively or predominantly intended for spinal administration. It is more likely that spinal options will be evaluated only following the introduction of drugs for use upon systemic administration, irrespective of the initial indication, whether pain (e.g. μ-opioids) or other (e.g. α_2-AR agonists, hypotension).

12.3.2. Spinal strategies for reproducing descending inhibition

12.3.2.1. Mimicking multiple mechanisms of descending inhibition. One potential drawback to the use of highly-selective agonists is that activation of a single receptor type may not fully mimic the global effect of DI, which is expressed via multiple mechanisms. For example, co-activation of specific serotonergic, noradrenergic and

other mechanisms in the DH may be critical for the mediation of supraspinal opioidergic antinociception (Section 7.5). Further, the antinociceptive actions of NA may be mediated via several subtypes of α_2-AR and accentuated by, for example, the concomitant release of GABA or ENK (Section 5.8). While supraspinal approaches upstream of DI should, in principle, mimic the physiological activation of DI, this presents a problem for spinal delivery of monoreceptorial agents acting at individual classes of receptor post-synaptic to descending pathways. Several spinal strategies relevant in this regard are discussed in the following paragraphs.

12.3.2.2. Modulation of transmitter uptake and metabolism. Drugs preventing monoamine reuptake by occupation of 5-HT and/or NA transporters permit the activation of a broad, "physiological" complement of receptors. Correspondingly, independently of their influence upon mood, antidepressant agents have been shown to exert antinociceptive properties upon both systemic and, in rodents, spinal administration (Eschalier et al., 1988; Eschalier, 1990; Ardid and Guilbaud, 1992; Ardid et al., 1995; McQuay et al., 1996; Kawamata et al., 1999; Monks and Merskey, 1999; Ansari, 2000; Bardin et al., 2000a,b; Sawynok and Reid, 2001). In this regard, interference with NA as compared to 5-HT reuptake imparts superior analgesic properties (Schreiber et al., 1999; Ansari, 2000; Bohn et al., 2000; Sahebgharani and Zarrindast, 2001). Indeed, drugs selectively interacting with NA transporters exert antinociceptive properties both alone and in association with opioids (Eschalier, 1990; Mestre et al., 1997; Monks and Merskey, 1999; Reimann et al., 1999; Ansari, 2000; Hernandez et al., 2001). The novel and clinically-effective analgesic, tramadol, appears to reproduce this dual mechanism of action in behaving as a weak μ-opioid agonist and an inhibitor of NA reuptake (Kayser et al., 1992a,b). (In addition to monoamine reuptake inhibition, it should be noted that several other mechanisms have been implicated in antinociceptive actions of antidepressants: Na^+-channel blockade, recruitment of GABAergic ININs, indirect stimulation of adenosine (A_1) receptors and blockade of NMDA receptors (Eschalier, 1990; Eisenach and Gebhart, 1995; Pancrazio et al., 1998; Sawynok, 1998; Monks and Merskey, 1999; Sabetkasai et al., 1999; Asahi and Yonehara, 2001)). The design of other drug classes which either decrease (DI) or accelerate (DF) the reuptake and/or degradation of specific (tonically-active) transmitters is an attractive proposition. For example, drugs inhibiting the activity of enzymes for the metabolic conversion of adenosine (adenosine kinase and adenosine deaminase) display antinociceptive properties both in experimental and clinical studies (Sawynok and Sweeney, 1989; Sawynok, 1998; Lavand'homme and Eisenach, 1999; Yaksh, 1999a). Further, robust antinociception is elicited by peptidase inhibitors which prevent the metabolism of ENK (Dickenson et al., 1988; Millan et al., 1996; Honoré et al., 1997; Yaksh, 1999a; Mas Nieto et al., 2001). There is considerable scope for the exploitation of enzymes for manipulation of the activity of other classes of neuropeptide involved in DI or DF.

12.3.2.3. Adrenal chromaffin cell implants. The implantation of cultured, adrenal medulla chromaffin cells under the subarachnoid space reduces nociception in a variety of models including PAF injury (Sagen et al., 1993; Pappas et al., 1997; Yu et al., 1998; Czech and Sagen, 1995; Eaton, 2000). This approach may even promote recovery of a "normal" neuronal organization of the DH which is perturbed by damage to PAFs in: (1) restituting local GABAergic transmission, loss of which has drastic consequences for nociceptive processing and (2) normalizing levels of NMDA receptors, stimulation of which enhances DH excitability (Willis, 1994; Hama et al., 1995; Ibuki et al., 1997; Millan, 1999) (Section 10). The encapsulation of bovine chromaffin cells in a dialysis cartridge facilitates access to nutrients and prevents the penetration of inflammatory cells, so attenuating immune rejection and obviating the need for immunosuppressive therapy (Décosterd et al., 1998; Yu et al., 1998). The ability of chromaffin cells to generate catecholamines and ENKs as well as various neuropeptides and trophic factors accounts for the earlier-mentioned functional effects and suggests that this approach more satisfactorily mimics DI in the spinal cord than the administration of a selective pharmacological agent (Unsicker and Krieglstein, 1996; Décosterd et al., 1998; Yu et al., 1998). Pharmacological analyses support the concept that implants synergistically co-activate adrenergic and opioidergic mechanisms in that antagonists of both opioid receptors and α_2-ARs attenuate the induction of antinociception (Hama and Sagen, 1994; Yu et al., 1998). Nevertheless, the production of other potentially antinociceptive peptides, such as GAL (Section 9.7) may also contribute to pain relief (Unsicker and Krieglstein, 1996). Initial clinical reports are promising as regards the pain-relieving potential of chromaffin implants (Winnie et al., 1993; Buchser et al., 1996).

12.3.2.4. Clonal cell line implants. In a complementary approach, the implantation of a clonal cell line releasing catecholamines (mouse B16 melanoma) in mice and rats suppressed SP-induced nociception and enhanced antinociceptive actions of both NA reuptake inhibitors and morphine, actions shown to be mediated by α_2-ARs (Wu et al., 1994a,b; Eaton, 2000). Such cell lines can, in principle, be genetically engineered to improve their characterisics and it has been shown that a serotonergic, neuronal raphe-derived cell line (RN46A) transfected with the neurotrophin, brain-derived neurotrophic factor, survives for extended periods upon transplantion into the lumbar cord of rats with PAF injury. Hyperalgesia and allodynia are reduced and, in analogy to chromaffin implants, the disappearance of GABergic ININs is reversed (Eaton et al., 1997, 1998; Eaton, 2000).

These implantation approaches are of special interest inasmuch as they not only afford symptomatic pain relief but

even, presumably via provision of trophic factors, reverse pathological changes underlying chronic pain. Moreover, the use of cell lines allows for the integration into the genome of specific genes for modification of their phenotype and improvement of their therapeutic properties: for example, factors improving their viability, permitting drug-induced control of their functional activity and adding to their complement of analgesic transmitters.

12.3.3. Strategies for interference with descending facilitation

12.3.3.1. Pharmacological strategies. As discussed earlier, the use of agonists to reproduce the actions of neurotransmitters mediating DI, such as α_2-AR agonists, either alone or in association with other analgesic agents, can provide effective pain relief in man. One may also envisage the administration of antagonists to block mechanisms of DF. In principle, their utilization alone would be intended to interrupt "hyperalgesic" mechanisms of DF which aggravate chronic painful states (Section 4.4). Although the distinction may be somewhat artificial (Section 4.5), their co-administration with agents acting via recruitment of DI would aim to block "anti-analgesic" actions of transmitters involved in DF.

Currently, no clinical studies have been undertaken to explore the therapeutic validity of the first of these approaches. Of the various mechanisms implicated in the spinal expression of DF, 5-HT_{1A} antagonists and D_1 antagonists, for example, have not been evaluated clinically, while studies of the potential analgesic properties of α_1-AR antagonists have concentrated on peripheral populations engaged by sympathetic fibres (Millan, 1999; Raja et al., 1999; Fuchs et al., 2001; Hord et al., 2001b). NO inhibitors, and non-opioidergic DYN "antagonists" have not, to date, been clinically examined. Furthermore, the pain-relieving properties of the NMDA channel blocker, ketamine, are most convincingly attributed to its abrogation of glutamatergic PAF input—independently of DF—rather than the blockade of hypothetical pronociceptive actions of glutamate released from descending pathways (Watkins et al., 1994; Millan, 1999; Yaksh, 1999a). Thus, a clinical "proof of concept" study showing that selective interference with the expression of DF alleviates pain is awaited.

As outlined in Section 9.5, a key role of CCK has been evoked in both hyperalgesic and anti-analgesic mechanisms. Currently, there is no evidence that selective blockade of the actions of CCK can provide clinically-relevant pain relief. However, initial clinical studies indicate that elimination of the inhibitory influence of CCK upon opioidergic mechanisms of analgesia may be of therapeutic utility. Thus, the mixed $CCK_{1/2}$ antagonist, proglumide, enhanced the analgesic actions of morphine and potentiated placebo-induced analgesia, which is partially mediated by endogenous opioidergic mechanisms (Price et al., 1985; Lavigne et al., 1989; Benedetti, 1996, 1997). There remains a need for more extensive, controlled and focussed clinical studies of the potential influence of selective CCK_1 and CCK_2 antagonists upon the analgesic actions of morphine and other opioids (McCleane, 2000). Nonetheless, these data underpin the conviction that simultaneous interference with DF and reinforcement of DI may improve analgesia as compared to either mechanism alone.

12.3.3.2. Other strategies. As an alternative to pharmacological strategies, other more radical approaches may directly eliminate DH neuronal units transducing DF.

Following release of SP from PAFs, NK_1 receptors are internalized in PNs (Mantyh et al., 1995; Nichols et al., 1999). The conjugation of the mitochondrial toxin, saporin, to SP leads to the destruction of NK_1 receptor-bearing neurones and antinociception against inflammatory pain (Mantyh et al., 1995; Nichols et al., 1999; Huo, 2000). Whether such events are relevant to potential pronociceptive actions of SP released from descending pathways mediating DF (Section 10.1) remains to be elucidated. In any case, they illustrate the principle that, likely as a last resort, spinal delivery-based techniques may allow for the discrete obliteration of PNs, EXINs and/or PAF terminals bearing pronociceptive receptors involved in the generation of DF. Interestingly, the utility of this approach has—at least as an experimental tool—been established with the demonstration that i.c.v. conjugation of saponin to an antibody directed against DA β-hydroxylase permits selective suppression of descending noradrenergic pathways to the DH (Wrenn et al., 1996; Martin et al., 1999b; Sawamura et al., 2000). Further, a comparable procedure was recently adopted for the selective deletion of a RVM-derived pathway mediating DF following PAF injury in rats: the cells of origin possess μ-opioid receptors permitting their elimination by coupling of the toxin to an agonist for these sites (Porreca et al., 2001).

Spinal administration of highly selective antisense probes (oligonucleotides neutralizing specific mRNA sequences) may allow for modification of the production by PNs, EXINs and PAFs of receptors and other gene products mediating DF (Huo et al., 2000). The technical feasability of this approach has been explored in rodents. Thus, an antisense probe directed against 5-HT_3 receptors was shown to interfere with the induction of antinociception by 5-HT (Paul et al., 2001), while antisense supression of GAL_1 receptors interferes with the antinociceptive properties of GAL (Pooga et al., 1998). Further, antisense-induced disruption of the synthesis of NK_1 receptors was found to elicit antinociception in parallel with a reduction in levels of the protein targetted (Hua et al., 1998; Pohl and Braz, 2001). More speculatively, viral gene transfer (spinal application or via PAF input) could be employed to either amplify or suppress the production of transmitters/receptors mediating DI and DF, respectively (Marsh et al., 2001; Pohl and Braz, 2001).

Finally, selective antibodies and protein constructs may be utilized to sequester and neutralize specific transmitters or modulators participating in mechanisms of DF in the DH.

To date, the feasibility of such approaches has been principally investigated for peripheral actions of the neurotrophin, neural growth factor, the pronociceptive properties of which may be blocked either by specific antibodies or fusion proteins comprising an immunoglobulin coupled to the neurotrophin receptor, trk-A (Lewin et al., 1994; Millan, 1999; Luo, 2000).

12.4. Developmental issues

Amongst numerous other considerations, a crucial question is whether interventions such as cell implantations, neurotoxins and antisense or gene therapy exert effects which are rapid, temporary, controllable and reversible, or whether they initiate, in an unpredictable fashion, delayed and possibly irreversible changes not necessarily conducive to pain relief. Although it has been pointed out that chromaffin cell implants can be retrieved from the spinal cord (Décosterd et al., 1998), the discontinuation of such therapies cannot be achieved as simply as the suspension of drug administration, whether by the systemic or spinal route and may be too late to reverse pathological processes already initiated. More generally, then the above-specified technologies, while innovative and likely effective, present formidable technical, developmental and regulatory challenges, and require rigorous clinical evaluation. Despite their interest, they will likely find application only in restricted populations of otherwise refractory patients. Indeed, it is difficult to imagine that such techniques would supercede more conventional strategies of systemic and spinal administration of drugs interacting rapidly and reversibly with specific targets (one or several) involved in processes of either DI or DF.

12.5. Rationally-designed, multireceptorial agents

In Section 12.3, it was pointed out that analgesic approaches based upon an increase in synaptic concentrations of monoamines, opioids and other transmitters "physiologically" released by descending pathways may more satisfactorily mimic their operation and, as a consequence, more effectively relieve pain than selective drugs reproducing but a single mechanism of their global actions. However, counterbalancing this apparent advantage, such strategies will inevitably recruit mechanisms mediating DF as well as DI. This may impose a ceiling on their capacity for pain relief.

It may be possible to circumvent this problem by strategies offering a compromize between approaches fully mimicking mechanisms of DI and those targetting individual receptors. Namely, multireceptorial agents activating and blocking specific classes of receptor mediating DI and DF, respectively. This strategy attempts to reproduce the benefits of drug associations within a single molecule possessing an—at least dual mechanism of action. For example, the association of α_2-AR agonist and 5-HT_{1B} agonist properties to harness noradrenergic and serotonergic mechanisms of DI. On the other hand, combination of α_2-AR agonist and 5-HT_{1A} antagonist actions would concurrently recruit noradrenergic mechanisms of DI and diminish serotonergic mechanisms of DF. Though the chemistry would be more demanding, the expansion of such strategies to incorporate more disparate constellations of receptorial mechanisms, such as μ-opioid agonist plus CCK_2 antagonist properties, could also be imagined. Multi-target drugs may allow for particularly powerful and broad-based pain relief with an acceptable therapeutic window to disruptive side-effects. Such a strategy is reminiscent of the successful use of multireceptorial agents for the improved management of schizophrenia. These "atypical" agents-most prominently, clozapine-display pronounced antipsychotic efficacy in the relative absence of extrapyramidal side-effects (Brunello et al., 1995; Chakos et al., 2001).

13. General discussion

In concluding the present review, it is instructive to recall several major themes which are likely to inform future research into the physiological significance and therapeutic relevance of descending controls of nociceptive processing.

First, it is critical to establish patterns of neuronal connections both in the DH and in structures from which descending controls originate, in particular as regards the transmitters and multiple classes of receptor via which individual classes of neurone exert their actions. Together with a precise knowledge of the influence of specific receptors upon cellular transduction mechanisms, this permits reasonably concrete predictions concerning their likely influence upon nociception at specific sites of action. For example, a receptor positively coupled to PLC will increase neuronal excitability and, if localized on PNs, will inevitably fulfill a pronociceptive role at this level. On the other hand, a transmitter which enhances K^+-currents will hyperpolarize neurones: if localized on a RVM-localized cell type initiating DF, or neurones inhibitory to cells eliciting DI, it will likely express antinociceptive actions at that locus. In this light, however, it should be pointed out the influence of specific receptors upon transduction mechanisms may be cell- and even agonist-specific and it will be important to enhance our knowledge of the precise influence of receptors and their ligands upon intracellular signals and cellular excitability for defined classes and populations of neurone (Kenakin, 1995; Pan et al., 1998b; Abadji et al., 1999; Jin et al., 2001; Kukkonen et al., 2001; Moon et al., 2001).

Second, inasmuch as virtually all transmitters and receptor types involved in descending controls display multiple sites and/or mechanisms of action, it is difficult to anticipate the global influence of ligands upon nociception following their systemic administration (Tables 2 and 3, Figs. 5–7). This point underscores the importance of local drug administration in the characterization of the roles of transmitters/receptors in descending controls, and underpins interest in the clinical vectorization of drugs to their site(s) of

action, notably in the spinal cord. On the other hand, from a therapeutic perspective, it is critical to take account of the overall influence of drugs upon pain following their parental administration, the route most favoured for their clinical utilization.

Third, in line with the preceding remark, a single transmitter and even a single receptor class can exert a divergent influence of nociception at both spinal and supraspinal loci as a function of localization and influence upon neuronal excitability. Thus, for many transmitters and receptor classes, a bidirectional influence upon nociceptive processing at cerebral and/or segmental loci has been established (Tables 2 and 3). This point underlines the above-mentioned difficulty of predicting the influence upon nociception of even highly-selective ligands, and strongly supports the argument that the assignment of a particular role to individual classes of descending pathways, of transmitter and even of receptor may be misleading—if not frankly erroneous. This is particular true for—the majority of—neurones which contain and release several transmitters modulating nociceptive processing. In addition to receptor multiplicity per se, there is increasing evidence for functional interplay amongst co-localized receptors. This is manifest both at the level of second messenger systems (e.g. activation of one receptor may trigger the phosphorylation of a different class of colocalized receptor) and even in terms of their physical association. For example, protein–protein interactions and functional heterodimers have been demonstrated between various subtypes of opioid receptor and even between entirely unrelated receptor classes, such as mGluR and adenosine (A_1) receptors and $GABA_A$ and D_5 receptors (Xie et al., 1999b; Liu et al., 2000; Bouvier, 2001; Ciruela et al., 2001; Harkness and Millar, 2001; Marshall, 2001; Martin and Prather, 2001). If heterodimers genuinely occur in the CNS, this will have profound implications for future studies of the operation and therapeutic exploitation of descending controls. Confirmation that certain receptors display constitutive (spontaneous) activity would also have been important implications for interpretation of their roles in the control of nociception and for the design of drugs modulating their activity: notably, antagonists (or inverse agonists) at receptors mediating DF (Milligan et al., 1995; Abadji et al., 1999; Miller et al., 1999).

Fourth as exemplified by many recent studies, it is essential to characterize the roles of descending controls not only in the resting state, but also under conditions of clinically-relevant, acute and long-term inflammatory and neuropathic pain. In this regard, it is desirable to characterize both hyperalgesia and allodynia, to employ diverse modalities of noxious stimulus (e.g. thermal versus mechanical) and to take account of the cognitive-attentional dimension of pain.

Fifth, enormous progress has been accomplished over the past decade in our understanding of the daunting complexity of descending controls. A fundamental conceptual advance comprises the universal recognition that descending pathways do not exclusively dampen nociceptive transmission by processes of DI but also, and simultaneously, enhance its passage by mechanisms of DF. Both DI and DF have well-defined physiological roles and oscillations in their relative intensity serve to optimize signalling of noxious information and, where adaptive and appropriate, to encourage or suppress the sensation of pain. However, adjustments in their relative intensity are insufficient to negate clinical-in particular chronic-pain. Under these conditions, in common with other mechanisms of nociceptive processing, the interelationship between DI and DF ultimately becomes dysregulated. In this light, there is increasing evidence that excessive activity of mechanisms of DF contributes to chronic, painful states. Indeed, this "counterintuitive" contribution of mechanisms of DF to long-term painful states underlines their pathological and non-adaptive nature, an issue considered from an evolutionary perspective elsewhere (Millan, 1999).

Sixth, in line with the preceding comment, both reinforcement of DI and interference with DF offer complementary strategies for pain relief. However, whether interruption of DF alone will suffice for the attainment of clinically-robust analgesia remains to be determined. (Interruption of DF may actually interfere with processes recruiting DI). Nevetheless, drugs blocking DF may prove to be effective in conjunction with analgesic agents acting via the reinforcement of DI.

Seventh, the existence of multiple mechanisms eliciting and expressing both DI and DF highlights the importance of "multi-target" analgesic strategies for the manipulation of descending controls. Thus, judicious drug combinations may permit an increase in analgesic efficacy and a mimimization of side-effects, as illustrated by the co-administration of α_2-AR agonists with opioids or cholinergic agents. Correspondingly, rather than an obsessive and illusory search for highly-selective agents at a single receptor type, multireceptorial agents may permit the balanced and more efficacious manipulation of mechanisms of DI (reinforcement) and DF (inhibition). For example, dual α_2-AR and 5-HT_{1B} agonists or α_2-AR agonists and 5-HT_{1A} antagonists. This strategy is analogous to the use of multireceptorial agents for improvement in the therapeutic window of antipsychotic agents.

Eighth, intensive research over the past decade has revealed an extravagant repertoire of mechanisms involved in the modulation and expression of descending controls. With the exception of parenteral administration of μ-opioids (for which a component of analgesia may be attributed to supraspinal activation of DI) and spinal application of α_2-AR agonists (which reproduce noradrenergic mechanisms of DI in the DH), no other approach has been extensively validated in the clinic (Millan, 1986, 1997; Eisenach et al., 1996; Yaksh, 1999a), though initial experience with CCK antagonists and adenosine (A_1) agonists is encouraging. Despite many impressive experimental observations, the ultimate proof of concept is in the clinic, in particular for strategies designed to manipulate such a complex, dynamic, and interactive system as descending controls of nociception. In view of species differences, the huge complexity and

redundancy in descending control of nociceptive processing, diverse roles of individual transmitters and receptors and the overriding importance of the cognitive–affective dimension of pain in man, considerable caution must be excercised in extrapolating hypotheses to clinical pain.

14. Concluding comments

The proliferation of potential analgesic drug targets for the therapeutic manipulation of descending controls is testimony to the intensive and highly-successful research programme of the past decades. In parallel, great efforts have been invested in the characterization of peripheral and central mechanisms involved in the induction of nociception. Further, there is an increasing awareness of the importance of the cognitive–affective component of pain (appreciation, tolerance and coping). Mechanisms inducing pain, and higher centres involved in its emotional–cognitive dimension, are both interlinked with descending controls of nociception of which the extraordinary diversity now recognized provides a rich palette of novel mechanisms potentially available for the improved control of pain.

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