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SYMPOSIUM ON PAIN MANAGEMENT—Part I

Pathophysiology of Pain

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• *Objective*: To review the pain pathways in the central and peripheral nervous system and the actions of drugs used to treat pain.

• *Design*: An overview of pain pathways is presented, beginning in the periphery and progressing centrally, and the ascending and descending pathways are described in detail.

• *Results*: The nociceptive pathway, consisting of the classic three-neuron chain, is now understood to be a dual system at each level, and the sensation of pain is thought to arrive in the central nervous system with the discriminative component of pain ("first pain") carried separately from the affective-motivational component of pain ("second pain"). In addition to spinal control mechanisms of nociceptive transmission, descending pathways that originate in three major areas—the cortex, thalamus, and brain stem—can modify functions at the spinal level. At every level of the nervous system, a close relationship prevails between somatic pain pathways and visceral pathways. This relationship likely accounts for the transmission of visceral pain and also for autonomic responses to somatic pain and somatic responses to visceral pain.

• *Conclusion*: By understanding the pathways of pain and the transmitters involved, prevention and treatment of pain will be improved.

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ALQ = anterolateral quadrant; NRM = nucleus raphe magnus; NS = nociceptive-specific; PAG = periaqueductal gray; SRT = spinoreticular tract; STT = spinothalamic tract; VMM = ventromedian medulla; WDR = wide-dynamic-range

THE CLASSIC PAIN PATHWAY

The pain pathway, as classically understood, consists of a three-neuron chain that transmits pain signals from the periphery to the cerebral cortex. The first-order neuron has its cell body in the dorsal root ganglion and two axons, one that projects distally to the tissue it innervates and the other that extends centrally to the dorsal horn of the spinal cord. In the dorsal horn, this axon synapses with the second-order neuron, the axon of which crosses the spinal cord through the anterior white commissure and ascends in the spinothalamic tract (STT) to the thalamus. At that site, it synapses with the third-order neuron, which projects through the internal capsule and corona radiata to the postcentral gyrus of the cerebral cortex, where information is somatotopically organized.

THE DUAL PAIN PATHWAY

In 1920, Henry Head proposed a *dual* system of afferent fiber projections in the nervous system—an epicritic system that conveys fine tactile sensitivity and discrimination and a protopathic system that participates in sensations produced by nociceptive stimulation. Nearly three-quarters of a century later and after rounds of lively criticism of this proposal, the nociceptive system itself is, in fact, now thought to be dual, and the sensation of pain that is experienced arrives in the central nervous system by means of two pathways: (1) a sensory discriminative system that encodes the capacity to analyze the nature (for example, burning or pricking), location, intensity, and duration of nociceptive stimulation, subserved by a *lateral* phylogenically newer system, and (2) an affective-motivational component that gives rise to the unpleasant character of painful sensation, subserved by a *medial* phylogenically older and more primitive system.[1]

These two pathways are in parallel with each other, following the classic three-neuron spinothalamic pathway. In addition, current evidence indicates the presence of afferents from the spinal cord to pain-mediating areas of the brain stem, local modulating circuits in the spinal cord, and descending pain pathways from the cortex, hypothalamus, and brain stem to the spinal cord.

This overview will discuss pain pathways, beginning in the periphery and progressing centrally. Most research in

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this area has been done in animals. Analogous anatomic and physiologic features are inferred in humans but may be erroneous. When possible, a discussion of putative mechanisms of actions of drugs used to treat pain will be presented.

THE PERIPHERY

The dual ascending system has its origin in the periphery, where there are two main classes of dorsal horn neurons—high-threshold mechanoreceptors with A-delta axons and polymodal nociceptors with C (unmyelinated) axons. Both types of axons have naked nerve endings. High-threshold mechanoreceptors are recruited first. They transmit "first pain," a well-localized discriminative sensation (sharp, stinging, pricking) that lasts only as long as the acute painful stimulus.[2] The threshold for this first pain is uniform from person to person. Polymodal nociceptors are recruited when a nociceptive stimulus is sufficiently strong. They carry the sensation of "second pain," a more diffuse and persistent burning sensation that lasts beyond the termination of an acute painful stimulus. Second pain is associated with the affective-motivational aspects of pain. Tolerance to it varies from person to person. The composite afferent message induced by an acute noxious stimulus is complex; it results from activation of A-delta and C fibers and also some low-threshold fibers.[3] In acute pain of cutaneous origin, the concepts of first pain and second pain apply. In chronic pain and pain of visceral origin, second pain predominates.

Both high-threshold mechanoreceptors and polymodal nociceptors contain L-glutamate as a transmitter. In addition, polymodal nociceptors contain a variety of neuropeptides, particularly substance P and calcitonin gene-related peptide. How nociceptors are activated by various stimuli is incompletely understood. Some of the activation is probably direct (for example, by mechanical stimulation). Under certain circumstances, however, substances such as potassium and hydrogen ions, histamine, serotonin, bradykinin, prostaglandins, and adenosine triphosphate may act as intermediaries. These substances are released in the tissue by the action of nociceptive stimuli and during painful inflammatory states such as arthritis and abscess. They activate or sensitize nociceptors and, in addition, act on the local circulation to promote vasodilatation and further release of mediators[4] (Fig. 1). Sensitization, which may occur in neurons anywhere in the pain pathway, consists of a decreased threshold for activation of a nociceptor, increased intensity of response to a stimulus, and emergence of spontaneous activity.

NEUROGENIC INFLAMMATION

Nociceptive stimulation that activates C fibers causes a characteristic response known as neurogenic inflammation.[4]

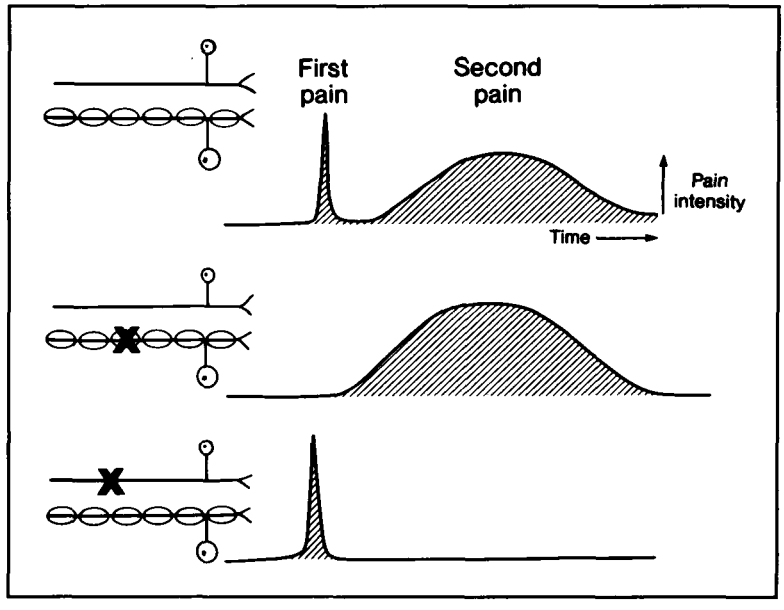

Fig. 1. Diagrams showing two types of axons that transmit painful sensations from periphery—small, myelinated A-delta fibers that carry "first pain" and unmyelinated C fibers that carry "second pain" (see text for definitions). When these fibers are selectively blocked, corresponding pain sensation is abolished, as shown in middle and bottom diagrams. (From Fields.[4] By permission of McGraw-Hill.)

This reaction consists of vasodilatation and increased capillary permeability in the periphery induced by retrograde transport and local release of inflammatory mediators, such as substance P and calcitonin gene-related peptide, from activated C fibers. The release of potassium and hydrogen ions, acetylcholine, histamine, and bradykinin into the tissue by direct injury or by the action of substance P (or by both) stimulates the production of prostaglandins and leukotrienes, which, in turn, may sensitize high-threshold mechanoreceptors. This sensitization may show resistance to nonsteroidal anti-inflammatory agents. Neurogenic inflammation spreads to surrounding tissue by means of antidromic impulses descending the sensory axons from their nerve cell bodies in the dorsal root ganglia and retrograde transport of substance P from the nerve cell bodies to the periphery (Fig. 2).

DRUGS ACTING IN THE PERIPHERY

Part of the rationale for using nonsteroidal anti-inflammatory agents for treating pain is their ability to inhibit prostaglandins, one of the sensitizers of nociceptive afferents. Because neurogenic inflammation shows resistance to these agents, a central nervous system mechanism of action for these drugs may be more important than any peripheral effects.

Although the mechanisms for the efficacy of corticosteroids in the treatment of pain are unknown, they may be useful for treating certain painful conditions partly because they inhibit the effects of histamine, serotonin, bradykinin, and prostaglandins. These considerations suggest that, when clinically indicated, drugs should be used early and aggressively to prevent sensitization and the consequent augmentation of pain.

Local anesthetic agents, which block nerve conduction by blocking sodium ion channels in the axon, may prevent the sensitization of afferent neurons in the spinal cord. A clinical application of this hypothesis is the presumptive use of a local anesthetic agent before an operative incision is made, with the aim of decreasing postoperative pain. This area is controversial, and further research remains to be done.[5,6]

Capsaicin, derived from the Hungarian red pepper, is a substance P antagonist. This drug is a topical agent for treating postherpetic neuralgia. It has also been used in the treatment of painful peripheral neuropathies. The capsaicin is transported up the C fibers to the nerve cell bodies, where it depletes them of substance P. Because of burning pain on application, slow axonal transport of capsaicin, and the need for sustained long-term use to achieve effect, results have been discouraging. Several agents, acting presynaptically, can inhibit the antidromic release of substance P. Such agents include opioids, serotonin agonists (used to treat migraine), baclofen, and clonidine hydrochloride (used to treat painful neuropathies). Inhibition of the release of substance P and consequent neurogenic inflammation is a rationale for their use.

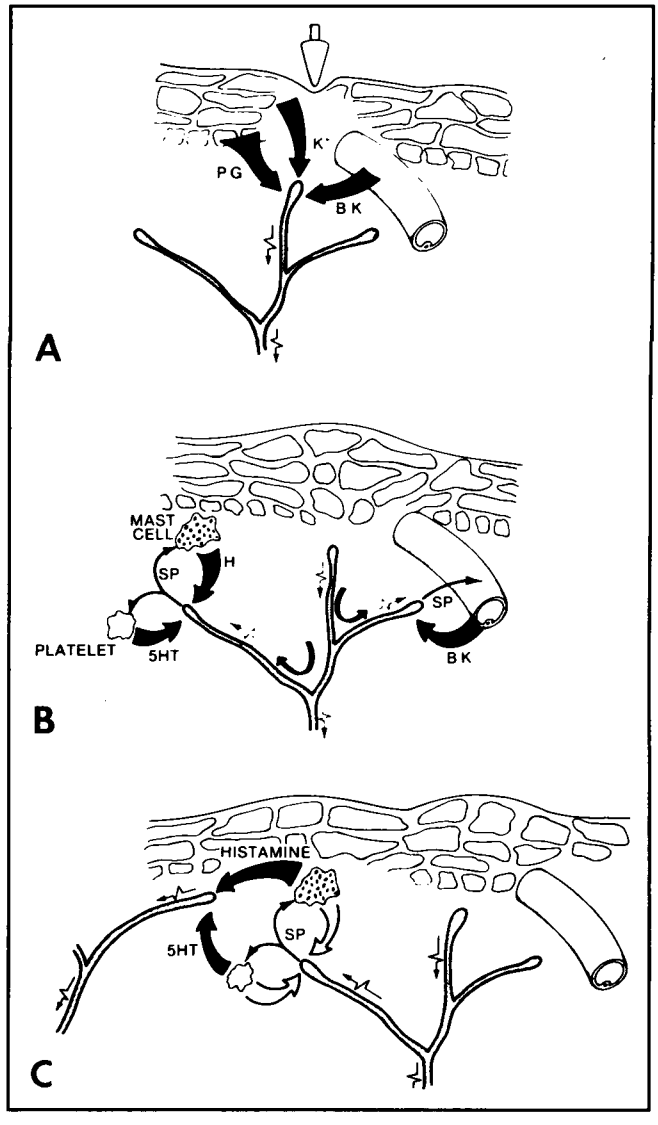

Fig. 2. Diagrams depicting neurogenic inflammation. *A*, Injury to tissues causes release of potassium (K^+), prostaglandins (*PG*), and bradykinin (*BK*), resulting in stimulation of sensory afferents. *B*, Sensory impulses propagate peripherally, causing direct release of histamine (*H*) from mast cells and 5-hydroxytryptamine (*5HT*; serotonin) from platelets. They also propagate centrally and cause retrograde release of substance P (*SP*), which, in turn, augments local reactions. *C*, Local reactions stimulate nearby axons and thereby spread inflammation, hyperalgesia, and tenderness. (From Fields.[4] By permission of McGraw-Hill.)

The actions of substance P have drawn attention to a relatively new concept in neurology, the "efferent" role of classic afferent nociceptive fibers. Sensory afferents have

several other newly recognized nonclassic features. Although most enter the spinal cord through the dorsal roots, some enter ventrally (where motor axons classically exit).[1] This anatomic variation may be one reason why dorsal rhizotomy may be ineffective for managing pain. In addition, a single cell body in the dorsal root ganglion may have more than one axon arriving from the periphery, and sometimes these axons originate from different peripheral nerves. Substance P may be transported antidromically to more than one peripheral site.

At times, peripheral nerves not only are stimulated but also are damaged by a noxious agent. Even when the noxious stimulus is removed, sensitized or damaged neurons or their axons may depolarize abnormally and send impulses centrally. Anticonvulsant drugs such as carbamazepine (Tegretol) may stabilize such sensitized or damaged neurons and are used in neuropathic pain syndromes characterized by shooting or lancinating sensations, such as postherpetic neuralgia and trigeminal neuralgia.

Pain that originates in damaged C fibers is often burning in quality. The local anesthetic agent mexiletine hydrochloride can occasionally alleviate this pain.[7] Mexiletine may act by blocking action potentials along injured axons. C fibers are unmyelinated and therefore "exposed," a feature that makes them sensitive to low circulating concentrations of mexiletine, whereas other types of fibers, being myelinated, are less affected.

The sympathetic afferents and efferents to and from the spinal cord are in close physical relationship to afferent nociceptive fibers (Fig. 3). This is the most peripheral level of somatic-visceral interaction. Segmental reflexes between the two systems can cause somatic responses to visceral pain (for example, muscle splinting and guarding) and visceral responses to somatic pain (such as vasodilatation).

DORSAL HORN AFFERENTS

Sensory afferents enter the dorsal horn, ascend one or two segments in Lissauer's tract, and terminate in the gray matter of the dorsal horn (Fig. 4). Fiber terminations are segregated in laminae. High-threshold mechanoreceptors (A-delta fibers) terminate in laminae I, V, and X. Polymodal nociceptors (C fibers) terminate in laminae I through V. Termination patterns of primary afferents are characteristic of their functional properties rather than their diameters.

Nociceptive afferents terminating in the dorsal horn release numerous transmitters, many of which are polypeptides. Some of these act directly, and some serve a modulatory role (autotransmitters). Just as it does in the periphery, substance P plays an important role in the dorsal horn. It can be released both synaptically and extrasynaptically and may be a transmitter, an autotransmitter, or both. Hyperalgesic effects have been shown after the intrathecal injection of substance P. Dorsal rhizotomy exacerbates the excitatory effects of substance P; this reaction could be part of the mechanism of denervation hypersensitivity and could account for the common failure of dorsal rhizotomy to control pain.[8,9] In the case of nerve root avulsion injury, a more effective management technique than dorsal rhizotomy is the dorsal root entry zone procedure.[10] Radio-frequency lesions are made within the substance of the cord, where the rootlets enter. The entering axons, their terminations, and some surrounding interneurons are lesioned. The role of interneurons will be addressed in the subsequent material.

DORSAL HORN NEURONS

The second-order nociceptive neurons, with their cell bodies in the dorsal horn and their axon terminations in the thalamus, are mainly of two types: those that respond to gentle

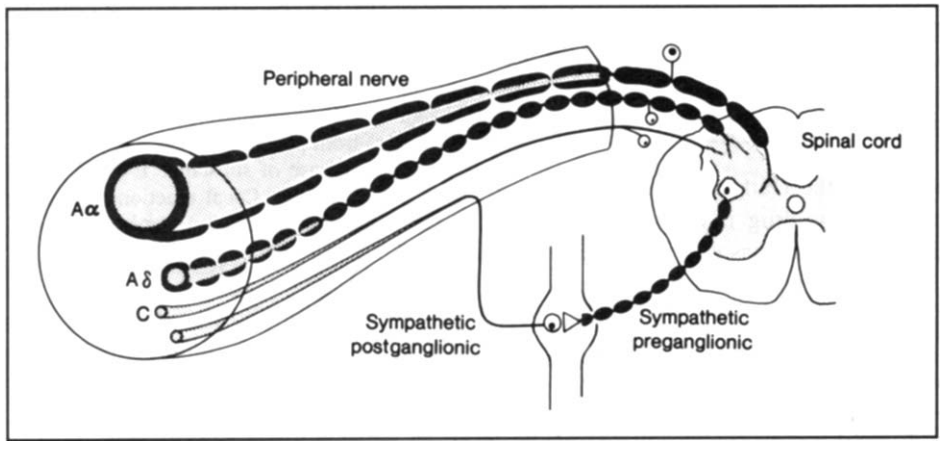

Fig. 3. Diagram illustrating close relationship between sensory afferents (including nociceptive afferents) and sympathetic outflow. (From Fields.[4] By permission of McGraw-Hill.)

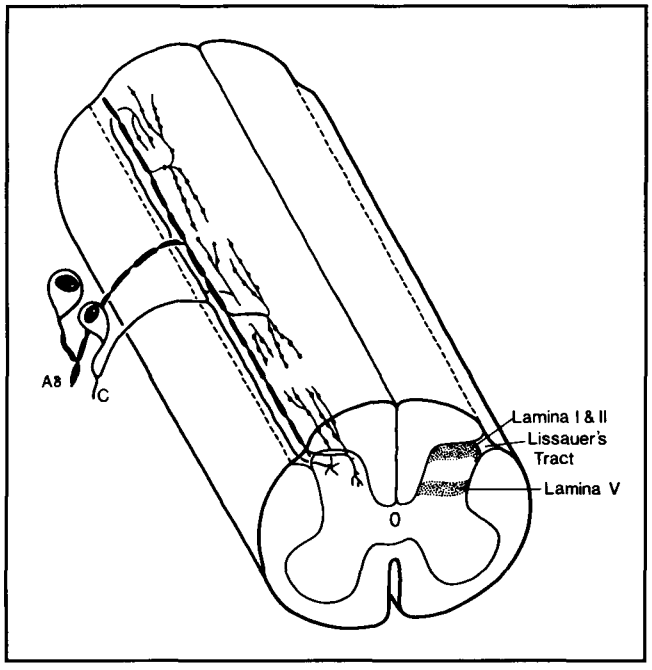

Fig. 4. Diagram of pain pathways in central nervous system. A-delta and C fibers enter dorsal horn and then ascend and descend several levels in Lissauer's tract. They ultimately terminate in gray matter of dorsal horn—C fibers predominantly in lamina II and A-delta fibers in laminae I and V. (From Fields.[4] By permission of McGraw-Hill.)

stimuli and increase their responses when the stimuli become intense (noxious) and those that respond exclusively to noxious stimuli. These neurons are termed "wide-dynamic-range" (WDR) and "nociceptive-specific" (NS) neurons, respectively.[1]

WDR neurons are found in laminae IV, V, and VI (especially in lamina V).[4] They respond to both A-delta and C fiber afferents. When these neurons are deafferented by damage to the sensory afferents in the periphery, they show responses that intensify as the stimuli on them increase. If C fibers are stimulated at a rate of once per second, the response of the WDR neurons increases progressively with each stimulus. This phenomenon, termed "wind-up," may account for the observation in humans that pain sensation increases with repetitive stimulation at this rate.[1] The wind-up phenomenon and sensitization of dorsal horn neurons support the argument that pain should be treated early and aggressively before these spinal cord neurons are so stimulated that they fire independently of signals from the periphery. WDR neurons also respond to visceral stimuli and are therefore one point of visceral-somatic convergence. Referred pain may be explainable on the basis of the convergence of visceral and somatic signals on the WDR neurons of the dorsal horn. Phenomena such as reflex sympathetic dystrophy (sympathetically maintained pain) may also depend on this relationship.

NS neurons are located in lamina I.[4] They respond only to noxious stimuli and can be sensitized by repetitive stimulation. Visceral-somatic convergence occurs on them just as it does on WDR neurons. NS neurons are thought to be involved in the sensory-discriminative aspects of pain, whereas WDR neurons participate in the affective-motivational component.

A third, and less well studied, group of dorsal horn neurons, termed "complex neurons," are located primarily in laminae VII and VIII. They have a highly convergent, often bilateral input that includes afferents from visceral receptors. They are another focus of somatic-autonomic convergence.

Nociceptive transmission in the dorsal horn can induce the expression of c-*fos*, a proto-oncogene, which may cause or be a marker for prolonged functional changes such as sensitization and the wind-up phenomenon in dorsal horn nociceptive neurons.[11]

ASCENDING PATHWAYS

Axons of both WDR and NS neurons cross in the anterior white commissure and ascend the spinal cord in the anterolateral quadrant (ALQ). (The ALQ subsumes the classic STT as well as several other ascending and descending pathways.) Lesioning of the ALQ (ventrolateral cordotomy) has been used to block nociceptive afferents ascending the cord[8,9] and alleviate unilateral lower extremity pain. Because the relief is temporary, pain of malignant origin has been the primary indication.

The ALQ has two major ascending pain pathways—the STT and the spinoreticular tracts (SRTs). Of the axons ascending to the thalamus, approximately 50% are WDR, 30% are NS, 10% are activated by stimulation of deep tissue, and 2% are exclusively activated by innocuous tactile stimulation[1] (Fig. 5).

Nociceptive STT neurons have as their destination two main groups of thalamic nuclei: *lateral nuclei* (the ventroposterolateral nucleus and the posterior nuclear group) and *medial nuclei* (the central lateral nucleus of the intralaminar complex and the nucleus submedius). Those axons that project *laterally* originate in laminae I and V of the dorsal horn, send signals from smaller, more discrete receptive fields in the periphery, and are thought to have a role in the discriminative aspects of pain. Those that project *medially* originate in laminae I, IV, and VI, reflect input from large receptive fields, and are implicated in affective-motivational aspects of pain. The medial projections are similar to spinoreticular afferents (see subsequent discussion). Communication between the two groups of thalamic afferents may occur. In addition, the SRT itself projects to the medial thalamus (see subsequent material).

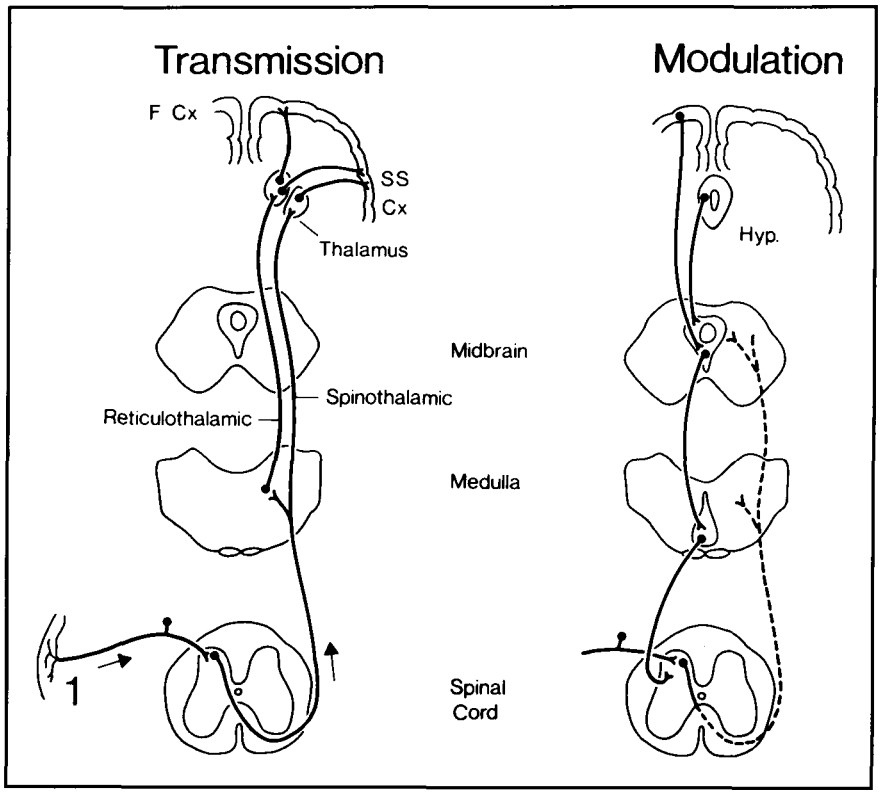

Fig. 5. *Left*, Diagram showing ascending pain pathways. First-order neurons (*1*), with their cell bodies in dorsal root ganglia, arrive from periphery and terminate in dorsal horn. Second-order neurons have cell bodies in dorsal horn, cross in anterior white commissure, and ascend; some axons terminate in reticular formation of brain stem and others project to thalamus. Axons that terminate more medially in thalamus synapse with third-order neurons, which project to frontal cortex (*F Cx*). Those that terminate more laterally synapse with third-order neurons, which project to somatosensory cortex (*SS Cx*). *Right*, Diagram depicting descending pain pathways. Projections arising in cortex and hypothalamus (*Hyp.*) descend to periaqueductal gray of midbrain, reticular formation of medulla, and, ultimately, dorsal horn of spinal cord, where they exert an inhibitory effect on ascending nociceptive transmission. (From Fields.[4] By permission of McGraw-Hill.)

The nociceptive SRTs ascend from the dorsal horn through the ALQ to the reticular formation of the brain stem. They are divided into two main groups—the bulbopontine group and the mesencephalic group. The bulbopontine group terminates in a number of nuclei in the pons and medulla, including the nucleus gigantocellularis, the nuclei reticularis pontis caudalis and oralis, the nucleus paragigantocellularis, and the nucleus subcoeruleus. The mesencephalic group projects to the periaqueductal gray (PAG), the deep layers of the superior colliculi, and the nucleus cuneiformis.[1] The reticular formation is a primitive core neural system essential to homeostatic and integrative functions of the organism. It has a role in affective-motivational aspects of sensory, motor, and visceral functions. It is the origin of a descending pain-modulating pathway that will be discussed subsequently in this article.

In addition to the aforementioned STT and SRT, several alternative nociceptive pathways exist outside the ALQ. There is a small uncrossed component of the STT. A multisynaptic propriospinal pathway ascends just ventral to the dorsal columns. Alternative pathways may be responsible for recurrence of pain months to years after anterolateral cordotomy.

THALAMOCORTICAL PROJECTIONS

The third-order neurons of the ascending pain pathway originate in the thalamus and project to the cortex (Fig. 5). Neurons from the *lateral* thalamic nuclei project to the primary somatosensory cortex and allow the conscious localization and characterization of painful stimuli. This system is a relatively recent phylogenic development. Neurons from the intralaminar and *medial* nuclear areas project to the anterior

cingulate gyrus and are thought to be involved in the perception of suffering and the emotional reaction to pain. This cortical projection is older and more primitive. The anterior cingulate gyrus has numerous opioid receptors. This area has been lesioned in an attempt to treat severe intractable pain, but results have been discouraging.

SEGMENTAL MODULATION

The dual ascending pain pathway is under both segmental and descending modulation[12] (Fig. 5). In the spinal cord, the controls are generally inhibitory. Nonnociceptive sensory afferents for position and vibration have their first-order cell bodies in the dorsal root ganglia and send incoming axons up the dorsal columns. They have inhibitory influences on nociceptive activity in the dorsal horn. Transcutaneous electrical nerve stimulation stimulates these large afferents in the periphery in an attempt to increase this inhibitory effect. Dorsal column stimulation attempts to achieve the same result more directly. Interestingly, the inhibitory effect can last hours beyond the cessation of the stimulus. A possible explanation for this effect is sustained alterations produced in the central nervous system by prolonged stimulation.[13]

The substantia gelatinosa of the dorsal horn most likely contains an interneuronal system without long projections. It may modulate messages that are about to ascend the spinal cord. The dorsal horn contains several transmitters important for pain signals. Opioid receptors are present on the terminals of primary afferent nociceptive fibers that enter the cord. Opioids block, in a naloxone-reversible manner, the potassium-evoked release of substance P. Opioids also act postsynaptically in the dorsal horn. How the endogenous spinal opioid system is activated is unknown, but its functional implications are well supported by the powerful long-lasting analgesic effect seen after the intrathecal and epidural administration of opiates. This route of opiate delivery is being more widely used than in the past, especially for major thoracic, pelvic, and lower extremity surgical procedures and in the management of severe chronic pain in the lower extremities or pelvis, such as that from invasion of the lumbosacral plexus by metastatic disease.[13,14]

In addition to the spinal opioid system, the dorsal horn contains several other peptides that are or may be important in transmission of pain, including γ-aminobutyric acid, substance P, somatostatin, neurotensin, avian pancreatic peptide, cholecystokinin, and neuropeptide Y.[1]

DESCENDING PATHWAYS

In addition to spinal control mechanisms, nociceptive transmission is under the influence of supraspinal controls.[12] Descending pathways that originate in three major areas—the cortex, the thalamus, and the brain stem—can modify functions at the spinal level (Fig. 6). Currently recognized transmitters in the descending pathways include epinephrine, norepinephrine, serotonin, and various opioids.

Stimulation of sensory and motor cortex can induce inhibitory, excitatory, or mixed effects on both WDR and NS dorsal horn neurons. These effects may be mediated by direct descending fibers or via intermediary brain-stem structures.

In the brain stem, descending projections originate in the reticular formation; in the midbrain, they originate from the ventral portion of the PAG (the dorsal raphe nucleus), and in the medulla, they originate from the nucleus raphe magnus (NRM) and the nucleus raphe centralis superior.[1] These reticular formation nuclei are also the targets of the nociceptive spinoreticular pathway. Stimulation of the dorsal raphe nucleus of the PAG markedly inhibits the responses of dorsal horn neurons to nociceptive stimuli that activate C fibers. Stimulation of the NRM profoundly depresses the activity of cells in the dorsal horn. These analgesic effects result from the activation of descending fibers traveling in the dorsolateral quadrant of the spinal cord. Only a few direct spinal projections originate from the PAG, but PAG-NRM connections have been clearly demonstrated, and projections descend from the NRM through serotoninergic axons in the dorsolateral cord. Stimulation of the dorsolateral cord inhibits dorsal horn nociceptive neurons.

In the medulla, the NRM is closely connected to two other reticular formation nuclear groups—the nucleus reticularis gigantocellularis-pars α and the nucleus reticularis paragigantocellularis. This combined unit, known as the ventromedian medulla (VMM), is rich in 5-hydroxytryptamine (serotonin). A tonic inhibitory effect on dorsal horn nociceptive neurons seems to occur through serotoninergic projections from the VMM.

Another monoamine apparently involved in pain modulation is norepinephrine. Intrathecal administration of norepinephrine results in analgesia mediated by α-adrenoceptors. Norepinephrine has a pronounced and selective tonic inhibitory effect on nociceptive neurons in the dorsal horn. Stimulation of the NRM releases both serotonin and norepinephrine. Major norepinephrine projections to the dorsal horn also arise in the region of the locus coeruleus in the pons. This area is, in turn, stimulated by the PAG or VMM. Electrical stimulation of the locus coeruleus induces analgesia and inhibits spinal nociceptive transmission.[8,9] The locus coeruleus, by means of norepinephrine as a transmitter, also reciprocally inhibits the PAG and VMM.

Understanding the importance of monoamines in descending pain-modulating circuits has prompted the use of tricyclic antidepressants such as amitriptyline hydrochloride (Elavil) and serotonin reuptake blockers such as fluoxetine hydrochloride (Prozac) for treating chronic pain.[15] The objective is to augment the descending antinociceptive path-

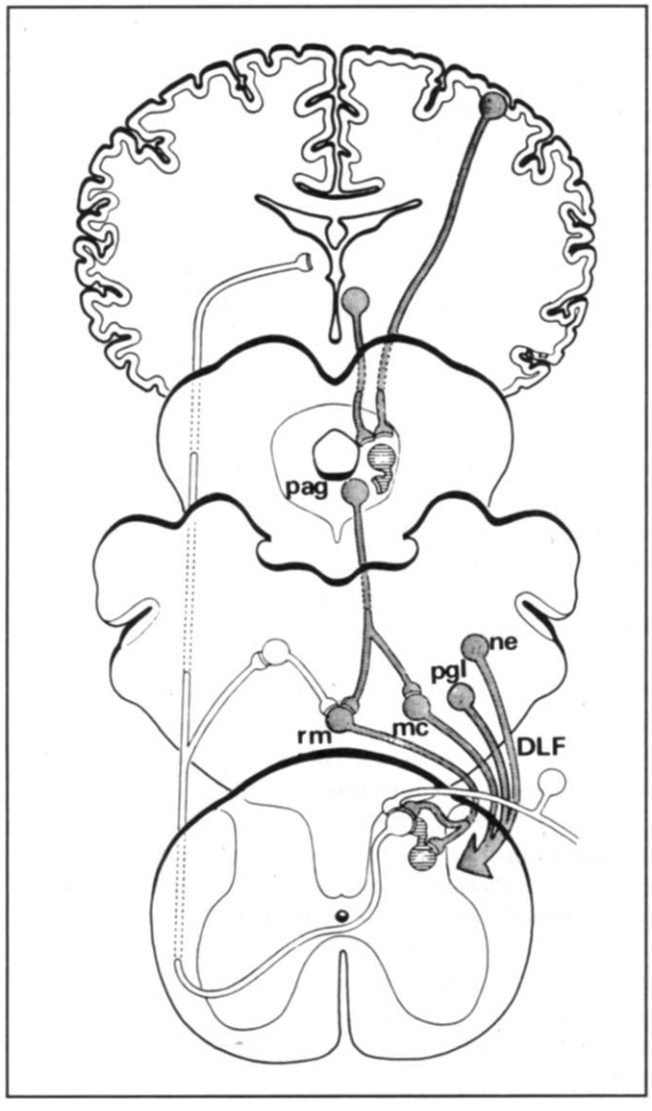

Fig. 6. Diagram showing descending pain-modulating pathways in more detail than in Figure 5. Neocortex and hypothalamus project to periaqueductal gray (*pag*), which, in turn, sends descending projections to nuclei in reticular formation of medulla—medullary nucleus, raphe magnus (*rm*)-reticularis magnocellularis (*mc*), nucleus paragigantocellularis (*pgl*), and noradrenergic medullary cell groups (*ne*). These nuclei, in turn, project through dorsolateral funiculus (*DLF*) to dorsal horn of spinal cord. Some of these projections are direct, and others occur by means of interneurons. Ascending pathway is shown as clear structures; descending pathway is hatched. (From Fields HL, Basbaum AI. Endogenous pain control mechanisms. In: Wall PD, Melzack R, editors. Textbook of Pain. Edinburgh: Churchill Livingstone, 1984: 142-152. By permission.)

way. Knowledge of descending inhibitory pathways from the thalamus and PAG has led to placement of electrodes to stimulate these areas in an attempt to manage intractable pain attributable to neural injury.[16]

Opioid receptors, in addition to being in the periphery and the dorsal horn, are located in the brain stem, where endogenous opioids including enkephalin, β-endorphin, and dynorphin act on various opioid receptors as part of the internal antinociceptive mechanisms.[17,18] Exogenous opiates act in the brain stem, dorsal horn, and probably also the periphery. Lesions in the brain stem can diminish the analgesic effects of systemically administered morphine, and naloxone can reduce the analgesic effects of PAG and NRM stimulation.

The anatomic and functional relationships among serotonin, norepinephrine, and opioid neurons are under investigation. Other transmitters such as neurotensin and acetylcholine may also play a role. Current evidence supports the existence of two classes of neurons in the PAG and VMM—"off" neurons, which decrease their firing in association with noxious stimulation (antinociceptive neurons), and "on" neurons, which (directly through descending pathways or indirectly by inhibiting "off" neurons) facilitate nociceptive transmission. Opioids disinhibit "off" neurons and inhibit "on" neurons. Norepinephrine inhibits "on" neurons.[4] "Off" neurons inhibit, and "on" neurons facilitate, nociceptive transmission in the dorsal horn.

The brain-stem analgesic system and its descending projections to the dorsal horn constitute a powerful negative feedback system that is activated by nociceptive stimulation (through the aforementioned spinoreticular, spinothalamic, and spinocortical pathways) and that, in turn, produces inhibition of the spinal transmission of nociceptive signals. This descending system is thought to participate in the analgesia produced by stress on the organism, a condition in which pain suppression may be more adaptive than pain sensation.[19,20] In addition, it has been implicated in the phenomenon of diffuse noxious inhibitory control, in which a diffuse noxious stimulus far from the site of the receptive field of a peripheral nociceptive neuron can inhibit the ability of this neuron to activate dorsal horn nociceptors. This phenomenon may explain the analgesic effect of counterirritation.

A close relationship exists between the brain stem and thalamic reticular formation structures that subserve pain and the brain stem and hypothalamic components of the autonomic nervous system. Visceral responses to pain likely originate, in part, from interactions between these systems.

At each level of the pain pathway, the close relationship between visceral and somatic neurons has been noted. In addition to visceral responses to somatic pain, and visceral pain itself (mediated by C fibers, autonomic afferents, or both), the autonomic nervous system participates in sympathetically maintained pain (reflex sympathetic dystrophy), possibly by regulating the excitability of mechanoreceptors such that even very mild stimulation activates nociceptors.[21] This phenomenon extends over contiguous axons and their

neurons in the periphery and in the central nervous system as well.

CONCLUSION

The nociceptive pathway consists of the classic three-neuron chain. This pathway is double at each level, with two types of neurons from the periphery, two types of neurons ascending from the posterior horn to the brain stem and thalamus, and two sets of projections to the cortex. Discriminative pain is carried separately from the affective-motivational aspects of pain. Even in the periphery and in the spinal cord, this distinction can be made. A segmental modulating system in the spinal cord and a descending modulating system from the cortex, diencephalon, and brain stem have inhibitory effects on dorsal horn neurons. The entire system is plastic, responding to a wide variety of stimuli in the environment and to the needs—both physical and emotional—of the organism. Not only inhibitory controls but also augmentative ones are so plastic that nociceptive neurons can fire even when the stimulus that initially activated them is no longer present. The affective-motivational aspects of pain originate in the periphery, and suffering is not merely a matter for the neocortex; it is profoundly more ancient and primitive phylogenically and is reflected in fiber tracts and neural networks throughout the nervous system. Understanding these pathways and their transmitters makes possible the rational and effective prevention and treatment of pain.

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