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Neuroanatomy of the Pain System and of the Pathways That Modulate Pain

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Abstract

We review many of the recent findings concerning mechanisms and pathways for pain and its modulation, emphasizing sensitization and the modulation of nociceptors and of dorsal horn nociceptive neurons. We describe the organization of several ascending nociceptive pathways, including the spinothalamic, spinomesencephalic, spinoreticular, spinolimbic, spinocervical, and postsynaptic dorsal column pathways in some detail and discuss nociceptive processing in the thalamus and cerebral cortex. Structures involved in the descending analgesia systems, including the periaqueductal gray, locus ceruleus, and parabrachial area, nucleus raphe magnus, reticular formation, anterior pretectal nucleus, thalamus and cerebral cortex, and several components of the limbic system are described and the pathways and neurotransmitters utilized are mentioned. Finally, we speculate on possible fruitful lines of research that might lead to improvements in therapy for pain.

Rapid advances in our knowledge of the pain system have been made in the recent past. Discoveries have increased our understanding of nociceptors and of the processing of nociceptive information in the spinal cord, brainstem, thalamus, and cerebral cortex. Furthermore, there have been new findings concerning the descending pathways that modulate nociceptive activity. In this review, we highlight some of these new findings and, when feasible, indicate how this information might lead to improvements in patient care.

Keywords

Pain; Pain modulation; Sensitization; Nociceptive pathways; Analgesia systems

NOCICEPTORS

Nociceptors have now been described in most of the structures of the body that give rise to pain sensation, including the skin, muscle, joints, and viscera (reviewed in Willis, 1985; Willis and Coggeshall, 1991). Human studies involving microneurography and microstimulation in peripheral nerves have demonstrated that repetitive activation of cutaneous mechanoreceptors at high rates does not lead to pain (Ochoa and Torebjork, 1983; Torebjork et al., 1987), whereas activation of nociceptors at even relatively low rates (e.g.,

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>=3 Hz) does result in pain (Ochoa and Torebjork, 1989). The quality of the pain sensation depends on the tissue innervated by the nociceptors being stimulated; e.g., stimulation of cutaneous A[delta] nociceptors leads to pricking pain (Konietzny et al., 1981), whereas stimulation of cutaneous C nociceptors results in burning or dull pain (Ochoa and Torebjork, 1989). Activation of nociceptors in muscle nerves by electrical stimulation produces aching pain (Torebjork et al., 1984). Electrical stimulation of visceral nerves at low intensities results in vague sensations of fullness and nausea, but higher intensities cause a sensation of pain (reviewed in Ness and Gebhart, 1990). Unless the experiments using microstimulation of single afferents are shown to be unsound technically, it is evident that pain sensation normally results from the activity of nociceptors and not from overactivation of other kinds of receptors (Wall and McMahon, 1985; Torebjork et al., 1987) and that there are distinct sensory channels for different qualities of pain (Willis and Coggeshall, 1991). However, pain can also result from activation of central nociceptive pathways without involving peripheral nociceptors, e.g., in cases of central pain which may follow damage to the central nervous system (Boivie et al., 1989). Motivational-affective circuits can also mimic pain states, most notably in patients with anxiety, neurotic depression, or hysteria (Chaturvedi, 1987; Merskey, 1989).

A major discovery in the 1980s was that many nociceptors, possibly most, are inactive and rather unresponsive under normal circumstances. This observation was first made in recordings from the nerves supplying the knee joint (Schaible and Schmidt, 1983a,b) and led to the description of these afferents as “silent” or “sleeping” nociceptors. However, inflammation can cause the sensitization of these nerve fibers, after which they “awaken,” by developing spontaneous discharges and becoming much more sensitive to peripheral stimulation (Fig. 1)(Schaible and Schmidt, 1985, 1988). Silent nociceptors have now been described not only in joint nerves but also in cutaneous and visceral nerves (Habler et al., 1990; Handwerker et al., 1991; Davis et al., 1993). Sensitization of nociceptors depends on the activation of second-messenger systems by the action of inflammatory mediators released in the damaged tissue, such as bradykinin (BK), prostaglandins, serotonin, and histamine (Dray et al., 1988; Schepelmann et al., 1992; 1993; Birrell et al., 1993; Davis et al., 1993).

Primary hyperalgesia is believed to be a consequence of the sensitization of nociceptors during the process of inflammation (Meyer and Campbell, 1981; LaMotte et al., 1982; 1983). Hyperalgesia can be defined as an increase in the painfulness of a noxious stimulus and a reduced threshold for pain (see Bonica, 1992). Whereas primary hyperalgesia is enhanced pain felt at the site of injury, secondary hyperalgesia is felt at a site remote from the original injury (Lewis, 1942; Hardy et al., 1952) (described herein).

Modulation of Nociceptors

The activity of nociceptors can be affected not only by adequate stimuli, such as strong mechanical, thermal, or chemical stimuli (see Willis, 1985; Willis and Coggeshall, 1991), but also by chemical actions on surface membrane receptors of their axons. For example, primary afferent nociceptors normally have several types of pharmacological receptors on their surface membranes, including opiate, [gamma]-aminobutyric acid (GABA), BK,

histamine, serotonin, and capsaicin receptors (Dray, 1994). In addition, the effectiveness of a population of pharmacological receptors on nociceptors can be changed in certain circumstances; e.g., opiate receptors are ineffective in modulating the normal activity of joint nociceptors, but they were shown to become effective after the development of inflammation (Stein, 1994). After peripheral nerve injury, many afferent fibers express newly formed adrenoreceptors (Sato and Perl, 1991; Campbell et al., 1992; Bossut and Perl, 1995; Xie et al., 1995). Furthermore, afferent fibers supplying the knee joint and also the skin have excitatory amino acid receptors (Fig. 2), and intraarticular administration of excitatory amino acid receptor antagonists can reduce hyperalgesia in rats with experimental arthritis (Lawand, W. D. Willis, and K. N. Westlund, unpublished observations, 1996).

Damage to a peripheral nerve can cause the upregulation of several neuropeptides, including galanin and vasoactive intestinal polypeptide (VIP) in dorsal root ganglion cells and their central branches, but downregulation of others, such as substance P (SP), somatostatin, and calcitonin gene-related peptide (CGRP) (reviewed in Zhang et al., 1993). In addition, Schwann cells in damaged nerves produce increased amounts of messenger RNA for neurotrophins and their receptors (Ernfors et al., 1993; Funakoshi et al., 1993). Presumably neurotrophins play a role in regenerative events. However, growth factors may well cause aberrant forms of regeneration and abnormal pain states; e.g., they may be responsible for the in-growth of sympathetic postganglionic axons into dorsal root ganglia, where they encircle the cell bodies of dorsal root ganglion cells (Chung et al., 1993; McLaughlin et al., 1993). In addition, in the case of peripheral nerve injury, large myelinated afferents, presumably supplying mechanoreceptors, grow into lamina II after peripheral nerve injury (Woolf et al., 1992, 1995). Abnormal connections of these large afferents to the nociceptive processing circuits of the dorsal horn may contribute to allodynia, a sensation of pain that is provoked in pathological circumstances by innocuous stimuli (Bonica, 1992).

Dorsal Horn

The central pathways for processing nociceptive information begin at the level of the spinal cord (and medullary) dorsal horn. Interneuronal networks in the dorsal horn are responsible not only for the transmission of nociceptive information to neurons that project to the brain, but also help modulate that information and pass it on to other spinal cord neurons, including flexor motoneurons and nociceptive projection neurons; e.g., certain patterns of stimulation can lead to enhanced reflex actions and to sensitization of projection neurons and increased nociceptive transmission. Other inputs result in the inhibition of projection neurons. The balance of these excitatory and inhibitory processes is the basis of the gate theory of pain transmission (Melzack and Wall, 1965) and of the mechanism referred to by LeBars et al. (1979a,b) as “diffuse noxious inhibitory controls” or DNIC.

The neurotransmitters contained in the terminals of nociceptive afferent fibers in the dorsal horn include excitatory amino acids, particularly glutamate (De Biasi and Rustioni, 1988), as well as neuropeptides, such as SP, CGRP, VIP, somatostatin, and others (reviewed in Willis and Coggeshall, 1991). These can be demonstrated by immunohistochemical staining of sections of the spinal cord. Certain experimental conditions, such as peripheral nerve damage, can lead to an upregulation or downregulation of these transmitters; e.g., after the

sciatic nerve is cut, the levels of stainable galanin in the dorsal horn increase (Zhang et al., 1993). However, the increased stores of galanin do not appear to exist in the synaptic terminals but rather in axons coursing through the dorsal horn (Carlton and Coggeshall, 1996). Another example is the increased stores of glutamate in the dorsal horn that occur after the development of experimental arthritis (Fig. 3A and top panels) (Sluka et al., 1992; Sluka and Westlund, 1993). There is an initial decrease in staining for SP (Fig. 3B)(Sluka et al., 1992), presumably due to release of this peptide (and also of CGRP) into the dorsal horn during the onset of arthritis (Schaible et al., 1990, 1994). However, SP and CGRP stores increase as these neuropeptides are produced and transported from dorsal root ganglion cells to the dorsal horn (Fig. 3B and C) (Sluka and Westlund, 1993). The increase in glutamate stores helps explain the higher concentration of glutamate that can be detected by microdialysis in the dorsal horn in experimental arthritis (Sluka et al., 1994).

After strong or damaging stimuli, such as repeated noxious heating or squeezing of the skin, intradermal injection of capsaicin, or induction of acute arthritis, nociceptive neurons in the dorsal horn develop an enhanced responsiveness to peripheral stimuli applied to undamaged regions of the skin (Fig. 4) (Kenshalo et al., 1979, 1982; Owens et al., 1992; Simone et al., 1991; Dougherty et al., 1992b). Sensitization of neurons in the dorsal horn has been attributed to the combined effects of excitatory amino acids (such as glutamate and aspartate) and peptides (such as SP and CGRP) released into the dorsal horn (Randic et al., 1990; Dougherty et al., 1991, 1992a,b; 1993, 1994, 1995; Dougherty and Willis, 1992; Neugebauer et al., 1993, 1995; Thompson et al., 1994; Urban et al., 1994). Nociceptive dorsal horn neurons, including spinothalamic tract neurons, receive synaptic connections from glutamate-containing terminals (Westlund et al., 1992) as well as from peptide-containing endings (Carlton et al., 1990). Coapplication of excitatory amino acids and SP by iontophoresis onto dorsal horn neurons results in an enhanced responsiveness of these cells (Randic et al., 1990; Dougherty and Willis, 1991). Furthermore, sensitization can be blocked by antagonists of glutamate receptors (Dougherty et al., 1992b) or of neurokinin 1 (SP) receptors (Dougherty et al., 1994).

As for peripheral nociceptors, sensitization of dorsal horn nociceptive neurons appears to result from the activation of second messenger systems. Particular signal transduction cascades that are involved include the protein kinase C system (Mao et al., 1993; Palecek et al., 1994; Lin et al., 1996b) and probably other pathways as well.

The consequences of central sensitization include allodynia and hyperalgesia of the secondary type (Lewis, 1942; Hardy et al., 1952; Bonica, 1992). The nociceptors in an area of secondary hyperalgesia show no change in their responsiveness to stimulation (Baumann et al., 1991; LaMotte et al., 1992; Schmelz et al., 1996). Instead, the increased responses of dorsal horn neurons result in the enhancement of behavioral nociceptive responses and of pain. Increased responses of wide dynamic range neurons, i.e., neurons that respond not only to noxious but also to innocuous stimuli, to tactile stimulation can account for allodynia in the area of secondary hyperalgesia (Willis, 1993).

Inhibition in the nociceptive circuits of the dorsal horn is mediated by a number of neurotransmitters, including inhibitory amino acids, such as GABA and glycine (Curtis et

al., 1968, 1971a,b; Willcockson et al., 1984a; Lin et al., 1994), as well as neuropeptides, such as enkephalin (Duggan et al., 1977; Willcockson et al., 1984b). GABA is involved in both pre- and postsynaptic inhibition and glycine in postsynaptic inhibition (Eccles et al., 1963; Curtis et al., 1971a,b; 1977; Carlton and Hayes, 1990; Todd, 1990; Carlton et al., 1992). Presynaptic receptors that mediate presynaptic inhibition include GABAA and GABAB receptors (Curtis et al., 1977; Curtis and Lacey, 1994). These same receptor types can also be involved in postsynaptic inhibition, along with glycine receptors. Inhibition of a spinothalamic tract by activation of GABAB receptors is shown in Fig. 5.

Projection Neurons

Nociceptive projection neurons in the spinal cord transmit information to a number of regions of the brainstem and diencephalon, including the thalamus, periaqueductal gray, parabrachial region, and bulbar reticular formation, as well as to limbic structures in the hypothalamus, amgydaloid nucleus, septal nucleus, and other sites (see Willis, 1985). Recently, existence of a visceral nociceptive pathway in the dorsal columns involving the postsynaptic dorsal column pathway was also demonstrated (Al-Chaer et al., 1996a,b; Hirshberg et al., 1996). In the following sections, the best studied of these pathways are reviewed. Available information about primates, will be emphasized.

PATHWAYS IN THE ANTEROLATERAL QUADRANT

Spinothalamic Tract

The spinothalamic tract in humans is believed to help mediate the sensations of pain, cold, warmth, and touch (Willis, 1985; Gybels and Sweet, 1989; Willis and Coggeshall, 1991). This belief is based largely on the results of anterolateral cordotomies performed to relieve pain (Spiller and Martin, 1912; Foerster and Gagel, 1932; White and Sweet, 1969) or deficits due to damage to the spinal cord by disease or trauma (Gowers, 1878; Spiller, 1905; Head and Thompson, 1906; Noordenbos and Wall, 1976). However, results of experimental studies of primates in which changes in behavioral responses to noxious stimuli before and after spinal lesions were measured are consistent with the clinical evidence (Yoss, 1953; Vierck and Luck, 1979; Vierck et al., 1990).

The cells of origin of the spinothalamic tract have been mapped in monkeys, cats, and rats (Willis and Coggeshall, 1991). Presumably, the pattern in monkeys will prove to be closest to that in human organization. In monkeys, a large fraction of spinothalamic tract cells is located in the lumbar and sacral enlargements, and these cells are concentrated in the marginal zone and neck of the dorsal horn in laminae I and IV-VI (Fig. 6) (Willis et al., 1979; Apkarian and Hodge, 1989a). However, some spinothalamic cells are located in other laminae, including lamina X, which is around the central canal, and in the ventral horn. Comparison of the populations of spinothalamic tract cells projecting to the lateral thalamus, including the ventral posterior lateral nucleus, and those projecting to the medial thalamus, including the central lateral nucleus, show clear differences between the two (Willis et al., 1979). Laterally projecting spinothalamic neurons are more likely to be situated in laminae I and V (Fig. 6), whereas medially projecting cells are more likely to be situated in the deep dorsal horn and in the ventral horn (Fig. 7). Most of the cells project to the contralateral

thalamus, although a small fraction projects ipsilaterally. A large group of spinothalamic tract cells is also located in segments C1 and C2 (Apkarian and Hodge, 1989a), in lamina VIII bilaterally and in laminae I-VII contralateral to the thalamic target.

The projections of the spinothalamic tract have been traced to the thalamus in humans, as well as in monkeys, cats, rats, and other experimental animals (Willis and Coggeshall, 1991). In primates, terminals exist in the following nuclei: the caudal and oral parts of the ventral posterior lateral nucleus (VPLc and VPLo of Olszewski, 1952), the ventral posterior inferior nucleus (VPI), the medial part of the posterior complex (POm), the central lateral (CL) nucleus, and other intralaminar and medial thalamic nuclei (Figs. 6 and 7) (Mehler et al., 1960; Mehler, 1962; Kerr, 1975; Boivie, 1979; Berkley, 1980; Mantyh, 1983; Apkarian and Hodge, 1989c; Gingold et al., 1991; Apkarian and Shi, 1994). A projection from lamina I has been traced to a medial thalamic nucleus, the posterior part of the ventral medial nucleus, VMpo (Craig et al., 1994).

The axons of spinothalamic neurons often decussate through the ventral white commissure at a very short distance from the cell body (Fig. 6) (Willis et al., 1979). They initially enter the ventral funiculus and then shift into the lateral funiculus as they ascend. Axons from spinothalamic tract cells of lamina I ascend more dorsally in the lateral funiculus than do the axons of spinothalamic tract cells in deeper layers of the dorsal horn (Apkarian and Hodge, 1989b). Clinical evidence from anterolateral cordotomies indicates that spinothalamic axons in the anterolateral quadrant of the spinal cord are arranged somatotopically. At cervical levels, spinothalamic axons representing the lower extremity and caudal body are placed more laterally and those representing the upper extremity and rostral body more anteromedially (Hyndman and Van Epps, 1939; Walker, 1940). Recordings from spinothalamic axons in monkeys are consistent with this scheme (Applebaum et al., 1975). How the somatotopic arrangement and the segregation of axons from lamina I as compared with deeper laminae remain consistent is unclear.

Primate spinothalamic tract cells that project to the lateral thalamus generally have receptive fields on a restricted area of the contralateral skin and are thus well suited to a function in signaling the sensory-discriminative aspects of pain (Willis et al., 1974). Most of the neurons show their best responses when the skin is stimulated mechanically at a noxious intensity. However, many spinothalamic tract cells also respond, although less effectively, to innocuous mechanical stimuli, and some respond best to innocuous mechanical stimuli (Willis et al., 1974; Price and Mayer, 1975; Price et al., 1978; Chung et al., 1979; Ferrington et al., 1987). A large fraction of spinothalamic tract cells also respond to noxious heating of the skin (Kenshalo et al., 1979; Surmeier et al., 1986a,b). Some spinothalamic neurons respond to stimulation of receptors in muscle (Foreman et al., 1979), joints (Dougherty et al., 1992c), or viscera (Milne et al., 1981; Blair et al., 1982, 1984; Ammons, 1989a,b). Spinothalamic neurons with a dominant input from viscera or muscle are situated in segments just rostral and caudal to segments containing spinothalamic tract cells with a dominant cutaneous input from the distal part of an extremity (Hobbs et al., 1992).

Primate spinothalamic tract cells that project to the region of the CL nucleus in the medial thalamus may also collateralize to the lateral thalamus (Fig. 6); these cells have response

properties identical to those of spinothalamic tract cells that project just to the lateral thalamus (Giesler et al., 1981). However, spinothalamic tract cells that project just to the CL nucleus (Fig. 7) have very large receptive fields, often encompassing the entire surface of the body and face (Giesler et al., 1981). Some of these have input from visceral structures, as well as from the skin (Ammons et al., 1985). The large receptive fields suggest that these neurons would be more suited for a role in the motivational-affective aspects of pain, rather than in sensory discrimination.

Spinothalamic tract cells have not only excitatory but also inhibitory receptive fields (Gerhart et al., 1981b). The strongest inhibition from stimulation of the skin occurs when noxious intensities of stimulation are used, suggesting that a mechanism similar to DNIC is involved. Inhibition of spinothalamic tract cells is prominent when the stimuli are applied contralaterally or to dermatomes remote from those of the excitatory receptive field (Gerhart et al., 1981b; Hobbs et al., 1992). Spinothalamic tract cells can be inhibited effectively by repetitive electrical stimulation of peripheral nerves (Chung et al., 1984a). The inhibition can outlast stimulation by 20–30 min. Some inhibition can be evoked by stimulation of large myelinated axons of a peripheral nerve, but the inhibition is much more powerful if small myelinated or unmyelinated afferents are included in the volleys (Chung et al., 1984b). The best inhibition is produced by stimulation of a peripheral nerve in the same limb as the excitatory receptive field, but some inhibition occurs when nerves in other limbs are stimulated. A similar inhibition results when high-intensity stimuli are applied to the skin with a clinical transcutaneous electrical nerve stimulator (TENS unit) in place of direct stimulation of a peripheral nerve (Lee et al., 1985).

Several other pathways accompany the spinothalamic tract in the white matter of the ventrolateral quadrant of the spinal cord. These include the spinomesencephlic tract, the spinoreticular tracts, and several recently described spino-limbic tracts (Willis, 1985; Willis and Coggeshall, 1991).

Spinomesencephalic Tract

The spinomesecephalic tract includes several projection systems that terminate in different areas in the midbrain. The cells of origin of the spinomesecephalic tract are distributed in the spinal cord in a manner similar to that of the cells of origin of the spinothalamic tract. In primates, most of the cells are in laminae I and IV-VI, although some are in the ventral horn and lamina X (Fig. 8) (Trevino, 1976; Willis et al., 1979; Mantyh, 1982; Wiberg et al., 1987). Some spinomesencephlic tract cells give off collaterals that end in the lateral thalamus (Yezierski et al., 1987; Zhang et al., 1990).

The spinomesencephalic projections are to the following midbrain nuclei: periaqueductal gray, nucleus cuneiformis (Fig. 8), intercolliculus nucleus, deep layers of the superior colliculus, nucleus of Darkschewitsch, anterior and posterior pretectal nuclei, red nucleus, Edinger-Westphal nucleus, and interstitial nucleus of Cajal (Mehler et al., 1960; Mehler, 1969; Kerr, 1975; Wiberg et al., 1987; reviewed in Willis, 1985; Willis and Coggeshall, 1991). A rough somatotopic organization exists, in that spinomesencephalic projections from more caudal parts of the body terminate more caudally in the midbrain, whereas

projections from more rostral parts of the body end more rostrally in the midbrain (Wiberg et al., 1987).

Spinomesencephlic neurons are nociceptive, responding either to noxious stimuli only or best to noxious but also to innocuous stimuli (Willis and Coggeshall, 1991). Recordings from spinomesecephalic tract cells in monkeys show that these cells often have complex receptive fields on widely separated areas of the body, in contrast to spinothalamic cells projecting to the lateral thalamus, which generally have receptive fields on a restricted area of the contralateral limb (Yezierski et al., 1987).

The different components of the spinomesencephalic tract may have different functions; e.g., the projections to the periaqueductal gray(PAG) could contribute to aversive behavior (Skultety, 1963; Nashold et al., 1969) as well as activate the descending analgesia system that arises from the PAG (described below). The projections to the nucleus cuneiformis could access the midbrain locomotor center (see Brooks, 1986) and the ascending reticular activating system (Magoun, 1963). Input to the deep layers of the superior colliculus are likely to play a role in orienting. Because the anterior pretectal nucleus is another locus that produces analgesia when stimulates (Rees and Roberts, 1993) (described below), the projections here may serve to limit nociception.

Spinoreticular Tracts

Many of the cells of origin of the spinoreticular tracts are located in the deep layers of the dorsal horn and in laminae VII and VIII of the ventral horn (Fig. 9) (Kevetter et al., 1982 reviewed in Willis, 1985; Willis and Coggeshall, 1991). Spinoreticular neurons have been identified by antidromic activation (Fields et al., 1975; Haber et al., 1982) and by retrograde labeling. The spinoreticular projections to the caudal medulla end in several nuclei, including the retroambiguus and superspinalis nuclei as well as dorsal and ventral parts of the nucleus medullae oblongatae centralis (Mehler et al., 1960). More rostral projections are to the lateral reticular nucleus, the nucleus gigantocellularis (Fig. 9), the nuclei paragigantocellularis dorsalis and lateralis, and the nuclei pontis caudalis and oralis. Enkephalin-containing cells with projections into the medulla have been described (Nahin and Micevych, 1986). The spinoreticular and spinothalamic tracts ascend together in the ventrolateral spinal cord and brainstem (Mehler et al., 1960). Both physiological (Haber et al., 1982; Giesler et al., 1981) and anatomic studies (Kevetter and Willis, 1982) have shown that some spinoreticular neurons are collateral branches of spinothalamic tract cells. There is no obvious somatopic organization of the spinoreticular tracts.

Another major termination of spinoreticular fibers in the brainstem is in the parabrachial region (Fig. 10) (Cechetto et al., 1985; Hylden et al., 1985; Hylden et al., 1986; Standaert et al., 1986; Menetrey and Basbaum, 1987; Wiberg et al., 1987; Blomqvist et al., 1989; Bernard and Besson, 1990; Lima et al., 1991; Craig, 1992, 1995; Kitamura et al., 1993; Slugg and Light, 1994; Feil and Herbert, 1995).

An additional source of spinoreticular input was recently described in experiments in which ascending pathways from lamina I cells of the spinal cord identified in monkeys and cats were traced with an anterograde label (Craig, 1995). The ascending fibers of the lamina I

cells are scattered throughout the lateral white matter (Craig, 1991). The lamina I projections ascend through the brainstem among the neurons of the catecholamine cell column in the ventrolateral medulla (Craig, 1995; Westlund and Craig, 1996). The pathway arches dorsally to travel among the cells of the ventral subcoeruleus, Kolliker-Fuse, and dorsal parabrachial nuclei in the dorsolateral pons. The pathway sends collaterals to terminate among almost all of the catecholamine cell groups of the medulla and pons (Fig. 11), including the locus ceruleus (Craig, 1992). Some synaptic contacts were observed at the electron microscopic level for cells of the A5 and A7 cell groups, and many other contacts were made with noncatecholaminergic structures (Westlund and Craig, 1996). Spinoparabrachial and other spinoreticular cells have been shown to contain an assortment of immunoreactive peptides, including SP, VIP, bombesin, dynorphin, and enkephalin (Leah et al., 1988).

Many reticular neurons respond preferentially to noxious stimuli (Wolstencroft, 1964; Casey, 1969, 1971a; Guilbaud et al., 1973; Foote et al., 1991). The primary functional significance of this input is undoubtedly to signal homeostatic changes to brainstem autonomic centers, but other brainstem responses include activation of endogenous analgesia systems and relay of information that triggers motivational-affective responses.

Spino-Limbic Tracts

A multisynaptic pathway is proposed as the means of carrying information about noxious inputs to the medial thalamus, where it is relayed to the limbic system (Bishop, 1959); this is sometimes termed the spinoreticulothalamic pathway. A possible anatomic substrate for this pathway would include the spinoreticular tracts described in the previous section. Ascending projections from the reticular formation have been reported to the medial thalamus, hypothalamus, and limbic structures (Fig. 12) (Nauta and Kuypers, 1958; Scheibel and Scheibel, 1958; Bowsher et al., 1968; Robertson et al., 1973; Bowsher, 1975; Blomqvist et al., 1989; Ma et al., 1989; Bernard and Besson, 1990; Carstens et al., 1990).

In addition, direct spinohypothalamic (Burstein et al., 1987, 1990) and spinoamygdalar (Bernard and Besson, 1990; Burstein and Potrebic, 1993; Menetrey and de Pommery, 1991) pathways have been described. The spinohypothalamic tract is a major bilateral projection to both the medial and lateral hypothalamus arising primarily from cells of the deep dorsal horn and lateral spinal nucleus (Fig. 12). Other cells are localized in laminae I, VII, and X. Some spinal projections also innervate the nucleus accumbens and the septal nuclei, suggesting that a component of this pathway is relevant to the motivational aspects of pain (Burstein and Giesler, 1989).

The spinopontoamygdalar pathway (Bernard and Besson, 1990; Menetrey and de Pommery, 1991; Burstein and Potrebic, 1993) arises from cells situated bilaterally in the lateral reticulated area of the deep dorsal horn and in the gray matter surrounding the central canal. Anterograde tracing studies indicate that the central nucleus of the amygdala is directly innervated innervated by terminals arising from the spinal cord (Fig. 12)(Cliffer et al., 1991).

PATHWAYS IN THE DORSAL QUADRANT

Spinocervicothalamic Pathway

The spinocervicothalamic pathway originates from neurons in the spinal cord dorsal horn and relays in the lateral cervical nucleus in segments C1 and C2 (reviewed in Willis, 1985; Willis and Coggeshall, 1991). The axons of neurons of the lateral cervical nucleus decussate and then ascend with the medial lemniscus to the thalamus (Ha, 1971). A lateral cervical nucleus has been identified in several species, including rat, cat, dog, raccoon, and monkey(for the last, see Mizuno et al., 1967). A comparable nucleus has been observed in at least some human spinal cords (Truex et al., 1965).

The cells of origin of the spinocervical tract have not yet been mapped with anatomic techniques in monkeys. In cats, the cells are situated mostly in lamina IV, although some are situated in adjacent laminae of the dorsal horn and a few are scattered in deeper layers (Craig, 1978; Brown et al., 1980). Antidromic mapping of spinocervical tract cells in monkeys is in general agreement with this distribution (Bryan et al., 1974).

The axons of spinocervical tract neurons ascend in the dorsal part of the lateral funiculus to the upper cervical level (Nijensohn and Kerr, 1975) and then terminate in the lateral cervical nucleus. Cervicothalamic neurons have been mapped in the lateral cervical nucleus of monkeys by the retrograde tracing technique (Smith and Apkarian, 1991). The projections of these cells are to the contralateral ventral posterior lateral nucleus and the medial part of the posterior complex (Berkley, 1980; Boivie, 1980). Many of the cells also give off collaterals to the midbrain (Willis and Coggeshall, 1991).

Numerous electrophysiological studies have been made of spinocervical tract neurons in the cat, particularly by the laboratory of A. G. Brown(reviewed in Willis and Coggeshall, 1991). Many spinocervical tract cells have tactile responses and thus would not be candidates for a nociceptive role. However, some spinocervical tract cells do respond to noxious stimuli, both in cats (Brown and Franz, 1969; Cervero et al., 1977) and in monkeys (Bryan et al., 1974; Downie et al., 1988). Therefore, the spinocervical tract is a potential pathway through which nociceptive signals can reach the lateral thalamus.

Postsynaptic Dorsal Column Pathway

Although dogma holds that the dorsal column subserves graphesthesia, two-point discrimination, and position sense, recent interest in the reasons for the great effectiveness of limited midline myelotomy in reducing intractable pelvic cancer pain in humans (Fig. 13) (Hitchcock 1970, 1972a,b; Schwarcz, 1976, 1978; Gildenberg and Hirshberg, 1984; Hirshberg et al., 1996) has stimulated renewed interest in an additional functional role of the dorsal column in the relay of visceral pain.

In an early report speculating on the passage of visceral nociceptive fibers in the dorsal column, Foerster and Gagel (1932) noted that awake human subjects experience unbearable, excruciating pain when the dorsal column or medial aspect of the nucleus gracilis is probed mechanically. The pain in the latter case is referred to the sacral region and perineum. Nociceptive activity, including responses to uterine and vaginal distension, has been

demonstrated in neurons of the dorsal column nuclei (Angaut-Petit, 1975b; Ferrington et al., 1988; Cliffer et al., 1992; Berkley and Hubscher, 1995). These nociceptive responses could be triggered by unmyelinated primary afferent fibers that have been shown to ascend in the dorsal column directly to the dorsal column nuclei (Patterson et al., 1989, 1990; Conti et al., 1990); alternatively, they could be mediated through the postsynaptic dorsal column pathway (Uddenberg, 1968; Angaut-Petit, 1975a,b; Bennett et al., 1984; Noble and Riddell, 1988).

The postsynaptic dorsal column pathway arises from cells distributed medial to laterally in lamina III in the dorsal horn, as well as from a few cells just lateral to lamina X (Fig. 13) (Rustioni, 1973, 1974; Rustioni et al., 1979; Bennett et al., 1983; Giesler et al., 1984). The postsynaptic dorsal column cells, in contrast to spinothalamic tract cells, are innervated by "serotonin-only" fibers, meaning that no coexisting peptide content could be identified in the serotonin-containing synapses (Wu and Wessendorf, 1992).

Although the postsynaptic dorsal column pathway in rats may not have a role in cutaneous pain (Giesler et al., 1984; Al-Chaer et al., 1996a,b), the postsynaptic dorsal column cells and cells of the gracile nucleus were shown to respond to both mechanical and chemical irritation of viscera (Al-Chaer et al., 1996b). The trajectories of postsynaptic dorsal column fibers are somatotopically organized in the dorsal column (Cliffer and Giesler, 1989; Hirshberg et al., 1996). Presumably, the visceral information is relayed together with cutaneous epicritic information in the medial lemniscus to the thalamus.

Thalamus

The spinothalamic tract projects to both the lateral and medial thalamus. The particular nuclei of termination include the VPL, VPI, and POm nuclei in the lateral thalamus and CL and other intralaminar nuclei, as well as VMpo in the medial thalamus. The spinomesencephalic and spinoreticular pathways relay in the reticular formation in areas that project heavily to medial thalamic nuclei, especially the intralaminar nuclei. The spinocervical tract relays in the lateral cervical nucleus, which projects to the VPL and POm nuclei. The postsynaptic dorsal column pathway projects to the dorsal column nuclei, which in turn project to the VPL and POm nuclei.

Electron microscopic studies have shown convergence of medial lemniscal and spinothalamic tract input onto the proximal dendritic trees of thalamocortical neurons (Ralston and Ralston, 1994). This would account for the observation that thalamic neurons respond to input conveyed through both the dorsal column and the lateral funiculus (Al-Chaer et al., 1996a).

Lateral Thalamus

Recordings have been made of nociceptive responses in the VPL and VPM nuclei of the monkey thalamus by many investigators (Gaze and Gordon, 1954; Perl and Whitlock, 1961; Pollin and Albe-Fessard, 1979; Kenshalo et al., 1980; Casey and Morrow, 1983, 1987; Chung, et al., 1986a,b; Bushnell and Duncan, 1987; Yokota et al., 1988; Bushnell et al., 1993; Chandler et al., 1992; Duncan et al., 1993; Apkarian and Shi, 1994; Bruggemann et al., 1994). In some of these experiments, the monkeys were examined in behavioral experiments without the potentially confounding effects of anesthesia. The proportion of

nociceptive neurons, as compared with neurons activated only by innocuous stimuli, was low in unanesthetized preparations (~10%). However, strong stimuli could not be applied in these animals; therefore, more neurons may have been judged nociceptive than were reported if intense noxious stimuli could have been used (Casey and Morrow, 1983, 1987; Bushnell et al., 1993). In anesthetized monkeys, a much larger percentage of nociceptive neurons is situated in the VPL nucleus (Chung et al., 1986a,b). The larger proportion of nociceptive neurons in the VPL nucleus in anesthetized animals may result from the more intense stimuli that can be used or possibly from sensitization of nociceptive neurons because of repeated strong stimuli.

Nociceptive neurons in the VPL nucleus generally respond weakly to innocuous cutaneous mechanical stimuli and maximally to noxious mechanical stimuli (Kenshalo et al., 1980; Casey and Morrow, 1983, 1987; Chung et al., 1986a,b). They also respond to noxious heat and to C fiber volleys (Chung et al., 1986b). The receptive fields are restricted in size and are situated on the contralateral side, and the location of the neurons in the VPL nucleus is somatotopic. Almost all of those tested were shown by antidromic activation to project to the SI cortex (Kenshalo et al., 1980). A surprising finding is that most neurons (85%) in the VPL nucleus respond to both cutaneous and visceral stimuli (Chandler et al., 1992; Bruggemann et al., 1994). The cutaneous input may be innocuous or noxious. Although the cutaneous input is somatotopic, the visceral input is not viscerotopic (Bruggemann et al., 1994).

The properties of the nociceptive neurons in the VPL nucleus are appropriate for a role of these neurons in the sensory-discriminative aspects of pain perception. Their projection to the SI cortex, implies that the SI cortex is also involved in the discriminative aspects of pain sensation.

Nociceptive neurons also exist in the VPI and POm nuclei (Pollin and Albe-Fessard, 1979; Casey and Morrow, 1987; Apkarian and Shi, 1994). The cutaneous receptive fields of neurons in the VPI nucleus are somatotopically organized but tend to be larger than those of the VPL nociceptive neurons. Presumably the nociceptive neurons in the VPI nucleus project to the SII cortex. The SII cortex is believed to be involved in memory processing through its connections to the limbic system (Friedman et al., 1986). The cells studied in the monkey POm nucleus had small, contralateral nociceptive receptive fields. The POm nucleus projects to the retroinsular cortex in monkeys (Burton and Jones, 1976).

Recordings have also been made from nociceptive neurons in the human ventral posterior thalamus, presumably including VPL, VPM, and VPI; stimulation at the same sites often evoked pain (Lenz et al., 1993a,b, 1994b). In one patient with angina pectoris, stimulation in the VPL nucleus caused anginal pain (with no accompanying cardiovascular changes), strongly suggesting that the VPL nucleus is involved in visceral and referred pain (Lenz et al., 1994a).

Medial Thalamus

Bushnell and Duncan (1989) made recordings from several intralaminar nuclei, including the CL, center median (CM), and parafascicular (Pf) nuclei, in awake trained monkeys.

Several of the neurons were shown to be nociceptive. These had large, usually bilateral receptive fields, suggesting that they do not play an important role in sensory discrimination. However, the responses of the neurons to two intensities of noxious heat showed that the neurons were able to distinguish these stimulus intensities as well as the behaving animal could, indicating that the neurons might indeed contribute to at least some aspects of sensory discrimination, although they may also play a role in motivational-affective behavior.

Craig et al. (1994) recorded from neurons in the VMpo nucleus in monkeys. Most of the neurons examined responded either to noxious or to cold stimuli. The cells had small, somatotopically organized receptive fields. The nucleus is believed to project to the insula, suggesting that it participates in motivational-affective responses to pain and may contribute to memory processing.

Cerebral Cortex

Although early in this century doubts were cast on the role of the cerebral cortex in pain (Head and Holmes, 1911; Holmes, 1927; Penfield and Boldrey, 1937), most recent evidence favors the participation of both the cerebral cortex and the thalamus, not only in the sensory-discriminative aspects of pain, but also in the motivational-affective aspects.

Although not much experimental work has been done on the involvement of the cerebral cortex in pain, responses have been recorded from nonciceptive cortical neurons in animal subjects (Robinson and Burton, 1980a–c; Kenshalo and Isensee, 1983; Kenshalo et al., 1988; Dong et al., 1989; Chudler et al., 1990; see review by Kenshalo and Willis, 1991).

Evidence that the human cerebral cortex participates in nonciceptive derives from imaging studies (Jones et al., 1991; Talbot et al., 1991; Casey et al., 1994; Coghill et al., 1994). Cortical areas most prominently involved include the SI and SII cortex, the anterior insula, and the anterior cingulate gyrus.

DESCENDING MODULATORY PATHWAYS

In 1969, Reynolds reported that he found it possible to perform abdominal surgery on rats without chemical anesthesia during stimulation in the region of the midbrain PAG. The rats did not have motor impairment, and they showed normal responses to innocuous stimuli. Since then, numerous investigations have been made of what became known as the”descending analgesia systems” (see Willis, 1982; Besson and Chaouch, 1987; Fields and Besson, 1988; Light, 1992). These pathways have been shown to utilize several different neurotransmitters, including opioids, serotonin, and/or catecholamines, and the anatomic structures giving rise to them include not only the PAG, but also the locus ceruleus, subceruleus, and Kolliker-Fuse nuclei, the nucleus raphe magnus (NRM), and several nuclei of the bulbar reticular formation. In addition, structures at higher levels of the nervous system, including the cerebral cortex, and various limbic structures, including the hypothalamus, contribute to the analgesia pathways. The major descending systems are reviewed in the following sections.

PAG

Investigators have explored the antinociceptive effect of stimulating in the PAG in awake, behaving animals (Mayer and Liebeskind, 1974; Oliveras et al., 1974; Gebhart and Toleikis, 1978; Hayes et al., 1979; Besson et al., 1991). The PAG has now been shown to have a rostrocaudal columnar organization (Beitz, 1985; Bandler et al., 1991; Shipley et al., 1991; Cameron et al., 1995a,b). Stimulation in the lateral column of the PAG evokes a defense response, which consists of avoidance behavior in rats, retraction of the ears or arching of the back in cats, sympathetic activation, vocalization, and sometimes a flight reaction (Bandler and Depaulis, 1991; Lovick, 1991), as well as analgesia. By contrast, stimulation in the ventrolateral PAG results in immobility and sympathoinhibition, as well as analgesia (Lovick, 1992). Therefore, the PAG is believed to be involved in complex behavioral responses to stressful or life-threatening situations or to promote recuperative behavior after a defense reaction.

These various complex behaviors are mediated by activation of the complex ascending and descending projections of the PAG (Cameron et al., 1995a,b). However, the analgesia is generally attributed to the action of the PAG on spinal cord neurons. Although some neurons in the PAG project directly to the spinal cord (Castiglioni et al., 1978), most of the connections between the PAG and the spinal cord are indirect; e.g., the PAG projects to the NRM and adjacent reticular formation, to several nuclei in the parabrachial area, including the locus ceruleus, and to the A5 cell group (Fig. 14) (Cameron et al., 1995b; Mantyh, 1983).

Stimulation in the PAG causes inhibition of nociceptive dorsal horn neurons (Carstens et al., 1979, 1980, 1981; Lin et al., 1996a; Peng et al., 1996a,b), including spinothalamic tract cells (Hayes et al., 1979; Yezierski et al., 1982; Gerhart et al., 1984; Lin et al., 1994). This inhibition can be at least partially blocked by antagonists of several different receptors, including 5-HT3 and 5HT1A receptors, [alpha]2-adrenoceptors, and GABAA and glycine receptors (Lin et al., 1996a,b; Peng et al., 1996a-c). Presumably, the actions on different classes of 5-hydroxytryptamine (5-HT) receptors are mediated by release of 5-HT from raphespinal axons, and those on adrenoceptors are mediated by NE, released from noradrenergic axons descending from the locus ceruleus/parabrachial complex or the A5 group. Whether the GABA and glycine actions are mediated by release of inhibitory amino acids from long descending axons from the rostral ventromedial medulla (Antal et al., 1996) or are released by inhibitory interneurons in the spinal cord is not clear. The inhibitory interneurons in the dorsal horn could be activated at least in part through an action of 5-HT on 5-HT3 receptors (Peng et al., 1996a), since 5-HT3 receptors open cation channels and thus are excitatory.

Locus Ceruleus, Subceruleus, Parabrachial Area

Stimulation in the dorsolateral pons is reported to produce both a catecholaminergic and a nonadrenergic antinociception (Duggan and North, 1984; Hodge et al., 1986; Proudfit, 1992). Because most of the spinally projecting neurons in the pons are noradrenergic, the nonadrenergic antinociception is most likely relayed through the many sites innervated by these cell groups, including the raphe magnus and pallidus, the PAG, and regions of the

ventrolateral reticular formation (Westlund and Coulter, 1980; Holstege, 1988; Kwiat and Basbaum, 1990).

Noradrenergic projections to all regions of the spinal cord arise almost entirely from the dorsolateral pontine catecholamine cell groups A5, A6, and A7. This includes the locus ceruleus, the subceruleus, and the Kolliker-Fuse nucleus (Fig. 14) (Westlund and Coulter, 1980; Stevens et al., 1982; Proudfit, 1992; Westlund et al., 1983, 1984). In monkeys and cats, bilateral projections descend from the locus ceruleus and subcerulear region to innervate laminae I, II, and V, primarily contralaterally (Westlund and Coulter, 1980; Holstege and Kuypers, 1982). Another dense input to the dorsal horn originates from the ipsilateral Kolliker-Fuse nucleus (Stevens et al., 1982; Westlund et al., 1983, 1984; Clark and Proudfit, 1991). Physiological studies have suggested that the subceruleus and Kolliker-Fuse nuclei are primary antinociceptive regions affecting spinal transmission (Yeomans and Proudfit, 1992).

Electrical or chemical stimulation of the dorsolateral pons produced analgesic effects mediated by [alpha]2-adrenoceptors that can be differentiated from cardiovascular effects, and such stimulation causes inhibition of nociceptive neurons in the deep dorsal horn (Segal and Sandberg, 1977; Margalit and Segal, 1979; Mokha et al., 1985, 1986; Hodge et al., 1986; Jones and Gebhart, 1988; Zhao and Duggan, 1988; Proudfit, 1992; Yeomans and Proudfit, 1992).

Noradrenergic terminals in the spinal cord have been demonstrated by immunocytochemical localization of NE in rats (Rajaofetra et al., 1992), cats (Lackner, 1980), and monkeys (Westlund et al., 1984). Such terminals make direct contacts on dorsal horn neurons (Doyle and Maxwell, 1991), including electrophysiologically characterized spinothalamic neurons in laminae V and retrogradely labeled spinothalamic cells in lamina I in monkeys (Westlund et al., 1990).

NE and [alpha]2-agonists applied to the spinal cord inhibit the responses of dorsal horn neurons, including spinothalamic tract neurons (Headley et al., 1978; Fleetwood-Walker et al., 1983; Fleetwood-Walker et al., 1985; Willcockson et al., 1984). These agents also reduce the stimulation-induced release of SP in the dorsal horn (Kuraishi et al., 1985). Intrathecal or direct spinal administration of NE has also been shown to produce antinociception, measurable as increased latencies in hot-plate and tail-flick tests (Yaksh, 1986) and, after inflammation, by increased paw withdrawal times (Hylden et al., 1991) or decreased dorsal horn neuronal activity (Stanfa and Dickenson, 1994). More specific receptor antagonist studies recently showed that after induction of knee joint inflammation, it was an imidazaline ligand(I2) rather than a selective [alpha]2-adrenoceptor antagonist that further reduced paw withdrawal latency (Houghton and Westlund, 1996). This study indicates that previous studies attributing antinociceptive effects to an[alpha]2-adrenoceptor may need to be reassessed in light of the possibility that the effects may be attributable to an I2 imidazoline receptor.

NRM

The brainstem raphe nuclei are a group of nuclei located near the midline in the medulla, pons and midbrain (reviewed in Willis, 1984). They include the nuclei raphe obscurus, raphe pallidus, and NMR in the medulla; the nuclei raphe pontis and the median raphe nucleus in the pons; and the dorsal raphe nucleus in the midbrain. Projections to the spinal cord originate from the nuclei raphe magnus, pallidus, obscurus, and pontis. A striking feature of the raphe nuclei is that a large proportion of the neurons contain 5-HT (Dahlstrom and Fuxe, 1964, 1965). The serotonergic projections from the raphe nuclei to the spinal cord (Bowker et al., 1981, 1983) are the major source of 5-HT in the spinal cord, although some intrinsic spinal cord serotonergic neurons exist (LaMotte et al., 1982; Bowker, 1986).

One of the key structures in the descending analgesia pathway from the PAG is the NRM and the adjacent reticular formation. The PAG has excitatory connections with the NRM (Fig. 14) (Behbehani and Fields, 1979; Pomeroy and Behbehani, 1979; Shah and Dostrovsky, 1980; Willis et al., 1984), suggesting that the antinociceptive effects of stimulation in the PAG are mediated by the NRM.

Stimulation in the NRM was shown to be antinociceptive in behavioral experiments (Oliveras et al., 1975; Basbaum et al., 1976). The antinociceptive effects of stimulation in the NRM have been attributed to the inhibition of nociceptive dorsal horn neurons (;Fields et al., 1977; Guilbaud et al., 1977 see reviews by Basbaum and Fields, 1978; Besson and Chaouch, 1987), including spinothalamic tract cells (Beall et al., 1976; Willis et al., 1977; Gerhart et al., 1981a; Yezierski et al., 1982).

Neurotransmitters involved in the antinociceptive actions of the pathway from the PAG through the NRM and adjacent reticular formation include endogenous opiates, 5-HT, and NE (reviewed in Willis, 1982; Akil and Lewis, 1987; Besson and Chaouch, 1987; Fields and Besson, 1988; Willis and Coggeshall, 1991).

Reticular Formation

Reticular formation neurons are selectively excited by noxious input, and one result of stimulation in the reticular formation in awake monkeys is aversive behaviour (Casey, 1971b). Strong antinociception, however, is evoked by stimulation of the ventrolateral medulla.

Stimulation of the ventromedial or ventrolateral medulla results in[alpha]2-adrenoceptor-mediated analgesia (Sagen and Proudfit, 1981; Barbaro et al., 1985; Hammond and Yaksh, 1984). Retrograde horseradish peroxidase (HRP) studies have also demonstrated nonnoradrenergic spinally projecting neurons in the ventrolateral medulla that are scattered among and sometimes immediately adjacent to the noradrenergic cells of the A1 and A2 cell groups (Westlund et al., 1983, 1984; Tucker et al., 1987). Adrenergic spinally projecting neurons in the rostral ventrolateral medulla (C1 adrenergic cell group) have also been identified (Ross et al., 1984; Carlton et al., 1989) and may have some involvement in the modulation of pain perception since they provide a small projection to the dorsal horn.

Anterior Pretectal Nucleus

Stimulation in the anterior pretectal nucleus results in long-lasting antinociception without aversive side effects, in contrast to stimulation in many other brainstem sites, including the PAG (Rees and Roberts, 1986, 1993; Roberts and Rees, 1986; Prado, 1989; Prado and Roberts, 1985). The anterior pretectal nucleus is located in the pretectal region near several pretectal nuclei that belong to the visual system. However, the main connections of the anterior pretectal nucleus indicate that it is part of the somatosensory system rather than the visual system (Wiberg and Blomqvist, 1984; Berkley et al., 1986; Wiberg et al., 1987; Yoshida et al., 1992).

Nociceptive dorsal horn neurons are affected in different ways after stimulation in the anterior pretectal nucleus, depending on the laminar position of the neurons. Nociceptive specific neurons in the superficial dorsal horn are excited by anterior pretectal stimulation, whereas nociceptive neurons in the deeper layers of the dorsal horn are inhibited (Rees and Roberts, 1987). Excitation of lamina I neurons has been proposed to activate a positive feedback loop whose inhibitory output to the deep dorsal horn neurons results in analgesia (Rees and Roberts, 1993).

Which descending pathways to the spinal cord and which neurotransitters are utilized by the anterior pretectal nucleus is still unclear. There are connections from the anterior pretectal nucleus to the rostral ventral medulla and to the C1 and A5 catecholamine cell groups (Zagon et al., 1995). Important relays include the deep mesencephalic nucleus (Wang et al., 1992), the parabrachial Ch5 group (Terenzi et al., 1992), and the ventrolateral medulla (Terenzi et al., 1991). A noradrenergic link appears to exist in the descending pathway, and 5-HT may also be involved (Rees et al., 1987; Prado, 1989; Rees and Roberts, 1993).

Thalamus and Cerebral Cortex

In human patients, stimulation of the VPL or VPM thalamic nuclei results in a reduction in pain in facial anesthesia dolorosa, postherpetic neuralgia, and the thalamic syndrome (Mazars et al., 1974, 1976; Hosobuchi et al., 1973; Turnbull et al., 1980). Thalamic stimulation also results in antinociception in monkeys (Goodman and Holcombe, 1976).

Stimulation in the VPL nucleus has been shown to cause inhibition of primate spinothalamic tract neurons (Gerhart et al., 1983). The inhibition was suggested to result from antidromic activation of the axons of spinothalamic tract neurons that send collaterals to such brainstem nuclei as the PAG or the NRM. Recordings from neurons in the NRM show that neurons in this nucleus can be excited when stimuli are applied in the VPL nucleus (Tsubokawa et al., 1982; Willis et al., 1984), and 5-HT is released in the spinal cord by such stimulation (Sorkin et al., 1992).

Another possible explanation is that the spinal cord inhibition resulting from stimulation in the VPL nucleus occurs through a cortical loop. Stimulation of the SI region of the cerebral cortex in monkeys causes the inhibition of spinothalamic tract cells (Coulter et al., 1974; Yezierski et al., 1983), whereas stimulation of the motor cortex excites spinothalamic tract cells (Yezierski et al., 1983). The excitation can be monosynaptic (Zhang et al., 1991a). However, the cortical inhibition acts mainly on the responses to innocuous mechanical

stimulation (Coulter et al., 1974; Yezierski et al., 1983; Zhang et al., 1991b), whereas the inhibition produced by stimulation in the PAG or NRM powerfully reduces nociceptive responses (Willis et al., 1977; Gerhart et al., 1981, 1984; Yezierski et al., 1982).

Limbic Structures

Pain is quite often accompanied by motivational-affective and autonomic responses. Examples are increased heart rate and blood pressure, endocrine changes, increased attention, arousal, anxiety, and suffering. The neural pathways that mediate these changes are likely to parallel those relaying information about somatic pain sensations, but include additional structures of the limbic system. Much of the information about painful experiences may be relayed through brainstem reticular systems receiving spinoreticular inputs, as detailed previously in the section on the spinoreticular tracts. Some of these brainstem sites then project to higher centers where they have impact on hypothalamic, limbic and neocortical function; e.g., the A1-A6 noradrenergic cell groups receive input from lamina I neurons (discussed in Westlund and Craig, 1996). Some of these regions then project rostrally to the paraventricular hypothalamic nucleus as well as to the central nucleus of the amygdala (Petrov et al., 1993). Catecholaminergic modulation of the hypothalamic-pituitary-adrenal stress axis was reviewed by Plotsky et al. (1989). Direct input to the amygdala from parabrachial regions that receive spinal projections has also been reported (Fallon et al., 1978). Focusing attention on painful stimuli and incorporation of information relevant to the stimuli has been discussed as another role of noxious input relayed through the locus ceruleus to the cortex (Foote et al., 1991; Segal et al., 1991). A pathway serving this role might include the lamina I projections to the locus ceruleus (Craig, 1995). Cortical and hippocampal regions receive their noradrenergic input exclusively from the locus ceruleus (Ungerstedt, 1971).

Dopaminergic inhibition of nociceptive dorsal horn cells, including spinothalamic tract neurons, has been reported (Willcockson et al., 1984; Fleetwood-Walker et al., 1988). This might arise from the All cell group (Blessing and Chalmers, 1979).

CLINICAL IMPLICATIONS OF RECENT FINDINGS ON THE PAIN AND PAIN MODULATION SYSTEMS

New findings in pain research often have the potential for clinical application. The following thoughts about potentially useful lines of investigation are derived from recent work.

The observation that most nociceptors are normally “sleeping” but “awaken” when they are sensitized, e.g., by inflammation, suggests that the pain of inflammation should be reduced if sensitization is minimized. A traditional approach has been use of nonsteroidal antinflammatory agents, such as aspirin, to block the synthesis of prostaglandins, which contribute to the sensitization of nociceptors. However, many other substances also contribute to peripheral sensitization, including BK, serotonin, and a variety of cytokines released from immune cells. Presumably, pharmacological agents directed against the actions of these agents should prove as useful as aspirin, at least under some conditions.

The function of nociceptors clearly can be modulated by drugs that act on their surface membrane receptors, which include not only BK and serotonin receptors, but also opiate, GABA, and capsaicin receptors. Activation of opiate receptors usually is not effective in reducing pain, but this approach becomes effective in inflammation. Whether peripheral administration of opiates will have an important clinical application is unclear, but it may be possible to design opioid-like drugs that have an effect that is restricted to the periphery. Adrenoceptors may be expressed in neuropathic pain states, such as causalgia. Antagonists to these adrenoceptors may prove useful in the treatment of neuropathic pain. Recently, a role for excitatory amino acid receptors on peripheral nerve fibers was proposed, and evidence indicates that blocking these receptors can reduce hyperalgesia (Lawand et al., 1996). Peripherally acting excitatory amino acid receptor antagonists may have a therapeutic use. Manipulations of capsaicin receptors are already being explored; e.g., the capsaicin receptor agonist resiniferotoxin has been shown to produce an excitotoxic action on C nociceptors through its action on capsaicin receptors. Resiniferotoxin very effectively desensitizes capspaicin receptors and may be able to destroy these nociceptors without causing the pain typically produced by capsaicin.

Peripheral nerve damage causes changes in the concentrations of several peptides in dorsal root ganglia and in the dorsal horn of the spinal cord. These changes may contribute to neuropathic or other pain states. Antagonists of the appropriate receptors may be a useful approach to treatment of these pain states.

Aberrant growth of sympathetic nerve fibers or of afferent fibers entering the dorsal horn may result from changes in growth factors after nerve damage. Control of this aberrant growth by the use of antibodies to the growth factors or by antagonists of the growth factor receptors should be explored in such conditions.

Central sensitization is produced after peripheral injuries and is likely to be a major factor in postoperative pain. Central sensitization can be prevented by several agents, including antagonists ofN-methyl-D-aspartate (NMDA) glutamate receptors and NK1 neurokinin receptors. To avoid the cognitive changes that NMDA receptor antagonists produce when they reach the brain, it may be possible to develop NMDA receptor antagonists that are selective for the spinal cord. Neurokinin receptor antagonists are becoming available and may block sensitization without the cognitive effects produced by NMDA antagonists.

Enhancement of pre- or postsynaptic inhibition of dorsal horn nociceptive circuits by drugs should be another useful means of treating pain. Spinal administration of morphine has already proved a successful therapy in certain types of pain. GABA receptor agonists, such as baclofen, are also useful.

Interruption of nociceptive tracts in the spinal cord has a long history. Anterolateral cordotomy has at least a limited success rate when used to treat cancer pain originating from one side of the body. However, it is less effective for visceral pain, since bilateral cordotomies are required and have many side effects. Cordotomies are often of limited usefulness for the treatment of pain when the patient survives for a long time, since pain may return after several months. The pain of pelvic visceral cancer can be effectively

relieved by a limited midline dorsal myelotomy; prior to the recent demonstration of a visceral nociceptive pathway that ascends in the dorsal column, there was no good explanation of this observation. This neurosurgical procedure is likely to be a convenient method of reducing pelvic cancer pain that is insufficiently controlled by morphine.

Our knowledge of the descending endogenous analgesia system is still very incomplete. Recent studies indicate that further work is needed to determine in detail the neural connections and the neurotransmitters of this system. That some structures, such as the PAG, produce mixed aversive and analgesic effects is consistent with the observation that electrical stimulation of these sites in human patients is not a useful therapeutic approach. However, other structures, such as the VPL and VPM nuclei, can be stimulated to produce an effective analgesia in certain types of patients. If a means for stimulating the anterior pretectal nucleus could be found, this region might be a suitable target for deep brain stimulation. However, a better approach may be to determine a more physiological way of utilizing this and other analgesia systems through suitable drug therapy.

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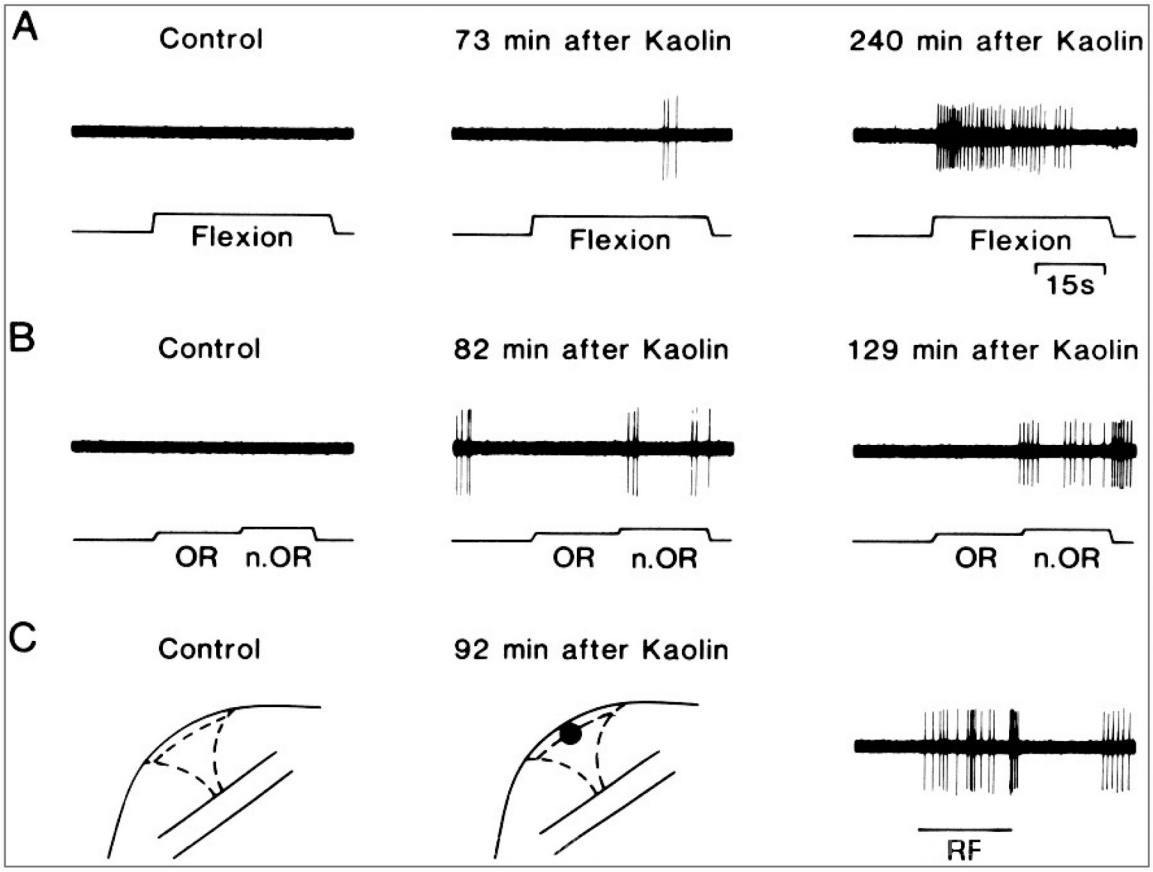

FIG. 1.

Sensitization of a “silent” C-nociceptor supplying the knee joint. A and B: Left: Absence of responses to flexion of the knee or to innocuous (OR) and noxious (n.OR) outward rotation of the knee in a cat before initiation of experimental arthritis by injection of kaolin and carrageenan into the knee joint. At this time, no receptive field could be demonstrated in the joint by mechanical probing (C: Left). Middle (A-C): A response to flexion and noxious outward rotation of the knee and a receptive field to probing the joint developed by 90 min after initiation of inflammation. The responses continued to increase (A and B: Right). The response to stimulation of the receptive field is shown in C (right). (Reprinted fromSchaible and Schmidt, 1988, with permission.)

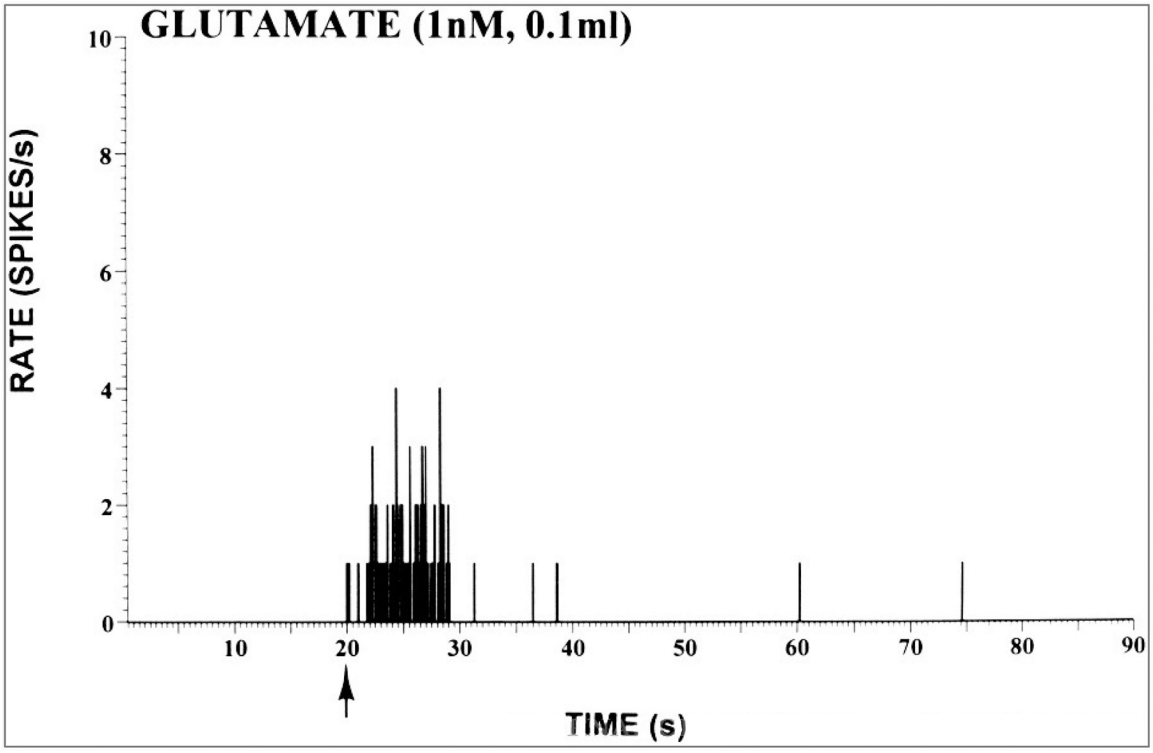

FIG. 2.

Peristimulus time histogram showing the response of afferent fibers in the medial articular nerve of a rat to intraarticular injection of glutamate. A dose of 0.1 ml of a 1-nM solution of glutamate was injected into the knee joint at the time indicated by the arrow. (From Lawand, W. D. Willis and K. N. Westlund, unpublished observations).

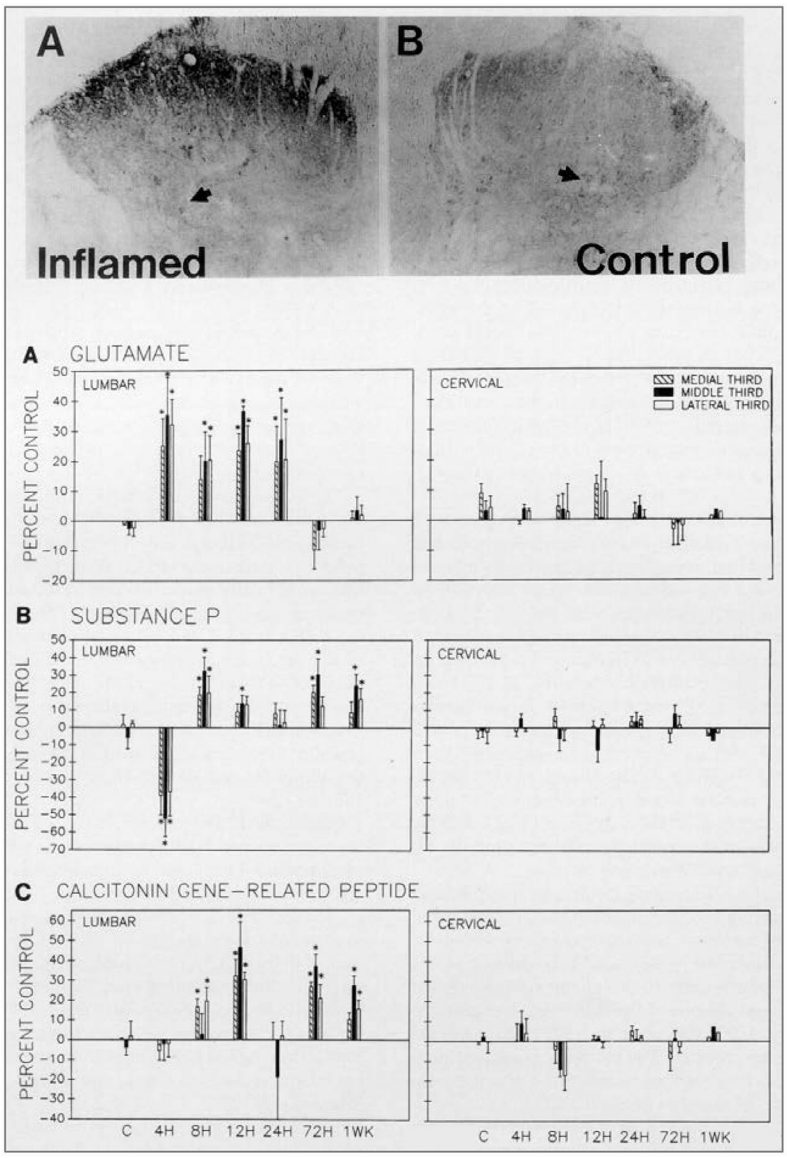

FIG. 3.

Changes in glutamate and peptide content in the dorsal horn during the development of experimental arthritis.Top: The photomicrographs show a section of the lumbar dorsal horn 24 h after the induction of arthritis by injection of kaolin and carrageenan into the capsule of the knee joint. The section is immunohistochemically stained for glutamate, which is increased on the inflamed side(left) as compared with the normal side (right).Bottom: The bar graphs in A-C show the changes in immunoreactivity of the dorsal horn for glutamate, substance P, and calcitonin gene-related peptide at different times after the induction of arthritis. Lumbar spinal cord (left). Staining density in the cervical spinal cord did not change (right). *Statistically significant changes. (From Sluka and Westlund, 1993.)

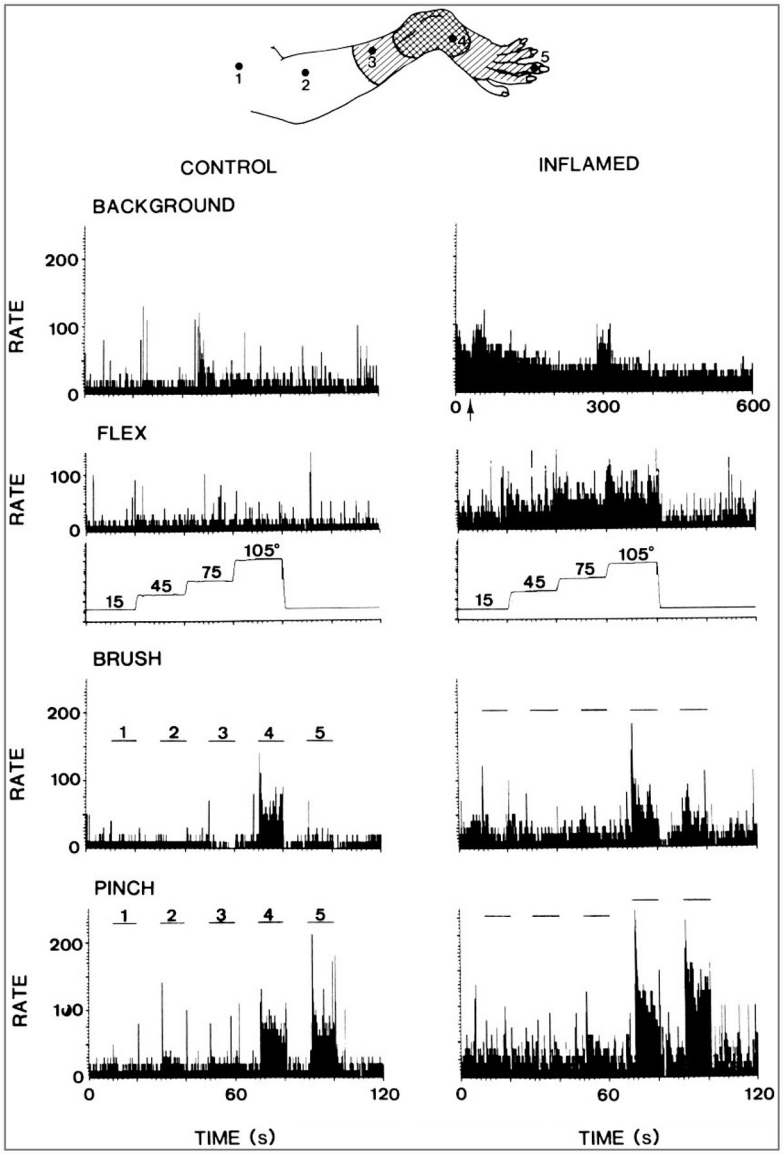

FIG. 4.

Increased responses of a primate spinothalamic tract cell after acute arthritis was induced by injection of kaolin and carrageenan into the knee joint. Top: Receptive field of the neuron on the ankle and foot before (doubly hatched area) and after(hatched area) the development of arthritis. Left columns: Peristimulus histograms show the background activity of the neuron and its responses to flexion of the knee, to brushing the skin at the points labeled 1–5 in the drawing, and to pinching the skin at the same points. Right columns: Histograms show the enhanced background activity and response after the development of arthritis. The increased background activity would presumably result in pain in an unanesthetized animal, and the increased response to knee flexion would be an indication of primary hyperalgesia. The increased responses to stimulation of the foot would presumably represent secondary mechanical allodynia and hyperalgesia. (From Dougherty et al., 1992b.)

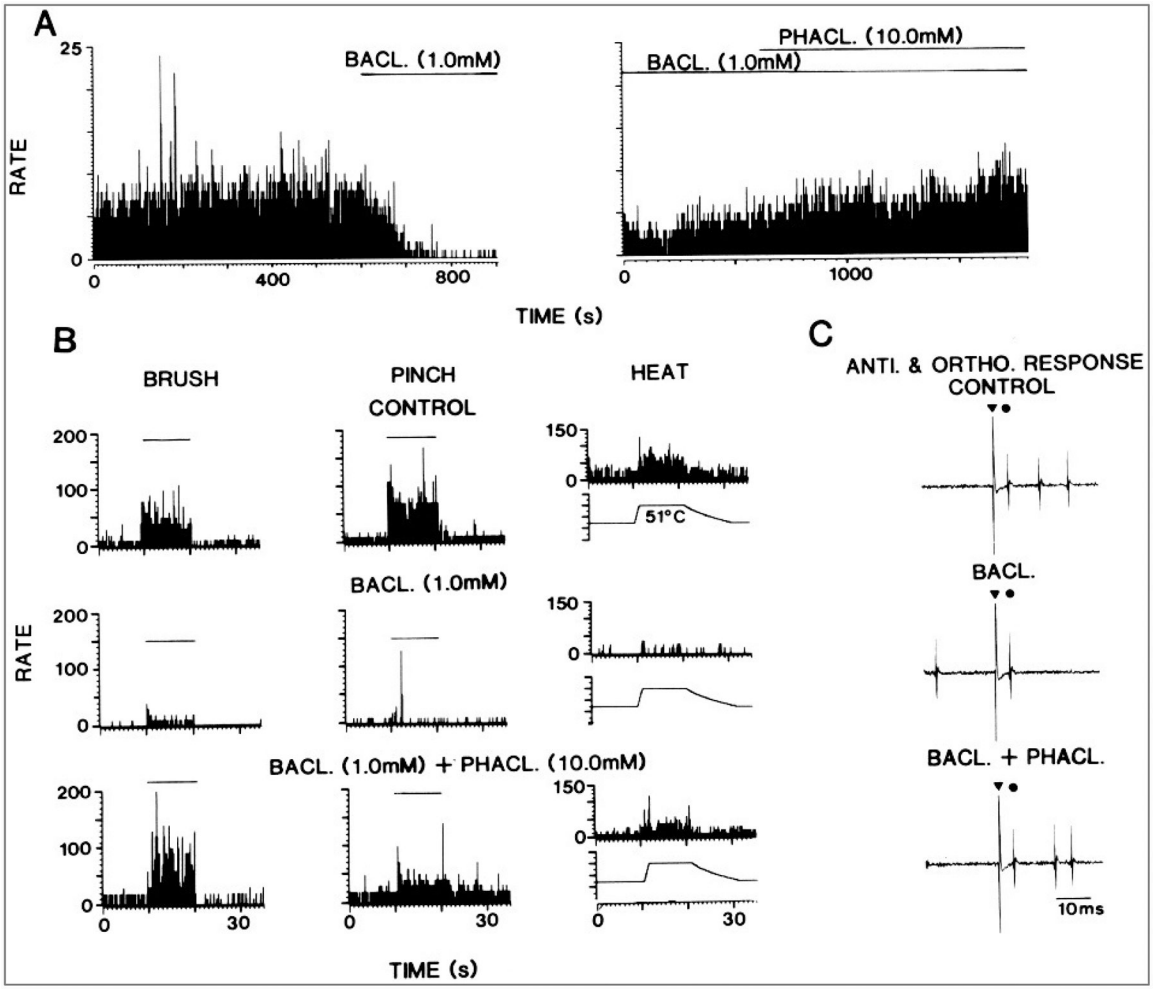

FIG. 5.

Inhibition of a primate spinothalamic tract cell by baclofen administered in the spinal cord by microdialysis. A: Background activity of the neuron is shown before and during the administration of the GABAB receptor agonist baclofen and (left) right during the coadministration of baclofen and the GABAB receptor antagonist, phaclofen (right).B: Responses of the cell to brush, pinch, and heat stimuli applied to the receptive field before and during baclofen administration and during coadministration of baclofen and phaclofen. C: Antidromic and orthodromic action potentials of the neuron at different times during the experiment. (From Lin et al., 1996c.)

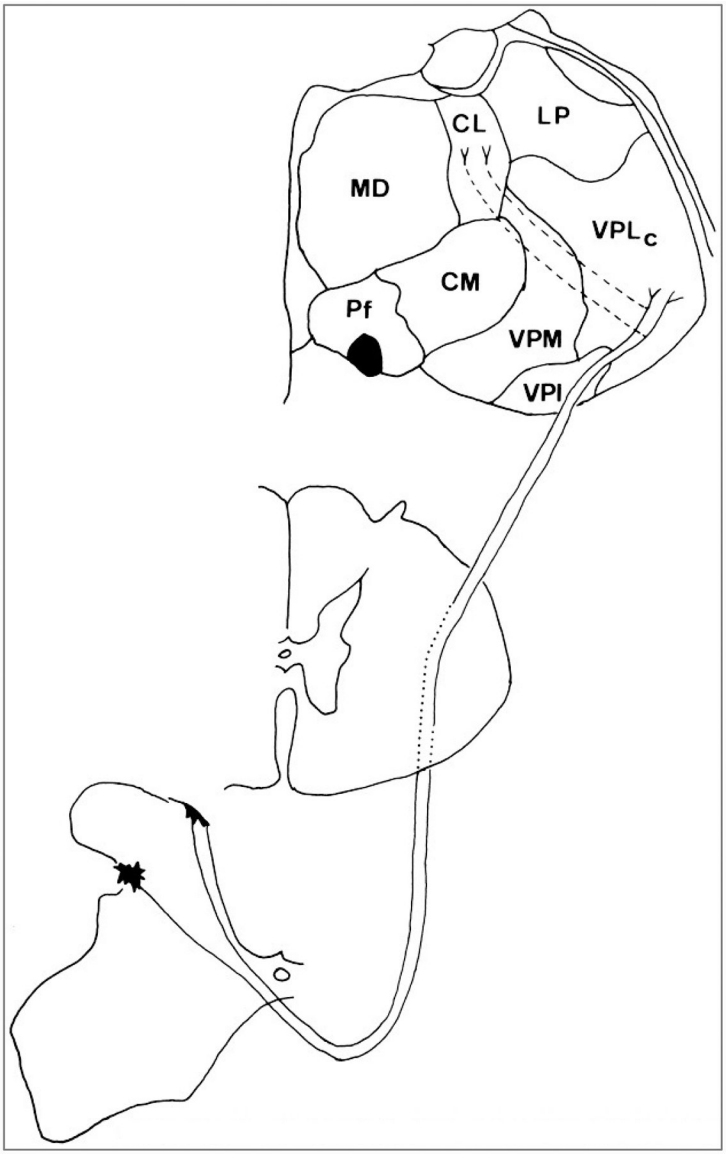

FIG. 6.

Course of the laterally projecting component of the spinothalamic tract in a macaque monkey. The cells of origin of the part of the spinothalamic tract that projects to the lateral thalamus are concentrated in laminae I and V of the spinal cord dorsal horn. The axons cross the midline in the ventral gray commissure at a level near that of the cell bodies of the neurons. The axons then ascend in the ventral and then in the ventrolateral quadrant. After passing through the brainstem, the axons terminate synaptically in the lateral thalamus. The nuclei of termination include the caudal part of the ventral posterior lateral nucleus (VPLc) and also the ventral posterior inferior (VPI) and the medial part of the posterior group (POm; data not shown). Some of the laterally projecting spinothalamic tract neurons send collaterals to the medial thalamus, where they end in the central lateral(CL) nucleus (dashed lines).

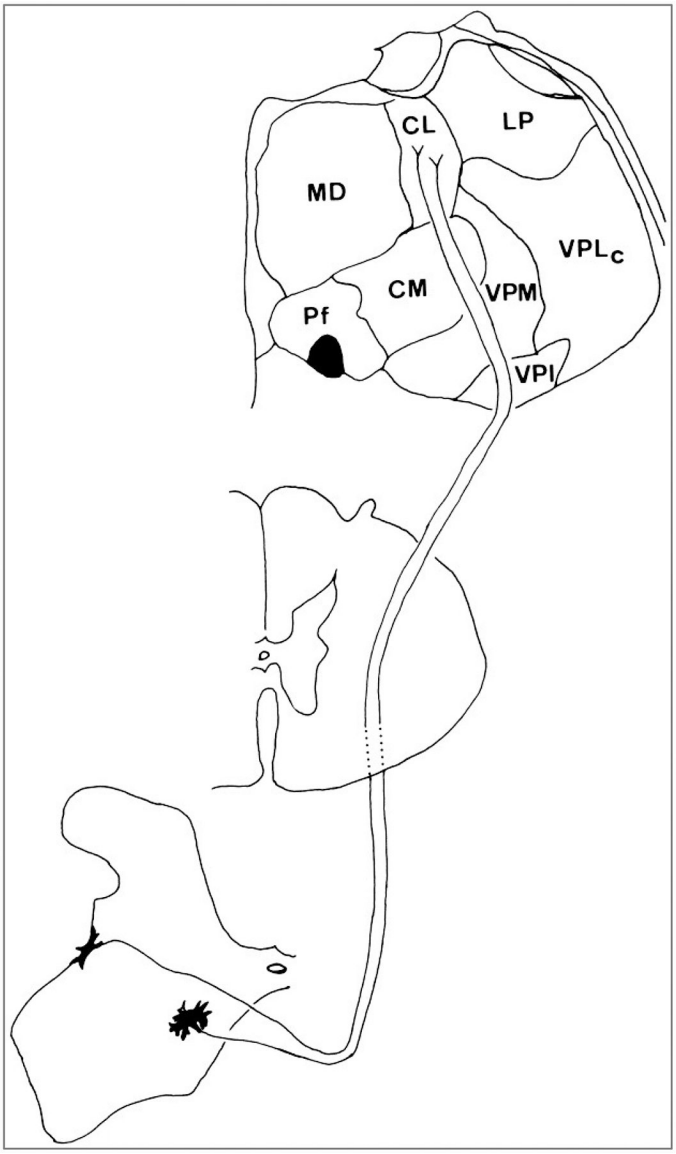

FIG. 7.

Course of the medially projecting component of the spinothalamic tract of a macaque monkey. The cells of the spinothalamic tract that project just to the intralaminar nuclei of the medial thalamus originate in the deep dorsal horn and the ventral horn of the spinal cord. The axons decussate immediately and then ascend in the ventral and then in the ventrolateral white matter. After passing through the brainstem, they terminate in the intralaminar nuclei, especially the central lateral (CL) nucleus.

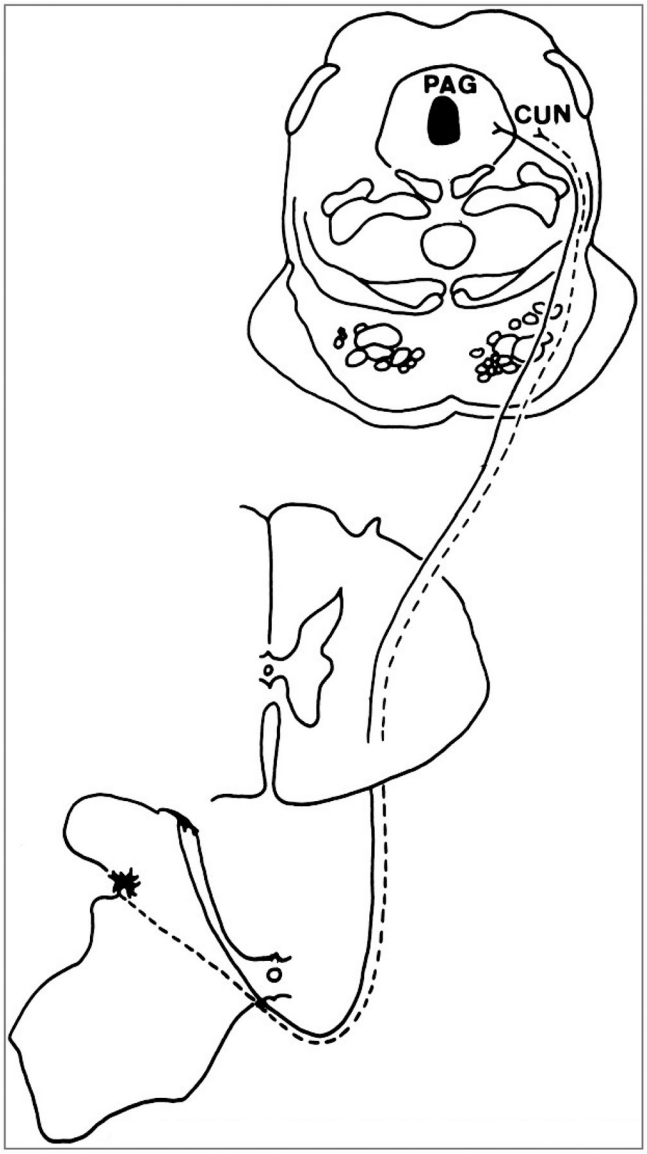

FIG. 8.

Course of the spinomesencephalic tract in a macaque monkey. The cells of origin of the tract are concentrated in laminae I and V. The axons decussate in the ventral white commissure and ascend to the midbrain in the lateral funiculus. They end in several midbrain nuclei, including the periaqueductal gray (PAG) and cuneiform nucleus(CUN).

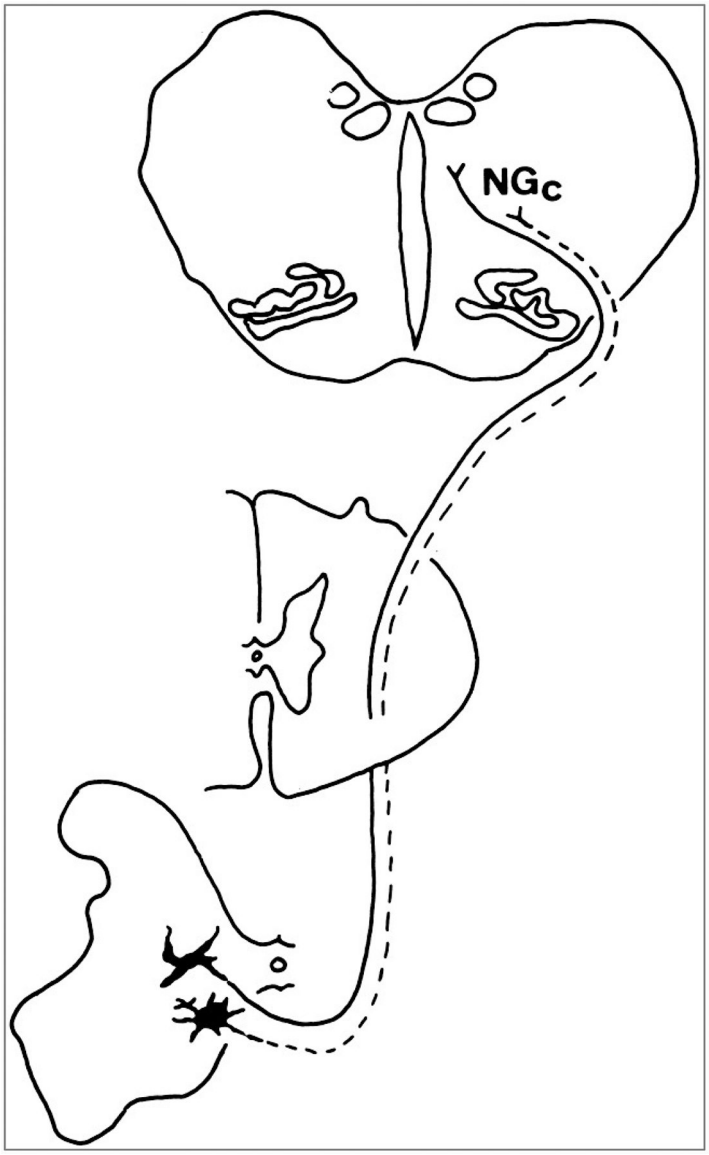

FIG. 9.

Course of the component of the spinoreticular tract that projects to the caudal reticular formation in a macaque monkey. The cells of origin are concentrated in the ventral horn in laminae VII and VIII. The axons decussate and ascend in the lateral funiculus and terminate in several nuclei of the reticular formation of the medulla and pons, including the nucleus gigantocellularis (NGc).

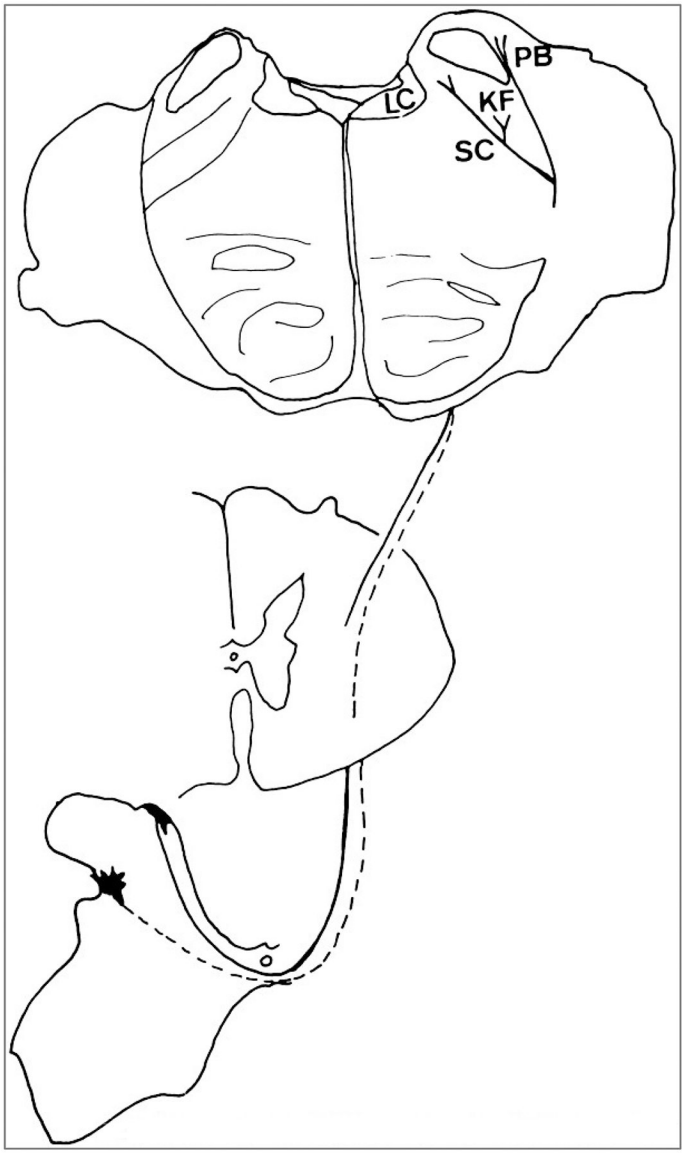

FIG. 10.

Course of the component of the spinoreticular tract that projects to the parabrachial region. The spinoreticular neurons are in the dorsal horn, including laminae I and V, and project to several nuclei in the parabrachial region, including the locus ceruleus, the Kölliker-Fuse nucleus, and the parabrachial nuclei.

FIG. 11.

Spinoreticular projection with connections to brainstem catecholamine cell groups. Sagittal sections of a monkey brainstem are shown from the side contralateral to an injection site in lamina I of the cervical spinal cord where an anterograde tracer was placed. The catecholamine cell groups (A1, A2, A5, A6, A7, C1; open circles) were demonstrated by immunocytochemical staining for tyrosine hydroxylase. Locations of the terminals of spinal projection neurons (small dots). (From Westlund and Craig, 1996.)

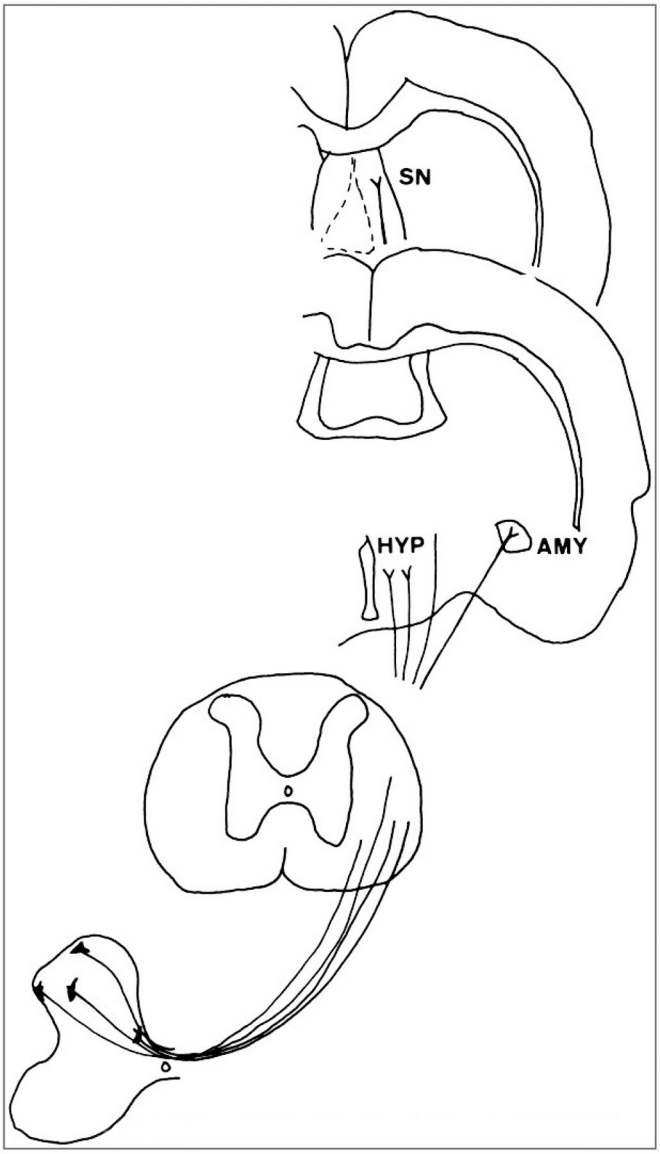

FIG. 12.

Course of spino-limbic projections in the rat. Neurons in the dorsal horn and also in the region of the central canal project through the lateral funiculus to the hypothalamus(HYP), amygdaloid nucleus (AMY), and the septal nuclei (SN).

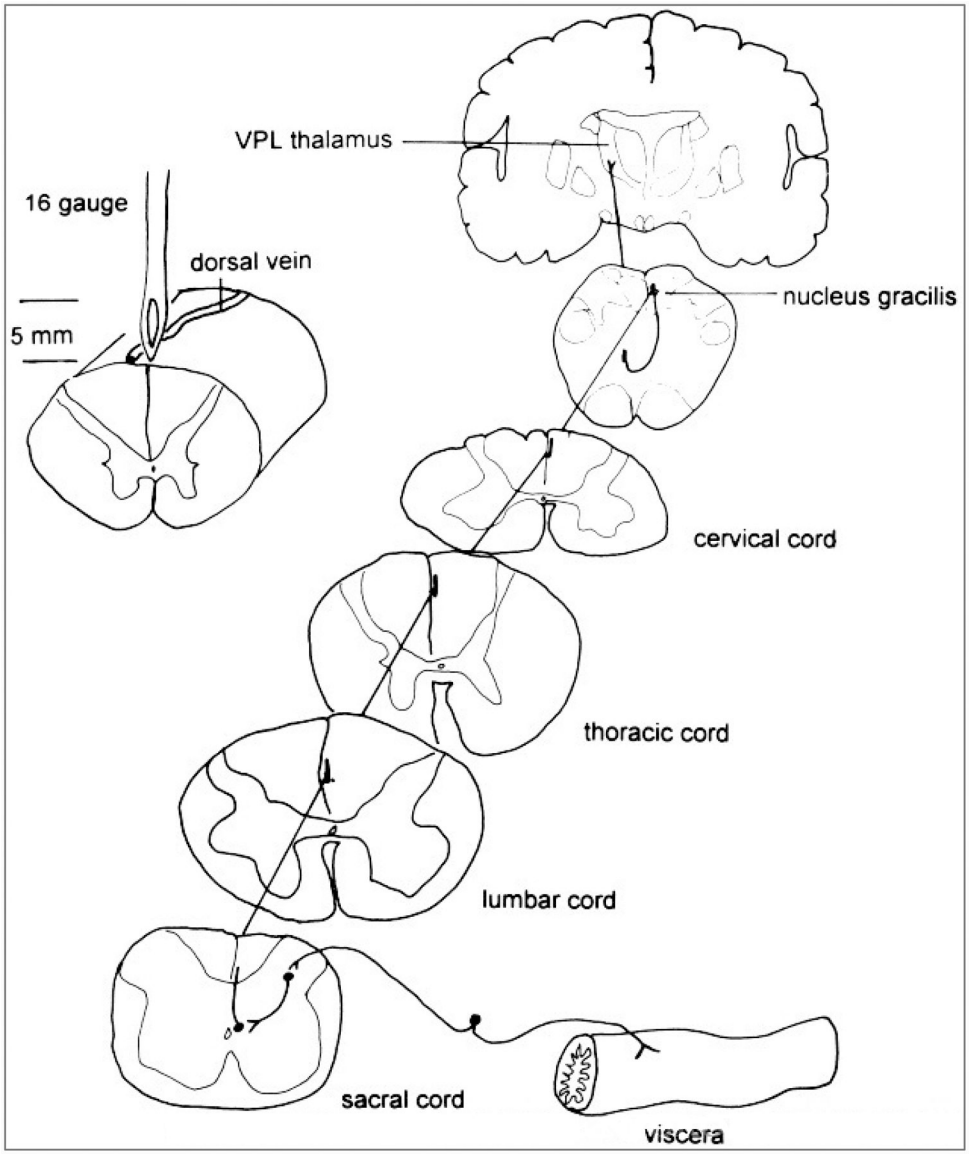

FIG. 13.

Course of the component of the postsynaptic dorsal column pathway that may mediate visceral pain. The afferent input to the sacral spinal cord from a pelvic visceral organ is shown by a drawing of a dorsal root ganglion cell and its peripheral and central processes. The afferent connects with a circuit that activates a projection neuron located in the central gray region (lamina X). The projection neurons sends its axon rostrally near the midline of the dorsal column to synapse in the nucleus gracilis. The gracile neuron projects to the contralateral ventral posterior lateral (VPL) nucleus in the thalamus.Left: Procedure for a limited midline myelotomy to interrupt this visceral pain pathway (H. J. W. Nauta, E. Hewitt, K. W. Westlund, W. D. Willis, unpublished observations).

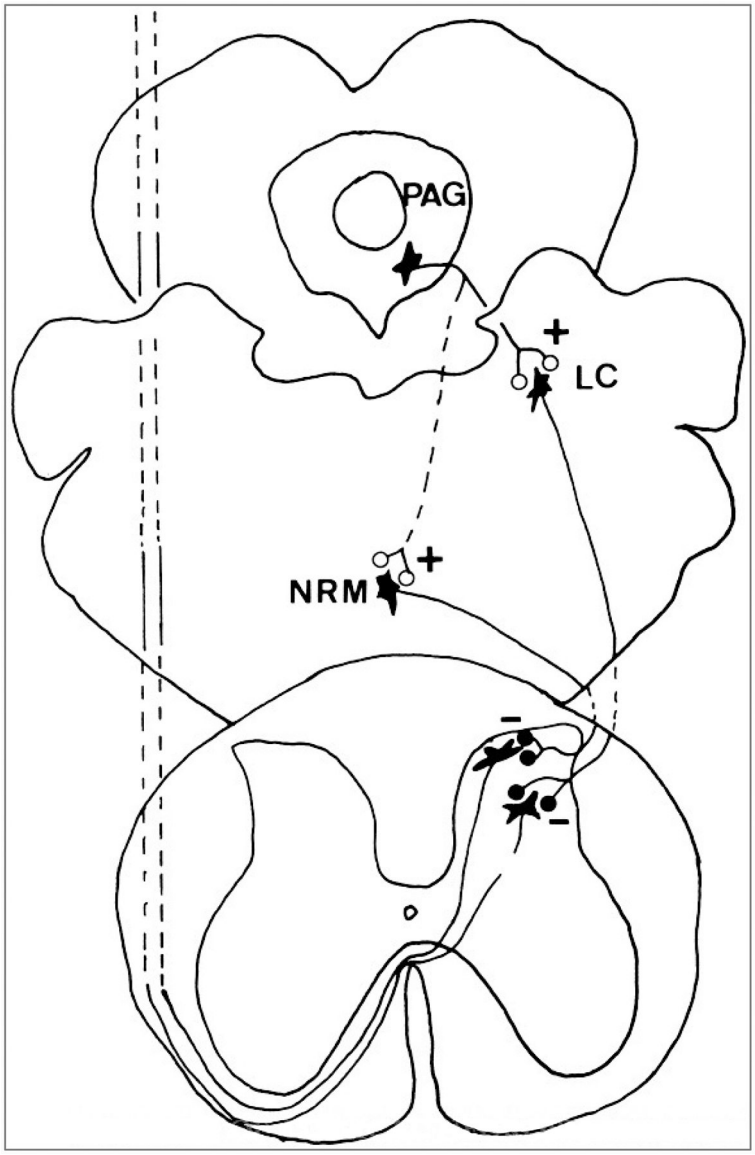

FIG. 14.

Descending analgesia systems. Two projection neurons in the spinal cord dorsal horn that receive descending inhibitory synapses (minus signs) from brainstem neurons are shown. The descending axons originate in the nucleus raphe magnus (NRM) and the locus ceruleus (LC) and adjacent nuclei of the parabrachial region. The periaqueductal gray (PAG) is shown to have excitatory connections (plus signs) to the NRM and LC.