Mechanisms of Chronic Pain

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Chronic pain differs from acute pain in that it serves no useful function, causes suffering, limits activities of daily living, and increases costs of healthcare payments, disability, and litigation fees. Pain perception begins with activation of peripheral nociceptors and conduction through myelinated Aδ and unmyelinated C fibers to the dorsal root ganglion. From here, signals travel via the spinothalamic tract to the thalamus and the somatosensory cortex. Modulation of sensory input (i.e., pain) occurs at many levels. Nociceptors are also neuroeffectors, and transmission can be modulated by their cell bodies, which secrete inflammatory mediators, neuropeptides, or other pain-producing substances. Descending pathways from the hypothalamus, which has opioid-sensitive receptors and is stimulated by arousal and emotional stress, can transmit signals to the dorsal horn that modulate ascending nociceptive transmissions. Modulation to alter the perception of pain also can occur at higher centers (e.g., frontal cortex, midbrain, medulla) by opioids, anti-inflammatory agents, as well as antagonists and agonists of neurotransmitters. This article will review our current knowledge of the mechanisms involved in (1) the transduction of tissue injury or disease signals (nociception and nociceptive receptors); (2) the transmission of signals rostrally to the thalamus and higher nervous system centers (involving perception of the quality, location, and intensity of noxious signals); and (3) the modulation of ascending sensory messages at all levels (periphery, spinal cord, and higher centers). *Am J Med.* 1996;101 (suppl 1A):6S–18S.

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Acute pain is biologically useful because it signals injury or disease and subsides as healing progresses. In contrast, chronic pain does not spontaneously resolve and serves no useful biologic function. For purposes of classification, four types of chronic pain are recognized (**Table I**). Chronic pain limits normal function, including recreation, employment, and daily activities. One in three U.S. citizens experiences some form of chronic pain that requires medical attention during their lifetime. More than 50 million people are either partially or totally disabled by chronic pain, which results in a loss of >700 million work days and costs $80–90 *billion* in healthcare payments and litigation fees annually.[2] Treatment of chronic pain should be directed at rehabilitation and control, because a cure is not always possible.

The perception of chronic pain is influenced by the interaction of physiologic, psychologic, and social processes. Neurophysiologic responses to nociception (i.e., pain) trigger psychologic responses; conversely, the psychologic state of the patient can modulate and dampen or heighten perceptions of noxious incoming signals through pathways involving the hypothalamus and the dorsal descending bundle. Furthermore, social (or environmental) factors can influence the patient's emotional state and determine the balance between pain and stoicism.

A brief review of neuroanatomy, neurophysiology, and neuropharmacology is necessary to understand the mechanism involved in the generation and perception of pain (nociceptive or neuropathic mechanisms). Nociception means the activation of peripheral nerve fibers in normal peripheral and central nervous systems by chemical, thermal, and/or mechanical stimuli. Neuropathic mechanisms occur secondary to pathologic functioning of peripheral or central nervous system tissue. This article will review our current knowledge of the mechanisms involved in (1) the transduction of tissue injury or disease signals (nociception and nociceptive receptors); (2) the transmission of signals rostrally to the thalamus and higher nervous system centers (involving perception of the quality, location, and intensity of noxious signals); and (3) the modulation of ascending sensory messages at all levels (periphery, spinal cord, and higher centers).

TRANSDUCTION OF SIGNALS

Afferent nerve fibers are labeled A, B, or C fibers. A fibers are large, myelinated fibers and respond to

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light touch, as well as mechanical and thermal nociception. The A fibers are further divided into α, β, γ, and δ fibers. The Aδ fibers are thinly myelinated and carry very strong noxious stimuli that are potentially or actually damaging to tissues. Other A and B fibers do not carry nociceptive impulses. The B fibers are myelinated preganglionic autonomic nerves. C fibers are nonmyelinated, slow-conducting fibers of which >50% carry afferent noxious stimuli. Their cell bodies are in the dorsal horn of the spinal cord. These afferent fibers exhibit polymodal responsiveness to tissue-damaging stimuli (e.g., mechanical, thermal, chemical).

Sensory input involves nociception, mechanoreception, thermal reception, and proprioception. Perception of pain results from stimulation of nociceptors located in skin and organs of the body. Nociceptors are located in muscle, fascia, blood vessel walls, tendons, joint capsules, ligaments, fat pads, and periosteum.[3] Nociceptors in visceral tissue respond to stretch and distortion of visceral organs.[4] Stimulation of nociceptors results in afferent impulses conducted through myelinated Aδ[5] and unmyelinated C fibers[6] passing through the dorsal root ganglion. The speed of afferent neural transmission is related to the size and myelination of the activated nerve fibers (**Table II**).

The peripheral nerve has three different types of axons (**Figure 1**), which include primary sensory afferents, motor efferent, and sympathetic postganglionic. The cell bodies of the primary afferent neurons are located in the dorsal root ganglion. They bifurcate, sending one process to the spinal cord and one to innervate body tissues. Sympathetic postganglionic afferents (unmyelinated) emerge from the paraspinal sympathetic ganglion and enter the peripheral nerve via the grey ramus communicans. Nociceptive afferents enter the spinal cord through the dorsal root ganglion and terminate at second-order dorsal horn neurons. The neuropeptides that transmit the nociceptive signal from the periphery to spinal cord neurons are substance P and calcitonin gene-related peptide (CGRP).[9,10]

TABLE I

Four Types of Chronic Pain

- Pain persisting beyond the normal healing time for a disease or injury
- Pain related to chronic degenerative disease or a persistent neurologic condition
- Pain that emerges or persists (even recurring for months to years) without an identifiable cause
- Cancer pain

From *The Management of Pain.*[1]

TABLE II

Peripheral Nerve Fibers that Conduct Nociception

Fiber Type	Velocity (m/s)	Stimuli	Myelination
Aβ	40–80	Light touch, hair movement	++
Aδ_1	2.5–36	Mechanical force	+
Aδ_2	2.5–36	Thermal, mechanical	±
C	0.5–1.7	Polymodal	–

Modified with permission from *Assessing Chronic Pain.*[7]

Nociceptors

Nociceptive receptors are free nerve endings found throughout the body in skin, viscera, blood vessels, muscle, fascia, and joint singular capsules. When activated by noxious stimuli, they generate impulses along afferent nerves to the central nervous system. Types of receptors include high-threshold, injury-sensitive, sensory organs with relatively small receptor fields that conduct impulses through small Aδ (myelinated-rapid) and C fibers (unmyelinated-slow). Polymodal nociceptors respond to chemical heat and pressure (C-fiber afferent),[6] or heat and mechanical stimuli (Aδ_2 afferent).[11] Modality-spe-

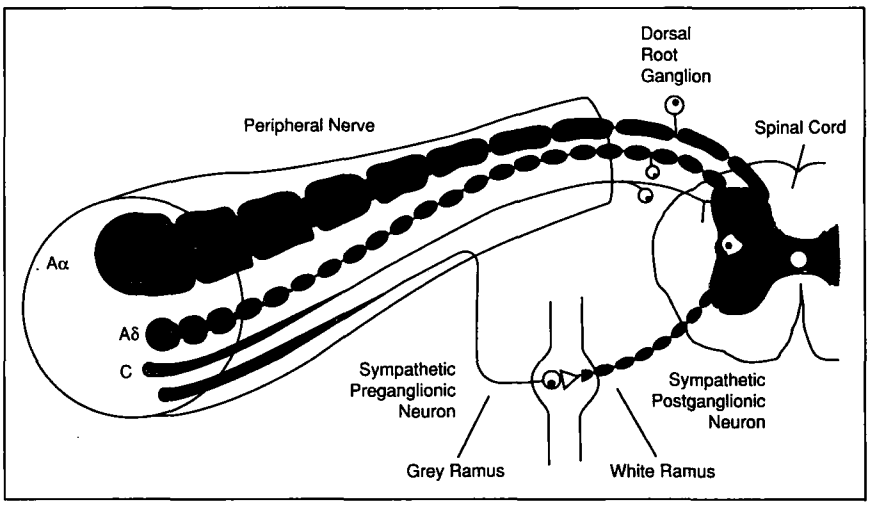

Figure 1. Schematic of a peripheral nerve. (Modified with permission from McGraw Hill.[8])

cific[5] mechanoreceptor units ($A\delta_1$ afferent) are nociceptors that are slow adapting, respond to strong pressure, and have little or no dynamic firing during stimulus onset. $A\delta$ fibers produce well-localized first pain sensations associated with immediate injury. In contrast, C fibers carry diffuse burning second pain sensations that can be dull, poorly localized, and persistent.[12]

Hyperalgesia or sensitization occurs when intense and repeated stimuli from tissue damage or inflammation is present. This results in a lowered threshold for activation of primary afferent nociceptors (PANs), which leads to innocuous stimuli causing severe pain. For example, slapping someone who has a bad sunburn on the back can be very painful. In patients with pharyngitis, swallowing can be extremely painful, as can micturition in the presence of a urinary tract infection.[13]

Neuroeffector Functions

In addition to transmission of afferent signals, nociceptors also have neuroeffector functions. When activated by noxious stimuli, they release neuropeptides from their cell bodies in the dorsal horn (e.g., substance P, CGRP) that act on peripheral cells. Most of these neuropeptides modulate (i.e., amplify or downgrade) the afferent response. In joint tissues, activation of PANs stimulates postganglionic sympathetic neurons and releases norepinephrine, adenosine triphosphate (ATP), adenosine, prostacyclin (PGI_2), interleukin 1 (IL-1), and neuropeptide Y.[14] This occurs either by local stimulation or by a spinal reflex.

PANs can be activated either primarily or secondarily by inflammatory mediators, neuropeptides, or other pain-producing substances (**Figure 2**). The sensitivity or threshold of PANs also can be altered positively or negatively by these same substances (**Table III**; e.g., inflammation or injury release mediators to facilitate the inflammatory process further).[8]

Bradykinin. Bradykinin is released following tissue injury and is present in inflammatory exudates. It can act directly on PANs to cause pain[16] and sensitize them to other stimuli, such as heat and touch.[17] Furthermore, bradykinin acts synergistically with prostaglandins and 5-hydroxytryptamine (serotonin; 5-HT). Bradykinin acts on the postganglionic sympathetic neurons causing release of arachidonic acid from membrane phospholipid and conversion to prostaglandin E_2 (PGE_2). Subsequently, PGE_2 directly stimulates PANs or sensitizes them to noxious stimuli. Norepinephrine (also produced by sympathetic neurons) converts membrane phosphatidyl inositol to PGI_2 (utilizing phospholipase C), which

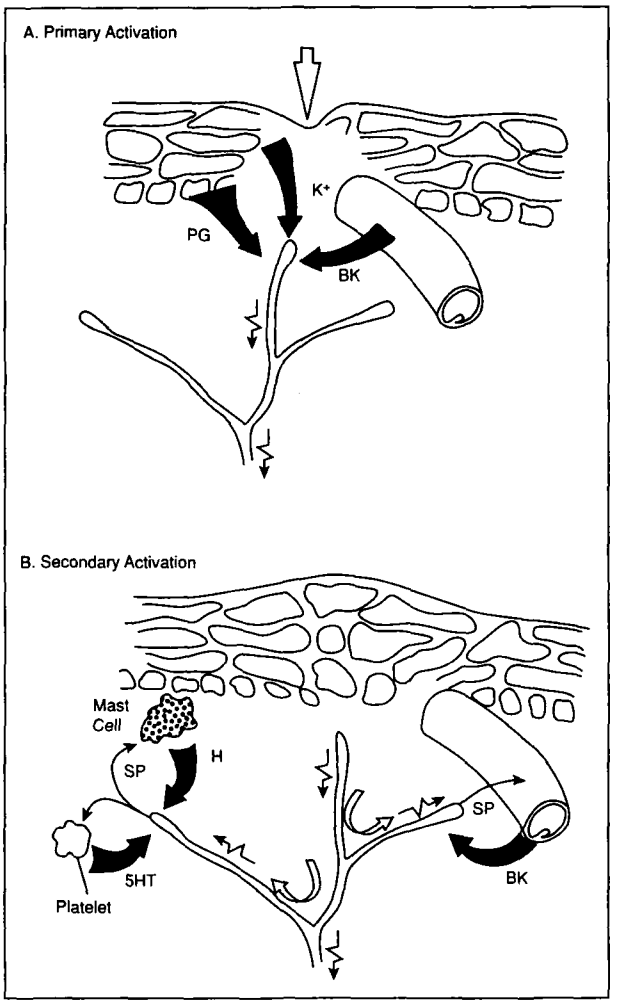

Figure 2. Primary (A) and secondary (B) activation of primary afferent nociceptors. (Reprinted with permission from McGraw Hill.[8])

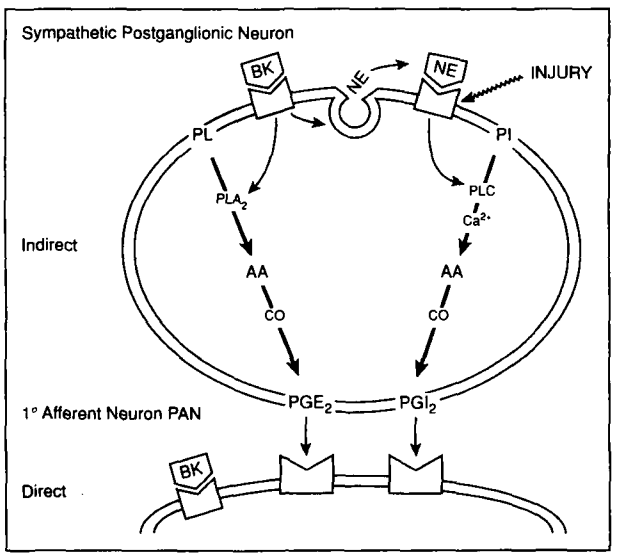

Figure 3. Direct and indirect stimulation of primary afferent neurons. (Modified with permission from Churchill Livingstone.[18])

TABLE III

Substances that Directly Stimulate and/or Sensitize Primary Afferent Nociceptive (PAN) Fibers

Stimulators	Direct Sensitizers	Indirect Sensitizers
Bradykinin	PGE_2	Bradykinin
Proton	8*R*,15*S*-diHETE	Interleukin-6
Serotonin	$PGF_{2\alpha}$	LTB_4
Histamine	PGE_1	Noradrenaline
Potassium	PGI_2	Interleukin-1
PGE_2	Adenosine	Interleukin-8*
PGI_2	Serotonin	TNF-α
	Bradykinin	NGF-OP*
	Proton	Nitric oxide

LTB_4 = leukotriene B_4; NGF-OP = the amino-terminal octapeptide of nerve growth factor; PGE_1, PGE_2, $PGF_{2\alpha}$ = prostaglandin E_1, E_2, $F_{2\alpha}$; PGI_2 = prostaglandin I_2 (prostacyclin); 8*R*,15*S*-diHETE = the 8*R*,15*S* stereoisomer of dihydroxyeicosatetraenoic acid; TNF-α = tumor necrosis factor α.

* Has been suggested to act via the postganglionic sympathetic nerve fibers. Bradykinin, however, has also been suggested to act without involvement of the sympathetic nervous system.

Modified with permission from *Arthritis Rheum.*[15]

TABLE IV

Role of Cytokines in Pain

Cytokine	Cell Origin	Mechanism of Pain
IL-1	Macrophage; epithelial cells	Induces PGE_2 in nonneuronal cells, which activates PAN[31]
IL-8	Macrophages	Causes hyperalgesia by stimulation of postganglion sympathetic neurons[32]
IL-6	T cells; macrophages	Induces release of PGE from mononuclear cells, which activate PAN[33]
TNF	Macrophage; natural killer cells	Induces release of IL-1, IL-6, and IL-8[34]
NGF	Fibroblasts; Schwann cells	Regulates synthesis and transport of substance P and CGRP[34–37]; increases release of histamine[38]

CGRP = calcitonin gene related peptide; IL = interleukin; NGF = nerve growth factor; PAN = primary afferent nociceptors; PGE_2 = prostaglandin E_2; TNF = tumor necrosis factor.

can sensitize or stimulate primary afferent neurons (**Figure 3**).

Bradykinin-induced hyperalgesia occurs in normal tissue, whereas norepinephrine-mediated hyperalgesia only occurs in areas of tissue injury.[19] The mechanism of bradykinin action is further complicated by the fact that in the acute pain situation, activation occurs via B_2 receptors[20] on PAN fibers and sympathetic neurons, whereas in prolonged inflammation and injury, B_1 receptors are upregulated and activated.[17,21] Depending on the situation (acute or chronic), antagonists of either B_1 or B_2 receptors are effective analgesic and anti-inflammatory agents.

Protons. Inflammation or tissue injury causes a decrease in the pH of the extracellular space secondary to local hypoxia, resulting in activation, excitation, and sensitization of PANs.[22] Protons, which lower pH, selectively activate nociceptors and sensitize them to noxious stimuli.

Serotonin. Following tissue damage, mast cells degranulate and release platelet-activating factor, which stimulates the release of 5-HT. PAN activation occurs via different mechanisms, depending on which receptor is affected. Direct activation occurs by stimulation of the 5-HT_3 receptor.[23] 5-HT may potentiate the pain induced by other mediators that occurs through action of a second messenger (G-protein) at the 5-HT_2 receptor.[24] Moreover, 5-HT can produce hyperalgesia by direct action on the PAN at the 5-HT_{1a} receptor.[25]

Histamine. The role of histamine in pain sensation is not clear but appears to mediate the effect of other mediators. When stimulated by substance P, mast cells degranulate and release histamine, which evokes sensations of pain and itch.[26] Interleukin-1 also causes mast cells to release histamine and can potentiate the stimulatory effects of histamine to release prostaglandins and other eicosanoids from endothelial cells.[27]

Prostaglandins. The major action of prostaglandin is sensitization of PANs to noxious stimuli (e.g., chemical, heat, mechanical),[28,29] probably via activation of cyclic adenosine monophosphate (cAMP).[30] Prostaglandins are not known to activate cutaneous afferents directly[28]. However, they may activate nociceptors directly during inflammatory conditions.[29] Leukotrienes also play a role in hyperalgesia[31] through activation of a second messenger, such as cAMP. Inhibition of both or either the cyclooxygenase or lipoxygenase pathways by nonsteroidal anti-inflammatory drugs (NSAIDs) can result in analgesia by blocking formation of prostaglandins or possibly leukotrienes.

Cytokines. Cytokines, such as interleukins, tumor necrosis factor, and nerve growth factor, are small, secreted, or membrane-bound proteins that mediate cell-to-cell interactions through specific cell surface receptors (**Table IV**).

Adenosine. Adenosine is produced following inflammation and tissue damage from hypoxia and ischemia and can stimulate unmyelinated afferents.[39] Adenosine acts directly on PANs, and the effect is mediated by the adenosine A_2 receptor.[40]

Substance P. Located in the dorsal root ganglion neurons, substance P is transported to the periphery and released after PAN activation.[41,42] Substance P intensifies pain by mechanisms involving inflammation, including prostaglandin release, cytokine stimulation, lysosomal enzyme release, and lymphocyte activation (**Table V**).[43–45] Substance P and CGRP

TABLE V

Actions of Substance P

- Vasodilation
- Vascular permeability
- Production and release of lysosomal enzymes
- Release of PGE_2 from synoviocytes
- Release of IL-1 and IL-6 from neutrophils
- Attraction and activation of leukocytes
- T-cell accumulation

IL = interleukin; PGE_2 = prostaglandin E_2.
From references 43–45.

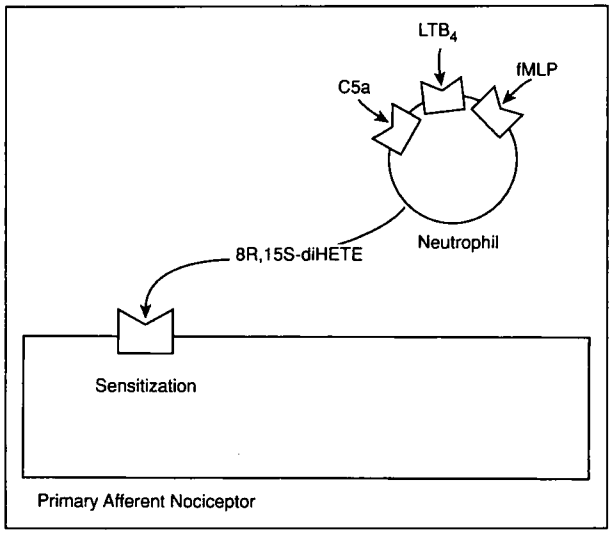

Figure 4. Sensitization of primary afferent nociceptor by the neutrophil. C5a = a fragment of the fifth component of the complement cascade; LTB_4 = leukotriene B_4; fMLP = formyl methionylleucylphenylalanine; 8*R*,15*S*-diHETE = the 8*R*,15*S* stereoisomer of dihydroxyeicosatetraenoic acid. (Reprinted with permission from Churchill Livingstone.[18])

also modulate pain perception both in the periphery and in the dorsal horn (see Modulation of Chronic Pain).

Nitric Oxide. The actual role of nitric oxide in nociception is unclear. Substance P and bradykinin cause release of nitric oxide from vascular endothelial cells. Dorsal root ganglion neurons can synthesize nitric oxide and inhibitors of nitric oxide synthase, which are antinociceptive.[46,47] Nitric oxide, formed from L-arginine utilizing nitric oxide synthase, functions in cell-to-cell communication in the periphery. It activates guanylate cyclase to produce guanosine monophosphate (GMP) and alter cell functions. Nitric oxide may be relevant for the actions of substance P and bradykinin in peripheral hyperalgesia. There is little evidence that nitric oxide directly activates sensory neurons; rather, it may indirectly alter their excitability. In addition, inhibitors of nitric oxide are thought to act centrally by blocking nitric oxide–induced activation of N-methyl-D-aspartate (NMDA) receptors, producing antinociception for neuropathic and chemically induced pain.

Neutrophils. The neutrophil is the primary effector cell in sites of inflammation. Neutrophils accumulate in large numbers, degranulate, and release mediators, which also cause pain. Leukotrienes B_4, C_{5a}, and formyl methionylleucylphenylalanine (fMLP), a bacterial cell wall fragment, attract and activate neutrophils to release 8*R*,15*S*-diHETE, which directly sensitizes PANs (**Figure 4**).[48–50]

Second Messenger

Several different mediators have been described that directly or indirectly stimulate the PAN to produce hyperalgesia. This diverse group of hyperalgesic agents produces similar effects on PANs often through activation of different PAN receptors. In an effort to determine whether all of these agents work through a common pathway, the search for a putative common second messenger was conducted. Several agents have been shown to elevate intracellular cAMP[51] and were found to be hyperalgesic[52] by blocking the phosphorylation of cAMP-dependent protein kinase.[30] Receptors on the PAN utilize a guanosine stimulatory (G_s) protein to couple and activate intracellular cAMP.[53] Agents that can activate the guanosine inhibitory (G_i) protein (e.g., opioids) can produce analgesia.[54] Stimulation of the G_s protein by such mediators as PGE and 5-HT causes hyperalgesia. These results are supportive of the role of cAMP as a putative second messenger in activating PAN fibers.

TRANSMISSION OF SIGNAL

The dorsal horn of the spinal cord is divided into layers based on cell morphology and stamina. The output neurons that transmit and project to the thalamus and brainstem are found in layers I and V and form the spinothalamic tract, which is conceptually two tracts. The direct spinothalamic tract (**Figure 5**) crosses to the contralateral anterolateral white matter of the spinal cord and ascends through the lateral edge of the medulla, lateral pons, and midbrain to the ventrobasal region of the thalamus. From here, thalamic neurons project to the somatosensory cortex. This pathway transmits aspects of acute pain (e.g., location, intensity, quality) and alerts the individual to biologically threatening events. The spinothalamic tract contains four different types of neurons with cell bodies in the dorsal horn (**Table VI**).

The spinoreticular system mediates autonomic and affective reaction to pain. These ascending fibers terminate in the brainstem reticular formation, pontine, medullary areas, and the medial thalamic

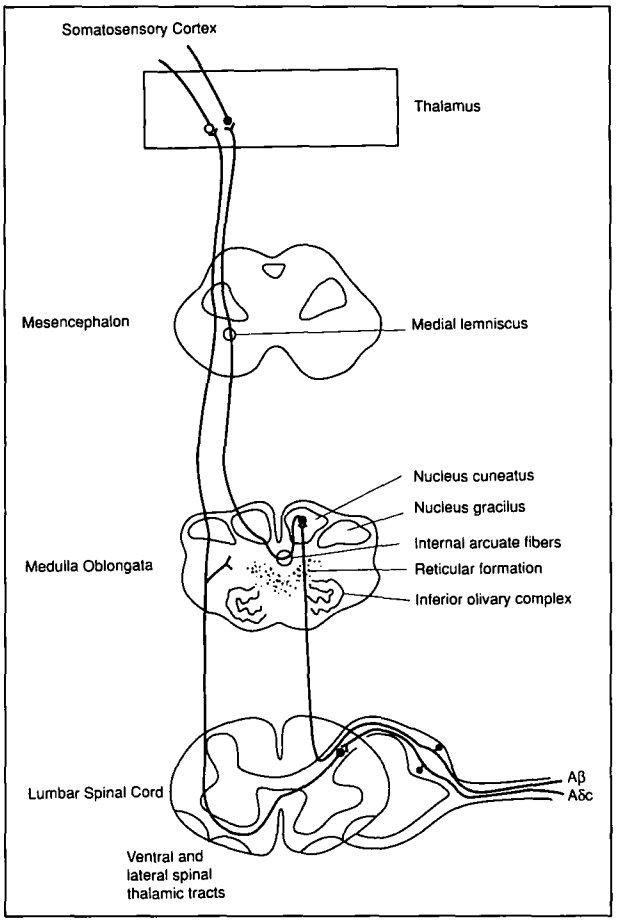

Figure 5. Ventral and lateral spinal thalamic tracts. (Reprinted with permission from Springer-Verlag.[7])

nuclei. This tract contributes to affective processing of nociception by connecting ascending information from the brain stem to limbic structures via the noradrenergic bundles.[4] Nociceptive impulses ascend to the locus coeruleus (a pontine nucleus near the fourth ventricle) and then ascend via the dorsal adrenergic bundle to the cortex. These pathways are responsible for the overall alertness, vigilance, and fear surrounding any noxious stimulus.[56] Norepinephrine is the major neuropeptide in the dorsal adrenergic bundle, where it accounts for >70% of this substance present in the nervous system.[57]

MODULATION OF CHRONIC PAIN

Pain produced by similar noxious stimuli is perceived differently by individuals under certain conditions. For example, athletes can endure pain that would incapacitate others. There are many stories of soldiers who endured extensive wounds without screaming in pain.[58] Moreover, there is the phenomenon of placebo relief of chronic pain. Implicit in these observations is the realization that the central nervous system can modulate incoming nociceptive signals.

Melzack and Wall[59] drew attention to this modulation when postulating their "gate theory" in 1967. They demonstrated that cells in lamina V of the dorsal horn were more responsive in the decorticate cat (spinal cord blocked)[60], indicating that structures in the brainstem can inhibit or modulate nociceptive input at the level of the spinal cord. In addition, the gate theory postulated that dorsal horn cells could modulate input from the periphery.[60]

Supraspinal descending signals also modulate nociceptive input. Stimulation of the periaqueductal grey (PAG) matter causes negative modulation of pain. This interaction was demonstrated experimentally by Reynolds[61] who showed that painless surgery could be performed on experimental animals if the PAG matter was activated.[62] Additional work by Mayer and Price[63] demonstrated that higher centers in the nervous system clearly modulated nociceptive input from tissue injury. Descending inhibitory messages can originate from several areas in the central nervous system, including (1) corticodiencephalic and diencephalic system; (2) mesencephalic, periaqueductal, and periventricular grey area; (3) medullary centers, including the nucleus raphe magnus; (4) spinal and medullary dorsal horns; and (5) descending pathways from the locus coeruleus via the noradrenergic pathway.[63-67]

The activation mechanism of these pathways has been a subject of great interest. Initially, the presence of endogenous morphine-like compounds was suspected because narcotic analgesics were known to act in the central nervous system (CNS) and binding sites were found in brain membranes.[68] Since then, other opiopeptide analgesics have been described.[69] The significance of these endogenous opiopeptides in pain modulation is demonstrated by the observation that the narcotic antagonists, such as naloxone and naltrexone, can reverse stimulation-produced analgesia in animals and humans, some forms of stress-induced analgesia in animals, and placebo analgesia in humans with postoperative pain.[70,71]

Opioid receptors are found on neuronal cell membranes and are the site of action for opioids, which themselves resemble the endogenous biologically active neuropeptides. Opioids bind throughout the brain and act at central sites, brain stem, and spinal cord to alter pain perception.

Opioids and Opioid Receptors

Three distinct endogenous opioid polypeptide families exist. They have different anatomic distributions and are cleaved from different precursors (**Table VII**).

Receptors serve two functions: (1) chemical recognition and (2) biologic action. Each function oc-

TABLE VI

Types of Neurons in the Spinothalamic Tract

Neuron Type	Comment
Nociceptive	Responsive to high-intensity noxious stimuli
Wide, dynamic range	Responsive to repetitive incoming stimuli of increasing intensity
Narrow, dynamic range	Responsive to thermal and tactile stimuli
Laminae IV, V	Responsive to proprioception

From *J. Invest Derm.*[55]

curs at a different site on the receptor complex. Opioids bind to receptors with different affinities, which correlates with their analgesic potency.[73] Most endogenous, synthetic, or naturally occurring opioids (endogenous prototype β-endorphin and exogenous prototype morphine) bind to μ-opioid receptors. Two subtypes of μ-opioid receptors exist[74]: the μ_1 receptor is responsible for analgesia and the μ_2 receptor mediates respiratory depression, bradycardia, and inhibition of gastrointestinal motility. All available synthetic opioid agonists activate both μ receptors. Activation of δ and κ receptors produces spinal analgesia. Enkephalin analogs are more potent than morphine when administered into the subarachnoid space.[75]

Activation of κ receptors causes sedation as well as analgesia without respiratory depression. The analgesic properties of opioid agonists are principally mediated by activation of the κ receptor. Other receptors such as the ϵ receptor are not well characterized and are thought to be activated by β-endorphin–mediated hormonal effects. The δ-opioid receptor is thought to mediate psychotomimetic effects, such as dysphoria and hallucinations, as well as tachycardia, tachypnea, and mydriasis.[76,77]

Beta-endorphins act as neurotransmitters, which contribute to descending control of nociception, and as hormones, which are released by the pituitary gland into the systemic circulation. Whether the circulating hormone plays any analgesic role is uncertain.[67] The mechanisms of endogenous opioids and other neurotransmitters (both serotonergic and noradrenergic) in modulating pain are not fully understood. For example, in the rostral ventral medulla there are two types of cells (off and on cells) with opposing effects on nociceptive transmission[68]: *off-cells* inhibit pain transmission and *on-cells* facilitate pain transmission. Morphine increases off-cell activity; naloxone decreases off-cell activity and increases on-cell activity.[78] This implies that morphine also acts at the level of the brainstem to modulate or block incoming signals of tissue injury at the spinal level.

Receptor action occurs through binding of an agonist, which activates biologic activity, or an antagonist, which prevents binding of the agonist to the receptor. Opioids may exert a full biologic effect or produce a submaximal response (i.e., partial agonists). Agonist–antagonist combinations can reduce the maximum response of the agonist. In addition, agonists and antagonists may have different actions depending on the receptor activated (Table VII).

All μ agonists cause a dose-dependent depression of the respiratory center to carbon dioxide tension (P_{CO_2}) and pontine and medullary centers involved in regulating respiratory rhythm.[79] Opioids alter mood, possibly via the limbic system, and may induce sleep at high doses, although arousal can be produced by noxious stimulation.[76,77] The effects of opioids on bowel motility appear to be locally and centrally mediated.[80] Injection of morphine into the cerebral ventricles inhibits bowel motility; the effect is reversed by intraventricular administration of naloxone. Opioids also affect cholinergic, serotonergic, and enkephalinergic receptors in the myenteric plexus of the intestine. The μ-agonists increase biliary pressure, and opioids produce chronotropic, inotropic, and peripheral vascular changes. Opioids can produce a dose-dependent bradycardia, which is caused by central stimulation of the vagal nucleus in the medulla.[81] All opioids produce some myocardial depression. However, it is not generally significant

TABLE VII

Endogenous Opioid Peptides

Precursor	Endogenous Opioid	Receptor	Location
Proenkephalin A	Enkephalin	δ	GI tract sympathetic, adrenal medulla, PAG, rostral ventral medulla, and rexed laminae I, II, V, X
Proopiomelanocortin	β-endorphin	μ_1 and μ_2	Released with ACTH from the pituitary, hypothalamus. Located in PAG, nucleus raphe magnus, medial thalamus, spinal cord, and locus coeruleus
Prodynorphin (Proenkephalin-B)	Dynorphin	—	Similar to that of enkephalins

ACTH = adrenocorticotropic hormone; GI = gastrointestinal; PAG = periaqueductal grey.
From *Information in the Brain.*[72]

even at high analgesic doses.[82] Morphine, meperidine, and codeine may cause arteriolar dilation and venodilation indirectly by stimulating histamine release. Morphine also has a similar direct action on vessels.[83,84]

Descending Modulating Pathways

Such factors as arousal, attention, and emotional stress can alter the response to pain by involving CNS mechanisms. A network linking the hypothalamus with the brain stem has been described, which is sensitive to opioids, influences dorsal horn neurons, and triggers their ascending nociceptive transmissions. Hagbarth and Kerr,[85] Carpenter et al,[86] and Wall[60] have described descending control of ascending sensory input. This description was strengthened by the experimental observation of stimulation-produced analgesia (SPA) in animals[61,87] and in humans with chronic pain,[88,89] during which stimulation of specific brain areas inhibits incoming noxious nociceptive afferents and results in analgesia. Inhibition of dorsal horn cells involved in afferent transmission of nociception to higher centers is accomplished by stimulation of analgesic areas in the brainstem.[90] This inhibition can be blocked by discrete lesions in the spinal cord dorsolateral funiculus.[66-68,91,92]

Periaqueductal gray matter. Inputs from the frontal cortex,[93] amygdala,[94] and hypothalamus[95] activate cells in the midbrain (i.e., PAG). Neurons descending from the midbrain synapse in the medulla at the midline nuclei (nucleus raphe magnus) before descending to the dorsal horn. Pathways ascending from the PAG to the medial thalamus and orbital cortex also may control nociception in an ascending fashion.[96] Inputs to the PAG also are received from the nucleus cuniformis, the locus coeruleus (origin of the descending adrenergic bundle), and other brainstem catecholaminergic nuclei.[97] The PAG contains large quantities of all the endogenous opioid peptides (i.e., enkephalin, β-endorphin, dynorphin). The rostral ventromedial medulla (RVM) includes the midline nucleus raphe magnus, the adjacent reticular formation, and the nucleus reticularis gigantocellularis. Input is received from the PAG and nucleus cuneiformis. Stimulation of opioid receptor in the PAG may influence nociception by altering the descending modulating pathway.

The RVM contains opioid receptors as well as receives neurons from the raphe nucleus that utilize 5-HT as a neurotransmitter.[98] Opioid inhibition of pain at the level of the brainstem and PAG can be reversed by coadministering 5-HT and norepinephrine antagonists at the level of the spinal cord.[99] 5-HT and norepinephrine neurons are the major descending modulators to the dorsal horn and function to inhibit and modulate nociception. Norepinephrine works through the α_2-adrenergic receptor[100] and 5-HT via the 5-HT_2 receptor at the spinal cord level.[101] The mechanism of action for 5-HT is complex and not fully understood.

Noradrenergic cells from their descending adrenergic bundle (area of the rostral medulla and dorsolateral pons) send input to the RVM.[102] Axons from the RVM descend to the spinal cord via the dorsal lateral funiculus (DLF), which terminates primarily in the superficial region of the dorsal horn as well as in lamina V. Input to these regions is mainly PAN C fibers carrying nociceptive impulses.[93] RVM stimulation inhibits dorsal horn ascending nociceptive transmission; this effect can be blocked by lesions in the DLF. Lesions or local anesthetic injections into the RVM abolish the analgesia produced by stimulation of the PAG[98]; opioids injected into the PAG produce analgesia and activate pain-inhibiting neurons in RVM.[103] This finding provided evidence that descending modulation from PAG is relayed through the RVM.

The dorsolateral pontomesencephalic tegmentum (DLPT) contains the nucleus cunieformis and lies adjacent to the PAG. It receives input from lamina I and projects to the RVM. The noradrenergic bundle passes through and sends a connection to the RVM as it descends to the dorsal horn.[104,105] Stimulation of this area inhibits ascending dorsal horn afferents[106] and relieves chronic pain.[107] Descending modulating networks start in the frontal cortex and hypothalamus and descend to the PAG and RVM before descending to the dorsal horn where they can inhibit ascending nociceptive impulses. Nerves in the DLPT, in addition to projecting directly to the dorsal horn, can input to the RVM.[106,107]

Modulation at the Dorsal Horn

Brain stem nuclei that send neurons to the dorsal horn have terminals densely located in laminae I, II, V, VI, and X. PANs in small C fibers also terminate and synapse primarily in laminae I and II. Projections to deeper laminae come from larger, myelinated PANs. Lamina II also has neuronal dendrites in the deeper layers and, as such, may control nociception in these deeper layers. Lamina I is the largest source of spinothalamic tract neurons. After peripheral injury or inflammation, the spinal cord is bombarded with impulses from Aδ and C fibers. Substance P and glutamate are stimulated and released from their terminals, causing activation on the postsynaptic neuron terminal of slow NMDA or fast α-amino-3-hydroxy-5-methyl-4-isoxalone (AMPA)[108,109] receptors on dorsal horn neurons. This action causes the phenomenon of windup, a two-dimensional amplification of transmitted signals. AMPA-receptor neurons are responsible for signal formation related to the

location, intensity, and duration of pain both temporally and spatially.[110]

Neuropeptides and proteins in the nervous system are coded by specific genes in the nucleus of the neuron. Genes transcribe messenger RNA (mRNA), which reaches the cytoplasm and translates to protein precursors of active neuropeptides. C-*fos* and C-*jun* are proto-oncogenes (cellular homologues of viral oncogenes).[111] Fos and Jun proteins are transcriptional factors that regulate the expression of a host of other genes. Fos protein may serve as a "third messenger" by signaling short-term neurologic events into long-term potentiation (e.g., acute to chronic pain). In the experimental animal, the number of fos protein neurons correlates with the pain behavior elicited by a noxious stimulus.[112] Stimulation of analgesic areas in the medullary raphe nucleus significantly reduces noxious-stimulus–evoked fos-protein expression.[113] Central sensitization, which represents modulation of pain perception (either inhibitory or excitatory), has three major components: (1) decrease in pain threshold; (2) expansion of receptive fields; and (3) windup. The cell bodies in lamina I receive C-type PANs and project pain impulses to the thalamus via the lateral spinothalamic tract (sharp pain). Cells of laminae V, VII, and VIII contain wide dynamic range (WDR) neurons that project to the reticular formation via the spinoreticular tract (slow, dull, aching pain) and the medial spinothalamic tract. By monitoring fos-protein expression in dorsal horn neurons, the mechanism of central sensitization, which occurs through activation of the NMDA receptor (located on dorsal horn neurons), can be studied.

NMDA-receptor antagonists[114] can block windup and c-*fos* expression,[115] which possibly are two areas of nociception modulation at the spinal cord level. NMDA-receptor antagonists may have potential use as analgesics. They have no effect in the absence of tissue or nerve injury in contrast to opioids, which reduce responsiveness to noxious stimuli with or without persistent tissue or nerve injury. Furthermore, combinations of opioids and NMDA-receptor antagonists may be useful.[116,117] In conditions of injury, the combination may act in an additive fashion to block perception of pain. NSAIDs also have been shown to affect the spinal cord directly, possibly blocking activation of the NMDA receptor stimulated by excitatory amino acids (EAA; e.g., L-glutamine) and substance P. This action is distinct from their anti-inflammatory activity in the periphery.[118]

Intense stimulation from nerve and tissue damage activates fibers that project to interneurons in the spinal cord. These interneurons are responsible for increasing transmission to higher centers, as well as to lateral and ventral horn cells in the spinal cord. The latter areas activate the sympathetic and somatic motor systems, increasing vasoconstriction and muscle spasm and supporting "the vicious cycle theory."[119,120]

Chronic compression of dorsal roots or peripheral nerves (as seen in carpal tunnel syndrome and herniated intervertebral discs) causes pain by a marked increase in their mechanosensitivity. Findings from animal models led to the conclusion that chronic compression of nerve roots can increase repetitive firing of that root, which is caused by low threshold mechanical pressure.[121,122] Phantom-limb pain, causalgia, and selected peripheral nerve injuries are thought to be caused by loss of inhibitory controls. The brain stem reticular formation is thought to exert tonic inhibitory influences on transmission at all synaptic levels of the somatosensory system. This tonic ability depends on normal sensory input. Loss of normal sensory input after amputation, peripheral nerve lesions, emotional stress, and use of certain drugs impairs the efficacy of this mechanism and leads to increased pain. Chronic stimulation by adding normal sensory input back to the injured area through electrical stimulation (i.e., TENS), acupuncture, or nerve blocks inhibits activity of self-sustaining interneuron pools and may reverse this phenomenon and decrease pain.[123,124]

Contribution of physiologic factors, psychologic behavior (e.g., personality, mood, attitude), and sociologic issues (e.g., family interactions, work, economic status, culture) contribute to the perception of chronic pain. None of these factors influences pain perception in a straightforward fashion. For example, in comparing cancer patients with and without chronic pain, a higher level of hypochondria, neuroticism, and other signs of emotional disturbances were found in all groups with pain[125] and the level of higher emotionality felt with treatment of pain.[126] Similar results were observed in patients with musculoskeletal and neurologic disorders.[127] Characteristics reported in patients with chronic pain include sleep disturbances, appetite changes, increased irritability, decreased libido and sexual activities, psychomotor retardation, and reduced pain tolerance.[126–128] These characteristics may involve depletion of 5-HT and endorphins. Terenius[129] has detected lower levels of endorphins and serotonin in patients with neuropathic and other types of "organic pain," as opposed to patients with psychogenic pain. Data suggest that the longer the duration of chronic pain, the greater the psychologic, emotional, and behavioral changes. Studies also have shown that as self-esteem and personal control decrease, symptoms increase.[130]

SYMPATHETICALLY MAINTAINED PAIN

The involvement of the sympathetic nervous system in recognition of pain started with observations in a syndrome called reflex sympathetic dystrophy (RSD) or causalgia. Some patients with peripheral nerve injuries (e.g., causalgia), fractures, soft-tissue trauma, myocardial infarction, or stroke developed severe burning pain in the region of injury accompanied by swelling of the extremity and osteoporosis. Blocking the sympathetic nervous system often relieved the pain.[131] Sympathetic nervous system reflexes also contribute to pain. Nociception increases sympathetic tone, which produces peripheral vasoconstriction presumably by repeated incoming afferent C fiber nociceptive impulses causing hypersensitivity in the dorsal horn of the WDR neurons. The WDR neurons connect with the lateral horn cells of the sympathetic system sending efferent motor impulses to cause vasoconstriction and peripheral ischemia, another stimulus to hyperalgesia.[132] It has been postulated that following trauma, norepinephrine is released from peripheral sympathetic terminals to activate nociceptors.[133,134] Injury causes a change in the sensory nerves left intact so that nerves previously unresponsive to sympathetic stimulation can be excited by sympathetic stimulation[135] or intra-arterial injections of norepinephrine. Sympathetic-induced excitation is thought to be mediated by an α_2 receptor on the PAN because it can be blocked by yohimbine, a selective α_2-adrenergic inhibitor. Binding studies show that there is an upregulation of adrenergic receptors in some sensory neurons after injury.[136] It is still unclear whether sympathetic–adrenergic interactions are mediated via the α_1 or α_2 adrenoceptor. However, it is clear that therapeutic measures aimed at blocking either receptor can relieve pain under the correct circumstances. An anesthetic block of the sympathetic ganglion is effective because it eliminates the efferent drive.[133] Topical application of clonidine activates the α_2 receptor, depleting norepinephrine from the sympathetic terminals.[134] Phentolamine,[137] phenoxybenzamine,[138] and prazosin[139] are α antagonists that block nociceptor activation. Intravenous guanethidine eliminates norepinephrine stores in the sympathetic terminals.

In summary, noxious stimulation from visceral organs releases substance P and can stimulate afferents or neurons and depolarize sympathetic ganglion cells.[140] In somatic afferent fibers, only after peripheral nerve damage or inflammation can it be demonstrated that sympathetic nerves interact with PANs to cause transmission of pain.[136] During inflammation, sympathetic fibers are stimulated and release prostaglandins, which stimulate afferent fibers.[141]

CONCLUSION

Chronic pain is one of the most important health problems in industrialized nations. Regardless of its cause, chronic pain results in severe physical, behavioral, psychologic, and psychosocial problems for the patient and family, as well as a large financial burden to society. Effective therapy should not only be directed at reducing or removing the cause of pain but also at rehabilitating the patient physically, socially, and psychologically. A basic understanding of the mechanism of chronic pain is essential for the physician to understand the pharmacologic management of pain effectively. Classification into peripheral, central, and physiologic–psychophysiologic mechanisms is helpful. Peripheral mechanisms include stimulation of nociceptors through injury or inflammation with liberation of serotonin, histamine, bradykinin, and prostaglandins. Receptor agonists and antagonists of these substances can alter the perception of pain. In addition, liberation of neurotransmitters, such as substance P and CGRP, also may act to mediate pain.

Sympathetic pain occurs after traumatic injury to a peripheral nerve, and therapy can be directed at sympathetic nerve blocks or chemical block of adrenergic receptors. Central mechanisms include neurotransmitters at the dorsal horn, spinothalamic tract, medulla, midbrain, thalamus, and somatosensory cortex. In addition, descending modulating pathways exist with other neurotransmitters, such as 5-HT and norepinephrine, as well as opioid receptors. Specific agonists and antagonists of these transmitters and receptors function to modulate or alter the perception of pain. Psychophysiologic mechanisms include the contribution of stress, which can produce muscle spasm, local vasoconstriction, visceral dysfunction, and liberation of endogenous pain-producing substances. Consequently, more stress may develop, adding to the vicious cycle. Agents that either relieve stress, decrease muscle spasm, or inhibit pain-producing substances (e.g., bradykinin, prostaglandins) may be efficacious as primary or adjunctive therapy.

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REFERENCES

1. Bonica JJ. Definition and taxonomy of pain. In: Bonica JJ, ed. The Management of Pain, 2nd ed. Philadelphia, PA: Lea & Febiger, 1990:18–27.
2. Bonica JJ. General consideration of chronic pain. In: Bonica JJ, ed. The Management of Pain. 2nd ed. Philadelphia, PA: Lea & Febiger, 1990:189–196.
3. Stacey MJ. Free nerve endings in skeletal muscle of the cat. *J Anat.* 1969;105:231–254.

4. Chapman CR. Psychological aspects of postoperative pain control. *Acta Anaesthesiol Belg.* 1992;43:41–52.
5. Fitzgerald M, Lynn B. The sensitization of high threshold mechanoreceptors with myelinated axons by repeated heating. *J Physiol.* 1977;265:549–563.
6. Bessou P, Perl E. Response of cutaneous sensory units with unmyelinated fibers to noxious stimuli. *J Neurophysiol.* 1969;32:1025–1043.
7. Fessler RG. Physiology, anatomy, and pharmacology of pain perception. In: Camic PM, Brown FD, eds. Assessing Chronic Pain. A Multi Disciplinary Clinic Handbook. New York: Springer-Verlag, 1989:5–19.
8. Fields HL, Martin JB. Pain: pathophysiology and management. In: Isselbacher K, Brunwald E, Wilson JD, Martin JB, Fauci AS, Kasper DL, eds. Harrisons Principles of Internal Medicine, 13th ed. New York: McGraw Hill, 1994:49–55.
9. Meyer RA, Campbell JN, Raja NJ. Peripheral neurologic mechanisms of nociception. In: Wall PD, Melzack R, eds. Textbook of Pain. London: Churchill Livingstone, 1984:13–44.
10. Perl ER. Afferent basis of nociception and pain, evidence from the characteristics of sensory receptors and their projection to the spinal dorsal horn. In: Bonica JJ, ed. Pain. New York: Raven Press, 1980:19–46.
11. Beck PW, Handwerker HO, Zimmermann M. Nervous outflow from the cat's footpad during noxious radiant heat stimulation. *Brain Res.* 1974;67:373–386.
12. Dubner R. Neurophysiology of pain. *Dent Clin North Am.* 1978;22:11–30.
13. Dubner R, Ruda MA. Activity-dependent neuronal plasticity following tissue injury and inflammation. *Trends Neurosci.* 1992;15:96–103.
14. Levine JD, Fields HL, Basbaun A. Peptides and the primary afferent nociceptor. *J Neurosci.* 1993;13:2273–2286.
15. Konttinen YT, Kemppinen P, Sergerberg M, et al. Peripheral and spinal neural mechanisms in arthritis, with particular reference to treatment of inflammation and pain. *Arthritis Rheum.* 1994;37:965–982.
16. Whalley ET, Clegg S, Steward JM, Vavrek RJ. Antagonism of the analgesic action of bradykinin on the human blister base. *Adv Exp Med Biol.* 1989;274A:261–268.
17. Khan AA, Raja SN, Campbell JN, Martke TV, Meyer RA. Bradykinin sensitizes nociceptors to heat stimuli. (Abstr.) *Soc Neurosci Abstr.* 1986;12:219.
18. Levine J, Taiwo Y. Inflammatory pain. In: Wall PD, Melzack R, eds. Textbook of Pain, 3rd ed. New York: Churchill Livingstone, 1994:45–56.
19. Taiwo YO, Heller PH, Levine JD. Characterization of distinct phospholipases mediating bradykinin and noradrenaline hyperalgesia. *Neuroscience.* 1990;39:523–531.
20. Farmer SG, Burch RM. Biochemical and molecular pharmacology of kinin receptors. *Ann Rev Pharmacol.* 1992;32:511–536.
21. Teranka LR, Manning DC, Dehaas JR, et al. Bradykinin as a pain mediator: receptors are localized to sensory neurons and antagonists have analgesic actions. *Proc Natl Acad Sci USA.* 1988;85:3245–3249.
22. Steen KH, Reech PW, Anton F, Handwerker HO. Protons selectively induce long lasting excitation and sensitization to mechanical stimulation of nociceptors to rat skin, in vitro. *J Neurosci.* 1992;12:86–95.
23. Richardson BP, Engle G, Donatsch P, Stadler PA. Identification of serotonin M-receptor subtypes and their specific blockade by a new class of drugs. *Nature.* 1985;316:126–131.
24. Todorovic S, Anderson EG. 5-HT_2 and 5-HT_3 receptors mediate two distinct depolarizing responses in rat dorsal root ganglion neurons. *Brain Res.* 1990;511:71–79.
25. Taiwo YO, Levine JD. Serotonin is a directly acting hyperalgesic agent in the rat. *Neuroscience.* 1992;48:485–490.
26. Simone DA, Alrejo M, LaMotte RH. Psychophysical studies of the itch sensation and itchy skin ("allokinesis") produced by intracutaneous injection of histamine. *Somatosens Mot Res.* 1991;8:271–279.
27. Falus A, Meretey K. Histamine and early messenger in inflammatory and immune reactions. *Immunol Today.* 1992;13:154–156.
28. Chahl LA, Iggo A. The effects of bradykinin and prostaglandin E1 on rat cutaneous nerve activity. *Br J Pharmacol.* 1977;59:343–347.
29. Birrell GJ, McQueen DS, Iggo A, et al. PGI_2-induced activation and sensitization of articular mechanoreceptors. *Neurosci Lett.* 1991;124:5–8.
30. Taiwo YO, Levine JD. Further confirmation of the role of adenyl cyclase and of cAMP-dependent protein kinase in primary afferent hyperalgesia. *Neuroscience.* 1991;44:131–135.
31. Dayer JM, deRochenouteix B, Burrus B, et al. Human recombinant interleukin-1 stimulates collagenase and prostaglandin E-2 production by human synovial cells. *J Clin Invest.* 1986;77:645–648.
32. Cunha FQ, Lorenzetti BB, Poole S, et al. Interleukin-8 as a mediator of sympathetic pain. *Br J Pharmacol.* 1991;104:765–767.
33. Cunha FQ, Poole S, Lorenzetti BB, Ferreira SH. The pivotal role of tumor necrosis factor alpha in the development of inflammatory hyperalgesia. *Br J Pharmacol.* 1992;107:660–664.
34. Lindsay RM, Harmar AJ. Nerve growth factor regulates expression of neuropeptide genes in adult sensory neurons. *Nature.* 1989;337:362–364.
35. Otten U. Nerve growth factor: a signalling protein between the nervous and the immune systems. In: Basbaum AI, Besson JM, eds. Towards a New Pharmacology of Pain. New York: John Wiley & Sons, 1991:353–363.
36. Lewin GR, Ritter AM, Menddell LM. Nerve growth factor-induced hyperalgesia in the neonatal and adult rat. *J Neurosci.* 1993;13:2136–2148.
37. Aloe L, Tuveri MA, Carcassi U, et al. Nerve growth factor in the synovial fluid of patients with chronic arthritis. *Arthritis Rheum.* 1992;35:351–355.
38. Bischoff SC, Dahinded CA. Effect of nerve growth factor on the release of inflammatory mediators by mature human basophils. *Blood.* 1992;79:2662–2669.
39. Bleehen T, Keele CA. Observations on the algogenic actions of adenosine compounds on the human blister base preparation. *Pain.* 1977;3:367–377.
40. Taiwo YO, Levine JD. Direct cutaneous hyperalgesia induced by adenosine. *Neuroscience.* 1990;38:757–762.
41. Harmar A, Keen P. Synthesis and central and peripheral axonal transport of Substance P in a dorsal root ganglion-nerve preparation in vitro. *Brain Res.* 1982;231:379–385.
42. White DH, Helme RD. Release of substance P from peripheral nerve terminals following electrical stimulation of the sciatic nerve. *Brain Res.* 1985;336:27–31.
43. Saria A. Substance P in sensory nerve fibers contributes to the development of oedema in the rat hindpaw after thermal injury. *Br J Pharmacol.* 1984;323:341–342.
44. Lotz M, Carson DA, Vaughan JH. Substance P activation of rheumatoid synoviocytes: neural pathway in the pathogenesis of arthritis. *Science.* 1987;235:885–893.
45. Johnson A, Endros GG. Release of histamine from mast cells by vasoactive peptides. *Proc Soc Exp Biol Med.* 1973;142:1252–1256.
46. Moncadq S, Palmer RM, Higgs EA. Nitric oxide physiology, pathophysiology and pharmacology. *Pharmacol Rev.* 1991;43:109–142.
47. Haley JE, Dickenson AH, Schachter M. Electrophysiological evidence for a role of nitric oxide in prolonged chemical nociception in the rat. *Neuropharmacology.* 1992;31:251–258.
48. Levine JD, Lam D, Taiwo YO, Donatoni P, Goetzl EJ. Hyperalgesic properties of 15-lipoxygenase products of arachidonic acid. *Proc Nat Acad Sci USA.* 1986;83:5331–5334.
49. Levine JD, Lau W, Kwiat G, Goetzl EJ. Leukotriene B_4 produces hyperalgesia that is dependent on polymorphonuclear leukocytes. *Science.* 1984;225:743–745.
50. Levine JD, Gooding J, Donatoni P. The role of the polymorphonuclear leukocyte in hyperalgesia. *J Neurosci.* 1985;5:3025–3029.
51. Collier HOJ, Roy AO. Morphine like drugs inhibit the stimulation by E prostaglandins of cyclic AMP formation by rat brain homogenate. *Nature.* 1974;248:24–25.
52. Taiwo YO, Levine JD. Prostaglandin effects after elimination of indirect hyperalgesic mechanisms in the skin of the rat. *Brain Res.* 1989;492:397–399.
53. Taiwo YO, Levine JD. Contribution of guanine nucleotide regulatory proteins to prostaglandin hyperalgesia in the rat. *Brain Res.* 1989;492:397–399.
54. Taiwo YO, Levine JD. Kappa and delta opioids block sympathetically dependent hyperalgesia. *J Neurosci.* 1991;11:928–932.
55. Price DD, Dubner R. Mechanism of first and second pain in the peripheral and central nervous system. *J Invest Derm.* 1977;69:167–171.
56. Svensson TH. Peripheral, autonomic regulation of locus ceruleus noradrenergic neurons in brain: putative implications for psychiatry and psychopharmacology. *Psychopharmacology.* 1987;92:1–7.

57. Butler PD, Weiss JM, Stout JC, Nemeroff CB. Corticotropin-releasing factor produces fear-enhancing and behavioral activating effects following infusion into the locus ceruleus. *J Neurosci.* 1990;10:176–183.
58. Melzack R, Wall PD, Ty TC. Acute pain in the emergency clinic. *Pain.* 1982;14:33–43.
59. Melzack R, Wall PD. Pain mechanisms: a new theory. *Science.* 1965;150:971–979.
60. Wall PD. The laminar organization of dorsal horn and effects of descending impulses. *J Physiol.* 1967;188:403–423.
61. Reynolds DV. Surgery in the rat during electrical analgesia induced by focal brain stimulation. *Science.* 1969;164:444–445.
62. Mayer DJ, Wolfle TL, Akil H, et al. Analgesia from electrical stimulation in the brainstem of the rat. *Science.* 1971;174:1351–1354.
63. Mayer DJ, Price DD. Central nervous system mechanisms of analgesia. *Pain.* 1976;2:379–404.
64. Bonica JJ. Biochemistry and modulation of nociception and pain. In: Bonica JJ, ed. The Management of Pain, 2nd ed. Philadelphia, PA: Lea & Febiger, 1990:95–121.
65. Sagen J, Proudfit HK. Release of endogenous monoamines into spinal cord superfusates following the microinjection of phentolamine into the nucleus raphe magnus. *Brain Res.* 1987;406:246–254.
66. Basbaum A, Fields HL. Endogenous pain control systems: brain-stem spinal pathways and endorphin circuitry. *Annu Rev Neurosci.* 1984;7:309–338.
67. Fields HL, Heinricher MM, Mason P. Neurotransmitters in nociceptive modulatory circuits. *Annu Rev Neurosci.* 1991;14:219–245.
68. Hughes J, Smith TW, Kosterlitz HW, et al. Identification of two related pentapeptides from the brain with potent opiate agonist activity. *Nature.* 1975;258:577–579.
69. Miller RJ. Peptides as neurotransmitters: focus on the enkephalins and endorphins. *Pharm Ther.* 1981;12:73–108.
70. Watkins LR, Mayer DJ. Organization of endogenous opiate and nonopiate pain control systems. *Science.* 1982;216:1185–1192.
71. Fields HL. Sources of variability in the sensation of pain. *Pain.* 1988;33:195–200.
72. Black IB. Molecules and modularity of brain function. In: Information in the Brain: A Molecular Perspective. Cambridge, MA: MIT Press, 1991:101–116.
73. Martin WR, Eades CG, Thompson JA, et al. The effects of morphine and nalorphine-like drugs in the nondependent and morphine-dependent cyclazocine-dependent spinal dog. *J Pharm Exp Ther.* 1976;197:517–532.
74. Wood PL, Richard JW, Thakur M. Mu opiate iso receptors: differentiation with Kappa agonists. *Life Sci.* 1982;31:2313–2317.
75. Yaksh TL, Huang SP, Rudy TA. The direct and specific opiate-like effect of met 5-enkephalin and analogs on the spinal cord. *Neuroscience.* 1977;2:593–596.
76. Freye E. The various effects caused by opioids. In: Freye E, ed. Opioid Agonists, Antagonists and Mixed Narcotic Analgesics: Theoretical Background and Considerations for Practical Use. Berlin, Germany: Springer-Verlag, 1987:27–53.
77. Kitahata LM, Collins JG, Robinson CJ. Narcotic effects on the nervous system. In: Kitahata LM, Collins JG, eds. Narcotic Analgesics in Anesthesiology. Baltimore, MD: Williams & Wilkins, 1982:57–65.
78. Bederson JB, Fields HL, Barbaro NM. Hyperalgesia during naloxone-precipitated withdrawal from morphine is associated with increased on-cell activity in the rostral ventromedial medulla. *Somatosens Mot Res.* 1990;7:185–203.
79. Mueller RA, Lundberg DB, Breese GR, et al. The neuropharmacy of respiratory control. *Pharmacol Rev.* 1982;34:255–285.
80. Burks TF. Gastrointestinal pharmacology. *Annu Rev Pharmacol Toxicol.* 1976;16:15–31.
81. Laubie M, Schmitt H, Vincent M. Vagal bradycardia produced by microinjections of morphine-like drugs into the nucleus ambiguous in anesthetized dogs. *Eur J Pharmacol.* 1979;59:287–291.
82. Barash P, Kopriva C, Giles R. Global ventricular function and intubation: radionuclear profiles. (Abstr.) *Anesthesiology.* 1980;53:A109.
83. Lowenstein E, Whitine RB, Bittar DA, et al. Local and neurally mediated effects of morphine on skeletal muscle vascular resistance. *J Pharm Exp Ther.* 1972;180:359–367.
84. Flacke JW, Flack WE, Boor BC, et al. Histamine release by four narcotics: a double blind study in humans. *Anesth Analg.* 1987;66:723–730.
85. Hagbarth KE, Kerr DIB. Central influences on spinal afferent conduction. *J Neurophysiol.* 1954;17:295–307.
86. Carpenter D, Engberg I, Lundberg A. Differential supraspinal control of inhibitory and excitatory actions from the FRA to ascending spinal pathways. *Acta Physiol Scand.* 1965;63:103–110.
87. Mayer DJ, Liebeskind JC. Pain reduction by focal electrical stimulation of the brain: an anatomical and behavioral analysis. *Brain Res.* 1974;68:73–93.
88. Boivie J, Meyerson AB. A correlative anatomical and clinical study of pain suppression by deep brain stimulation. *Pain.* 1982;13:113–126.
89. Baskin DS, Mehler WR, Hosobuchi Y, et al. Autopsy analysis of the safety, efficacy, and cartography of electrical stimulation of the central gray in humans. *Brain Res.* 1986;371:231–236.
90. Guilbaud G, Besson JM, Oliveras JL, et al. Suppression by LSD of the inhibitory effect exerted by dorsal raphe stimulation on certain spinal cord interneurons in the cat. *Brain Res.* 1973;61:417–422.
91. Basbaum AI, Clanton CH, Fields HL. Opiate and stimulus-produced analgesia: functional anatomy of a medullospinal pathway. *Proc Nat Acad Sci USA.* 1976;73:4685–4688.
92. Basbaum AI, Fields HL. Endogenous pain control mechanisms review and hypothesis. *Ann Neurol.* 1978;4:451–462.
93. Hardy SGP, Leichnetz GR. Cortical projects to the periaqueductal grey in the monkey: a retrograde and orthograde horseradish peroxidase study. *Neurosci Lett.* 1981;22:97–101.
94. Gray TS, Magnuson DJ. Peptide immunoreactive neurons in the amygdala and the bed nucleus of the stria terminalis project to the midbrain central gray in the rat. *Peptides.* 1992;13:451–460.
95. Reichling DB, Basbaum AI. Contribution of brainstem GABAergic circuitry to descending antinociceptive controls. I. GABA-immunoreactive projection neurons in the periaqueductal gray and nucleus raphe magnus. *J Compar Neurol.* 1990;302:370–377.
96. Coffield JA, Bowen KK, Miletic V. Retrograde tracing of projections between the nucleus submedius, the ventrolateral orbital cortex, and the midbrain in the rat. *J Comp Neurol.* 1992;321:488–499.
97. Herbert H, Saper CR. Organization of medullary adrenergic and nonadrenergic projections to the periaqueductal gray matter in the rat. *J Comp Neurol.* 1992;314:34–52.
98. Bitz AJ. The sites of origin of brain stem neurotensin and serotonin projections to the rodent nucleus raphe magnus. *J Neurosci.* 1982;2:819–824.
99. Yaksh TL. Direct evidence that spinal serotonin and noradrenaline terminals mediate the spinal antinociceptive effects of morphine in the periaqueductal gray. *Brain Res.* 1979;160:180–185.
100. Yeomans DC, Clark FM, Paice JA, et al. Antinociception induced by electrical stimulation of spinally projecting noradrenergic neurons in the A7 catecholamine cell group of the rat. *Pain.* 1992;48:449–461.
101. Crisp T, Stafinsky JL, Spanos LJ, et al. Analgesic effects of serotonin and receptor-selective serotonin agonists in the rat spinal cord. *Gen Pharmacol.* 1991;22:247–251.
102. Clark FM, Yeomans DC, Proudfit HK. The noradrenergic innervation of the spinal cord: differences between two substrains of Sprague-Dawley rats determined using retrograde tracers combined with immunochemistry. *Neurosci Lett.* 1991;125:155–158.
103. Cheng Z-F, Fields HL, Heinricher MM. Morphine microinjected into the periaqueductal gray has differential effects on 3 classes of medullary neurons. *Brain Res.* 1986;375:57–65.
104. Clark FM, Proudfit HK. Projections of neurons in the ventromedial medulla to pontine catecholamine cell groups involved in the modulation of nociception. *Brain Res.* 1991;540:105–115.
105. Clark FM, Proudfit HK. The projection of noradrenergic neurons in the A7 catecholamine cell group to the spinal cord in the rat demonstrated by anterograde tracing combined with immunochemistry. *Brain Res.* 1991;547:279–288.
106. Carstens E, Klumpp D, Zimmerman M. Differential inhibitory effects of medial and lateral midbrain stimulation on spinal neuronal discharges to noxious skin heating in the cat. *J Neurophysiol.* 1980;43:332–342.

107. Young RF, Tronnier V, Rinaldi PC. Chronic stimulation of the Kölliker-Fuse nucleus region for relief of intractable pain in humans. *J Neurosurg.* 1992;76:979–985.
108. Gerber G, Randic M. Excitatory amino acids-mediated components of synaptically evoked input from dorsal roots to deep dorsal horn neurons in the rat spinal cord slice. *Neurosci Lett.* 1989;106:211–219.
109. Gerber G, Randic M. Participation of excitatory amino acid receptors in the slow synaptic transmission in the rat spinal dorsal horn in vitro. *Neurosci Lett.* 1989;106:220–228.
110. Thompson SWN, King AE, Woolf CJ. Activity-dependent changes in rat ventral horn neurons in vitro; summation of prolonged afferent evoked postsynaptic depolarizations produce a D-2-amino-5-phosphonovaleric acid sensitive windup. *Eur J Neurosci.* 1990;2:638–649.
111. Morgan JI, Curran T. Stimulus-transcription coupling in neurons: role of cellular immediate-early genes. *Trends Neurosci.* 1989;12:459–462.
112. Gogas KR, Presley RW, Levine JD, et al. The antinociceptive action of supraspinal opioids results from an increase in descending inhibitory control: correlation of nociceptive behavior and c-fos expression. *Neuroscience.* 1991;42:617–628.
113. Jones SL, Light AR. Electrical stimulation in the medullary nucleus raphe magnus inhibits noxious heat-evoked fos protein-like immunoreactivity in the rat lumbar spinal cord. *Brain Res.* 1990;530:335–338.
114. Basbaum AI, Chi S-I, Levine JD. Peripheral and central contribution to persistent expression of the c-fos proto-oncogene in spinal cord after peripheral nerve injury. In: Willis WD, ed. Hyperalgesia and Allodynia. New York: Raven Press, 1992:295–304.
115. Woolf CJ, Thompson SWM. The induction and maintenance of central sensitization is dependent on N-methyl-D-aspartic acid receptor activation: implications for the treatment of post-injury pain hypersensitivity states. *Pain.* 1991;44:293–299.
116. Chapman V, Dickenson AH. The combination of NMDA antagonism and morphine produces profound antinociception in the rat dorsal horn. *Brain Res.* 1992;573:321–323.
117. Yamamoto T, Yaksh TL. Studies on the spinal interaction of morphine and the NMDA antagonist Mk-801 on the hyperalgesia observed in a rat model of sciatic mononeuropathy. *Neurosci Lett.* 1992;135:67–70.
118. Malmberg AB, Yaksh TL. Hyperalgesia mediated by spinal glutamate or substance P receptor blocked by spinal cyclooxygenase inhibition. *Science.* 1992;257:1276–1279.
119. Woolf CJ, Wall PD. The relative effectiveness of C-primary afferents of different origins in evoking a prolonged facilitation on the flexor reflex in the rat. *J Neurosci.* 1986;6:1433–1442.
120. Blumberg H, Janig W. Changes in reflexes of vasoconstrictor neurons supplying the cat hindlimb following chronic nerve lesions. A model for studying mechanisms of reflex sympathetic dystrophy? *J Auton Nerv Syst.* 1983;7:399–411.
121. Nordin M, Nystrom B, Wallin U, et al. Ectopic sensory discharges and paresthesiae in patients with disorders of peripheral nerves, dorsal roots, and dorsal columns. *Pain.* 1984;20:231–245.
122. Howe JF, Loeser JD, Calvin WH. Mechanosensitivity of dorsal root ganglia and chronically injured axons. A physiological basis for the radicular pain of nerve root compression. *Pain.* 1977;3:25–41.
123. Melzack R. Phantom limb pain: implications for treatment of pathological pain. *Anesthesiology.* 1971;35:409–419.
124. Melzack R, Loeser JD. Phantom body pain in paraplegics: evidence for a central "pattern generating mechanism" for pain. *Pain.* 1978;4:195–210.
125. Bond MR. The relation of pain to the Eyseneck Personality Inventory, Cornell Medical Index and Whitely Index of Hypochondriasis. *Br J Psychiatry.* 1971;119:671–678.
126. Sternbach RA, Timmermans G. Personality changes associated with reduction of pain. *Pain.* 1975;1:177–181.
127. Sternbach RA. Chronic pain as a disease entity. *Triangle.* 1981;20:27–32.
128. Sternbach RA. Pain patients: traits and treatment. In: Sternbach RA, ed. Psychological Effects of Chronic Pain. New York: Academic Press, 1974:12–19.
129. Terenius LY. Biochemical assessment of chronic pain. In: Kosterlitz HS, Terenius LY, eds. Pain and Society. Basel, Germany: Verlag Chemie, 1980:355–364.
130. Pennebaker JW. The psychology of physical symptoms. In: Pennebaker JW, ed. Personality and Developmental Correlates. New York: Springer-Verlag, 1982:133–151.
131. Perl E. Causalgia: sympathetically aggravated chronic pain from damaged nerves. *Pain Clin Updates.* 1993;1:1–4.
132. Roberts WJ. A hypothesis on the physiological basis for causalgia and related pains. *Pain.* 1986;24:297–311.
133. Campbell JN, Meyer RA, Raja SN. Is nociceptor activation by alpha-1 adrenoreceptors the culprit in sympathetically maintained pain? *APS J.* 1992;1:3–11.
134. Janig W. Can reflex sympathetic dystrophy be reduced to an alpha-adrenoreceptor disease? *APS J.* 1992;1:16–22.
135. Sato J, Perl ER. Adrenergic excitation of cutaneous pain receptors induced by peripheral nerve injury. *Science.* 1991;251:1608–1610.
136. McLachian EM, Janig W, Devor M, et al. Peripheral nerve injury triggers noradrenergic sprouting within dorsal root ganglion. *Nature.* 1993;363:543–546.
137. Raja SN, Treede RD, Davis KD. Systemic alpha-adrenergic blockade with phentolamine. A diagnostic test for sympathetically maintained pain. *Anesthesiology.* 1991;74:691–698.
138. Ghostine SY, Comair YG, Turner DM. Phenoxybenzamine in the treatment of causalgia. *J Neurosurg.* 1984;60:1263–1268.
139. Abram SE, Lightfoot RW. Treatment of long-standing causalgia with prazosin. *Reg Anesth.* 1981;6:79–81.
140. De Groat WC. Neuropeptides in pelvic afferent pathways. In: Polak JM, ed. Regulatory Peptides. Basel, Switzerland: Birkhhauser Verlag, 1989:334–361.
141. Koltzenburg M, McMahon SB. The enigmatic role of the sympathetic nervous system in chronic pain. *Trends Pharmacol Sci.* 1991;12:399–402.