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PHYSIOLOGY OF PAIN

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In 1900, Sherrington[91, 92] was among the first modern neural scientists to define pain as the psychical adjunct to an imperative protective reflex. This is a concise definition, and it underlines the urgent primitive dimension of pain—the motor response that is teleologically oriented to remove tissue from potentially damaging insults. More recently, the focus has expanded to encompass the subjective emotional and motivational-affective components of pain. The International Association for the Study of Pain has proposed the following definition: pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.[5, 18, 69] Thus, even though traditionally viewed as an entirely sensory phenomenon, pain differs fundamentally from other conventional sensory modalities in that numerous and diverse types of stimuli are capable of initiating a complex multifaceted pain response. In many ways, pain transcends attempts to define it and is best regarded as an experience involving both a physiologic sensation and an emotional or, as is the case for nonverbal animals, behavioral reaction to that sensation.

During the last decade, there has been an explosion in our collective knowledge of pain processing, and the implications for clinical practice have been substantial. The development of rational and effective pain management strategies requires a basic understanding of pain physiology, including (1) an appreciation of the different types of inciting stimuli, (2) the neural pathways involved in processing noxious stimuli, (3) the response of the nervous system to repeated or sustained noxious input, and (4) the systemic consequences of pain. With this knowledge, the anticipation and recognition of pain are facilitated, and the use of pharmacologic agents and various hypoalgesic techniques can be optimized to better manage a variety of pain syndromes.

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PHYSIOLOGIC PAIN

An important conceptual breakthrough in understanding pain physiology is the recognition that the pain that occurs after most types of noxious stimulation is usually protective and quite distinct from the pain resulting from overt damage to tissues or nerves.[107] This first type of pain is termed *physiologic* pain (Fig. 1). It plays an integral adaptive role as part of the body's normal defense mechanisms, warning of contact with potentially damaging environmental insults and initiating behavioral and reflex avoidance strategies. It is also often referred to as nociceptive pain because it is only elicited when intense noxious stimuli threaten to injure tissue.[108] It is characterized by a high stimulus threshold, is well localized and transient, and demonstrates a stimulus–response relationship similar to those of the other somatosensations.[112] This protective mechanism is facilitated by a highly specialized network of nociceptors and primary sensory neurons that encode the intensity, duration, and quality of noxious stimuli and, by virtue of their topographically organized projections to the spinal cord, their location.[105] Although the extrapolation of this physiologic model of pain to the clinical setting has several inherent limitations, an understanding of basic pain pathways is necessary before the complex dynamics of the system can be appreciated.

NOCICEPTIVE PROCESSING

The physiologic component of pain is termed *nociception*, which consists of the processes of transduction, transmission, and modulation of neural signals generated in response to an external noxious stimulus. It is a physiologic process

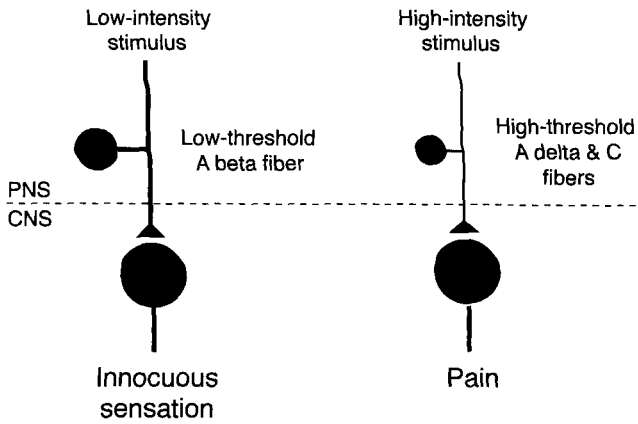

Figure 1. Functional specialization of primary sensory neurons enables, under normal circumstances, the responses to low- and high-intensity peripheral stimuli to be differentiated. The former activate low-threshold receptors generating innocuous sensations, and the latter activate high-threshold nociceptors, which can lead to the sensation of pain. This pain is a physiologic sensation, acting as a warning of potentially harmful stimuli. PNS = peripheral nervous system; CNS = central nervous system. (*From* Woolf CJ, Chong MS: Preemptive analgesia—treating postoperative pain by preventing the establishment of central sensitization. Anesth Analg 77:363–379, 1993; with permission.)

that results in the conscious perception of pain when carried to completion. In its simplest form, the pathway can be considered as a three-neuron chain, with the first-order neuron originating in the periphery and projecting to the spinal cord, the second-order neuron ascending the spinal cord, and the third-order neuron projecting to the cerebral cortex (Fig. 2). On a more complex level, the pathway involves a network of branches and communications with other sensory neurons and descending inhibitory neurons from the midbrain that modulate afferent transmission of painful stimuli.

Peripheral Nociceptors

The first process of nociception involves the encoding of mechanical, chemical, or thermal energy into electric impulses by specialized nerve endings termed *nociceptors*. Unlike other specialized somatic sensory receptors, nociceptors exist as free nerve endings of primary afferent neurons and function to preserve tissue homeostasis by signaling actual or potential tissue injury.[97] As such, they

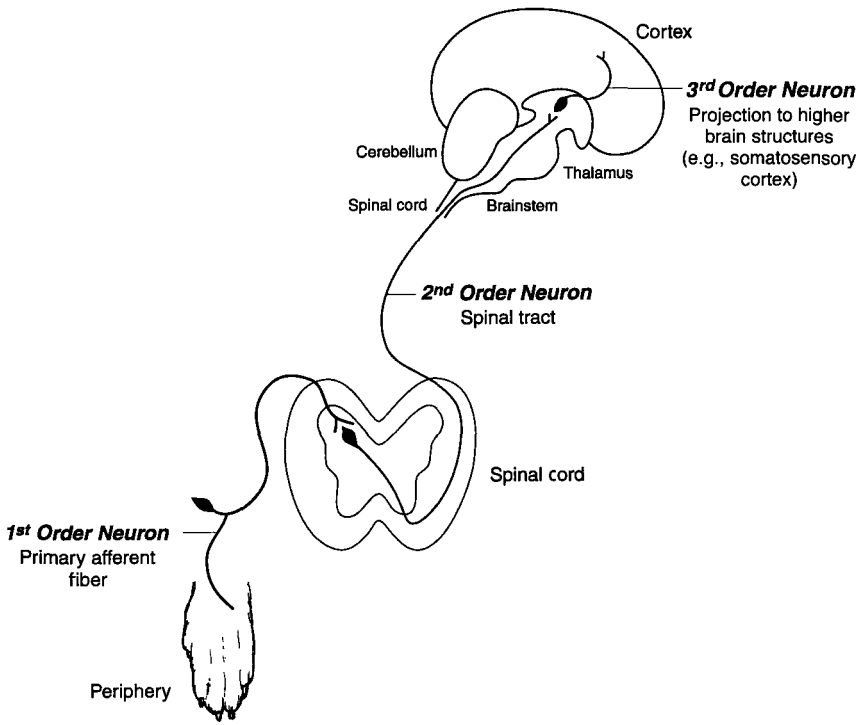

Figure 2. A simplified representation of nociceptive processing as a three-neuron chain. A noxious stimulus in the periphery activates a primary afferent fiber that transmits the information to the dorsal horn of the spinal cord. Here, a second order projection neuron that ascends in a spinal tract to the level of the thalamus intervenes. Finally, a tertiary neuron transmits the modified noxious stimulus to higher brain centers, notably the cerebral cortex, for perception.

have considerably higher stimulus thresholds for activation than thermoreceptors or low-threshold mechanoreceptors, which are capable of generating spontaneous action potentials under ambient conditions.[82] Conventional nomenclature based on neurophysiologic studies has classified nociceptors into two categories: A-fiber mechanoheat nociceptors and C-fiber mechanoheat nociceptors according to their associated afferent nerve fibers and stimulus sensitivities.[4, 82, 97] Typically, A-fiber mechanoheat nociceptors are responsible for signaling "first pain," which is often described as a sharp, stinging, or pricking sensation (Fig. 3). First pain is well localized and transient, lasting only as long as the acute painful stimulus is activating the nociceptor.[36, 82] In contrast, if a stimulus is of sufficient magnitude, C-fiber mechanoheat (or polymodal) nociceptors are recruited and mediate "second" or "slow pain," a more diffuse and persistent burning sensation extending beyond the termination of an acute painful stimulus.[24]

The ability of nociceptors to adapt to repeated presentations of suprathreshold stimuli is well established.[82, 97] Nociceptors are unique among sensory receptor classes in that under certain circumstances, repeated activation actually lowers their threshold and results in an enhanced response to subsequent stimuli. This phenomenon, as is discussed later, is called *sensitization*. Interestingly, nociceptors are also capable of exhibiting "fatigue" or "habituation," a characteristic of all other sensory systems whereby repeated or sustained presentation of a noxious stimulus actually leads to a diminished response.[79] Thus, the composite afferent message induced by a given stimulus is complex, resulting from the activation of various types of nociceptors with differing thresholds and response characteristics.

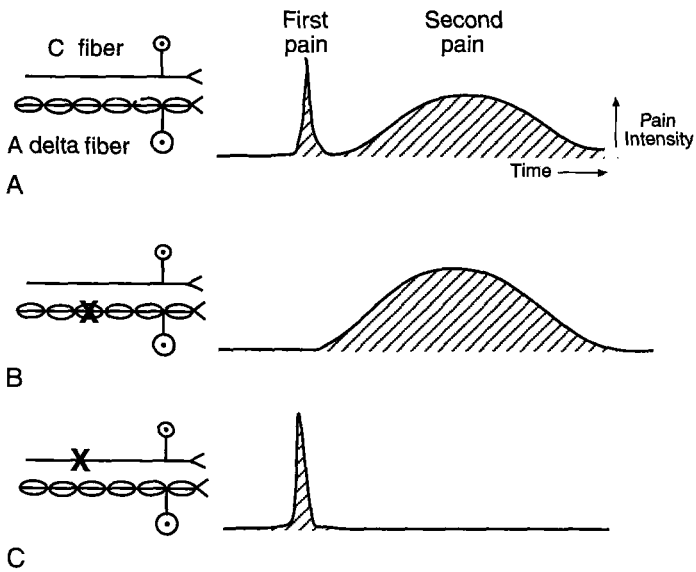

Figure 3. Primary afferent pain transmission. First pain and second pain sensations after a noxious stimulus *(A)*. The first pain sensation is abolished when the A fibers are blocked *(B)*, while the second pain sensation is abolished when the C fibers are blocked *(C)*. (*From* Fields HL: The peripheral pain sensory system. *In* Pain. New York, McGraw-Hill, 1987; with permission of The McGraw-Hill Companies.)

Afferent Nerve Fibers

The nociceptive signals generated by nociceptor activation are transmitted to the central nervous system by their associated afferent axons, which correspond to the subclasses of nociceptors outlined previously. Aδ fibers are large-diameter thinly myelinated axons and consequently conduct impulses rapidly,[50, 82] thereby facilitating the first pain signaled by the A fiber mechanoheat nociceptors. In contrast, transmission in the smaller unmyelinated C fibers is much slower[50] and acts to reinforce the immediate response of the A fibers, becoming increasingly important as the duration of the stimulus persists. Both Aδ and C fibers are located throughout the skin, peritoneum, pleura, periosteum, subchondral bone, joint capsules, blood vessels, muscles, tendons, fascia, and viscera, although their distribution density varies depending on the species and anatomic location.

Dorsal Horn Neurons

Cell bodies of both types of afferent nociceptive nerve fibers are contained in the dorsal root ganglia and extend axons to synapse with dorsal horn neurons within the gray matter of the spinal cord. The majority of Aδ fibers terminate in the most superficial layer, lamina I (also called the *marginal zone*), with some fibers projecting more deeply to lamina V (Fig. 4). Most C fibers are also destined for the superficial dorsal horn, with the focus in lamina II (the substantia

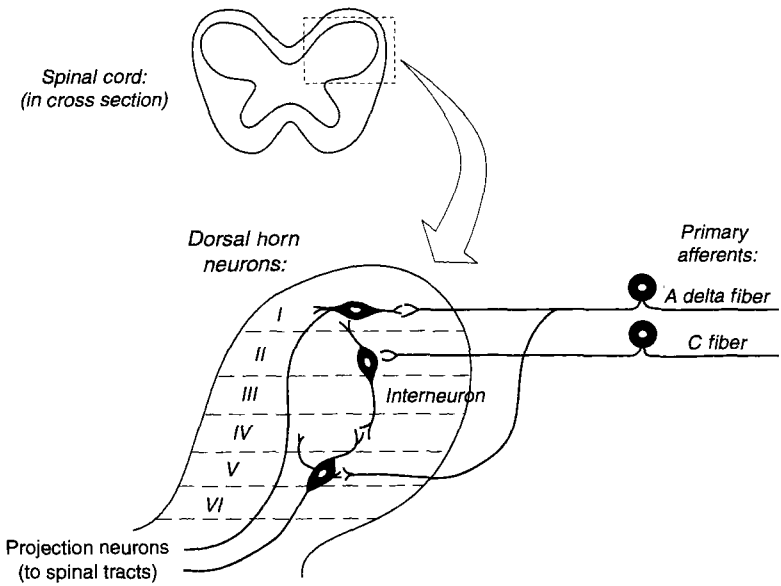

Figure 4. Laminar organization of spinal cord dorsal horn. Primary afferent fibers of nociceptors terminate on projection neurons in the dorsal horn of the spinal cord. Projection neurons in lamina I and lamina V receive direct input from myelinated Aδ fibers and indirect input from unmyelinated C fibers via interneurons in lamina II.

gelatinosa).[50, 96, 108] It is in the dorsal horn that initial integration and modulation of nociceptive input occur. Primary afferent axons may form direct or indirect connections with one of three functional populations of dorsal horn neurons: (1) interneurons, frequently divided into excitatory and inhibitory subtypes, which serve as relays and participate in local processing; (2) propriospinal neurons, which extend over multiple spinal segments and are involved in segmental reflex activity and interactions among stimuli acting at separate loci; and (3) projection neurons, which participate in rostral transmission by extending axons beyond the spinal cord to terminate in supraspinal centers such as the midbrain and the cortex.[50, 96] All three components are interactive and are essential for the processing of nociceptive information, which facilitates the generation of an organized and appropriate pain response.

Projection neurons have been subclassified into three groups. Nociceptive-specific (NS) neurons are concentrated in lamina I and are excited solely by noxious mechanical or thermal input from both Aδ and C fibers.[96] They are arranged somatotopically and respond to afferent impulses originating from discrete topographic areas.[50, 81, 97] Wide dynamic range (WDR) neurons predominate in lamina V and receive innocuous input from low-threshold mechanoreceptors as well as nociceptive information. They respond in a graded manner over a larger receptive field than do NS neurons and often receive convergent deep and visceral input. Although WDR neurons are considered to be ambiguous with regard to modality, they generate their strongest response to noxious stimuli, and their selective activation is capable of producing a painful sensation.[96] A third and less well-studied group of dorsal horn neurons are termed *complex* neurons and are typically located in lamina VII. It is believed that these cells function in the integration of somatic and visceral afferent activity.[16, 21, 24, 96]

Dorsal Horn Neurochemistry

Within the dorsal horn, the communication of nociceptive information between various neurons occurs via chemical signaling mediated by excitatory and inhibitory amino acids and neuropeptides which are produced, stored, and released in the terminals of afferent nerve fibers and dorsal horn neurons.[50, 81, 96] Electrophysiologic studies have shown that the release of the excitatory amino acids glutamate and aspartate, acting as neurotransmitters, evokes fast synaptic potentials in the superficial dorsal horn neurons, thereby facilitating nociceptive transmission.[24, 52, 70, 96] Nociceptive afferent neurons (in particular C fibers) also release a variety of other neuropeptides, including substance P, neurotensin, vasoactive intestinal peptide, calcitonin gene–related peptide, and cholecystokinin, which are capable of eliciting slow excitatory postsynaptic potentials in ascending projection neurons.[58, 70, 96] Just as a barrage of nociceptive input is capable of sensitizing peripheral nociceptors, so too can sustained afferent impulses produce altered response characteristics in dorsal horn neurons. Indeed, the recognition of the phenomenon of "central sensitization" has had a significant impact on the development of modern pain management strategies.

Ascending Spinal Tracts

Dorsal horn nociceptive input is conveyed to supraspinal centers by projection neurons extending through one of several ascending pathways. The spinothalamic tract (STT) is the most prominent nociceptive pathway in the spinal

cord; as such, it is almost synonymous with pain transmission. It originates from the axons of NS and WDR neurons in laminae I, V, VI, and VII which cross the midline and run in the anterolateral white matter, ultimately terminating in the thalamus.[24, 50] One group of STT axons projects into the lateral thalamic nuclei and transmits information from smaller and more discrete receptive fields in the periphery. These neurons are believed to play a role in the sensory discriminative aspects of pain. Axons projecting to the medial thalamic nuclei reflect input from larger and more diverse receptive fields and are implicated in the affective-motivational dimension of pain.[24, 102] Comparative anatomic data demonstrate species differences in the ascending fiber densities of the lateral and medial projections of the STT, which suggests that domestic animals have less refined stimulus characterization and localization capabilities compared with primates. Relatively larger medial pathways suggest that lower mammals may have an increased awareness of the affective aspect of the stimulus (i.e., autonomic responses and adversive stimulus qualities), however.[102]

Axons of nociceptive neurons located more deeply in laminae VII and VIII form the spinoreticular tract, which ascends bilaterally in the anterolateral quadrant of the spinal cord white matter.[96] Although most spinoreticular tract neurons terminate in various nuclei throughout the reticular formation, some fibers ascend in the medial pathway to the level of the thalamus.[24, 50, 102] Nociceptive neurons originating in laminae I and V project in the spinomesencephalic tract to the mesencephalic reticular formation, the lateral part of the periaqueductal gray region, and several other midbrain sites.[24, 50] Lesser contributions to nociceptive transmission are made from neurons located in laminae III and IV of the dorsal horn, which project axons through the spinocervical tract and the postsynaptic dorsal column pathway, which both relay impulses indirectly to the thalamus through the lateral cervical nucleus and the dorsal column nuclei, respectively.[50, 102] More recently, a direct projection transmitting primarily nociceptive information from the dorsal horn to the hypothalamus has been discovered. This is the spinohypothalamic tract,[9, 10] which provides an additional alternative route of activating the motivational component of pain and initiating neuroendocrine and autonomic responses.

Supraspinal Centers

The concept that a peripheral noxious stimulus generates an impulse that is transmitted to higher central nervous system structures to be perceived has long been appreciated as a philosophic construct.[22] Nociceptive neurons have been identified in portions of the medulla, pons, mesencephalon (midbrain), diencephalon (thalamus and hypothalamus), and cerebral cortex. The brainstem structures (medulla, pons, midbrain) contribute to nociceptive function through their contributions to the reticular system and the periaqueductal gray matter (PAG).

The reticular formation is a core of isodendritic neurons sending collaterals to the spinal cord, to other reticular neurons, to various sensory and motor nuclei of the brainstem, to the diencephalon, and to the cerebral cortex.[102] Reticular neurons can mediate motor, autonomic, or sensory function, and although there are circumscribed areas of specialized function within the formation, the interaction between such foci is substantial and provides the basis for unified activity of the reticular core. The reticular system is apparently critical to integration of the pain experience, as nociceptive input generates a profound effect on reticular neuronal activity. Ascending reticular neurons mediate the

affective and motivational aspects of pain through their projections to the medial thalamus and limbic system.

The PAG of the midbrain is a major locus of integration for homeostatic control. Although noted for its importance in the descending modulation of nociceptive information, it also extends ascending projections to the thalamus and hypothalamus, thereby providing an indirect alternative pathway for nociceptive sensory activity to reach diencephalic structures.[22]

The thalamus serves as the relay point for sensory information en route to the cerebral cortex and is composed of numerous complex nuclei, several of which play key roles in nociception.[22, 24, 102] As mentioned, ascending pathways that mediate the sensory-discriminative aspects of pain terminate in the laterally located thalamic nuclei, and pathways contributing to the affective dimension of pain are destined for the medial thalamic nuclei.

The limbic system, also called the paleocortex, is derived from phylogenetically antiquated telencephalic structures as well as components of the diencephalon and mesencephalon. It consists of the amygdala, hippocampus, septal nuclei, preoptic region, hypothalamus, and certain thalamic components. Limbic structures mediate aversive drive and thus influence the motivational component of pain and determine purposeful behavior.[102]

Impulse transmission to the cerebral cortex is believed to play a vital role in integrating pain perception. Imaging studies in human beings indicate that several discrete regions of cortex are activated by noxious stimulation: the first and second somatosensory cortices, the anterior insular cortex, and the anterior cingulate (a component of the limbic-associated cortex), providing convincing evidence that cortical regions are in fact targets for noxious input.[99] Although the functional and structural species differences occurring at this level are undoubtedly more significant than at any other points along the nociceptive pathway, it seems clear that the cortex is able to modulate both the cognitive and aversive affective aspects of pain sensation and to mediate increasingly complex behavior patterns.[70, 102]

Thalamocortical Neurochemistry

In comparison to the primary afferent and spinal cord terminal systems, relatively little is known concerning the neurotransmitters and receptors employed by nociceptive neurons or by the modulatory inputs to these neurons at the thalamic and cortical levels.[22] It is believed that as is the case in the dorsal horn, glutamate and aspartate constitute the principal excitatory mediators involved in signal transmission and processing in thalamocortical systems. The inhibitory amino acids (gamma-aminobutyric acid [GABA], glycine), the monoamines (norepinephrine, serotonin, dopamine), acetylcholine, and histamine affect the overall excitability of the thalamocortex in a state-dependent manner and function as part of the descending modulatory control system.

Descending Modulatory Pathways

It has been recognized for the better part of a century that descending inhibitory pathways modulate all types of sensory input. It has been established that nociceptive transmission in particular is subject to diverse and powerful inhibitory influences acting at many levels of the neuraxis. The descending modulatory system has been described as having four tiers: (1) the cortical and

thalamic structures, (2) the PAG of the midbrain, (3) the rostral medulla and pons of the brainstem, and (4) the medullary and spinal cord dorsal horn.[50, 102]

Perhaps the most important and well-studied anatomic area contributing to the endogenous analgesia system is the mesencephalic PAG. The PAG is a cell-rich region surrounding the cerebral aqueduct and is considered by some to be a caudal extension of the limbic system into the midbrain.[22, 47] The PAG receives descending input from the cortex, amygdala, and hypothalamus, and is modified by ascending projections from the medulla, reticular formation (including the locus coeruleus), and spinal cord.[43, 102] As noted previously, the PAG is also involved in ascending transmission via rostral connections to thalamic, hypothalamic, and limbic structures, and caudal efferents project to the rostral ventromedial medulla. The antinociceptive effects observed by direct stimulation of PAG neuronal cell bodies are thought to be mediated largely by opioid activation of PAG outflow, likely operating through a GABA-containing interneuron.[43] The dense concentration of opioid peptides and receptors found throughout the PAG underscores its importance as a substrate for opioid antinociception.[62]

The descending nociceptive inhibition arising from PAG activation is mediated through a relay in the rostral ventromedial medulla, facilitating projection caudally to the level of the dorsal horn. Several distinct rostral ventromedial medulla nuclei are implicated in antinociception, and all receive input from the PAG, send fibers to the spinal cord, and contribute to endogenous opioid analgesia.[43, 102]

The final site involved in the descending modulation of nociceptive information is at the level of the spinal cord. Just as dorsal horn processing is vital to the integration of ascending noxious input, its role in antinociception is equally crucial. Dense concentrations of GABA, glycine, serotonin, norepinephrine and the endogenous opioid peptides (enkephalins, endorphins, dynorphins) have been identified in dorsal horn neurons, and all produce inhibitory effects on nociceptive transmission.[24, 29, 81, 98, 102] Specifically, the spinal opioid system fine-tunes descending control mechanisms by acting presynaptically (by blocking release of substance P) as well as postsynaptically.[24, 102] Communication among dorsal horn neurons involves complex interactions, and it is now apparent that a single neuron may be influenced by many neurotransmitters, that each neurotransmitter may have numerous actions in a given region, and that multiple neurotransmitters may exist within a single neuron.[29, 98, 102] Simply stated on a more global level, nociceptive processing is a three-neuron chain with dual input at each level. Discriminative and affective aspects of pain are transmitted in related but distinct ascending pathways, with modifications made by both segmental and descending modulatory systems.

PATHOLOGIC PAIN

The traditional stimulus–response model of physiologic pain is conceptually appealing and has laid the foundation for a more comprehensive understanding of nociceptive pathways. Nevertheless, it must be recognized that physiologic pain alone is a rare entity in the clinical setting. In most situations, the noxious stimulus is not transient and may be associated with significant tissue inflammation and nerve injury. Under such circumstances, the classic "hard-wired" system becomes less relevant, and dynamic changes in the processing of noxious input are evident in both peripheral and central nervous systems. This type of pain is called *pathologic* pain (because it implies that the tissue damage has already occurred) or *clinical* pain, as ongoing discomfort and abnormal sensitivity are

features of the patient's clinical symptomatology (Fig. 5). Pathologic pain may manifest itself in several ways: spontaneous pain that may be dull, burning, or stabbing (causalgia); exaggerated pain in response to a noxious stimulus (hyperalgesia); and pain produced by a stimulus that is not normally noxious (allodynia) (Fig. 6).[108] Pathologic pain may arise from injury to a variety of tissue types invoking distinct neural mechanisms, and it is often further classified into inflammatory pain (involving somatic or visceral structures) or neuropathic pain (involving lesions of the nervous system). In addition, it is useful to characterize clinical pain from a temporal perspective and make the distinction between recently occurring (acute) and long-lasting (chronic) pain.

Acute Pain

Acute clinical pain typically arises from soft tissue trauma or inflammation, with the most common example being postoperative surgical pain. Although it does not serve a protective function in the sense that physiologic pain does, acute pain does play a biologically adaptive role by facilitating tissue repair and healing. This is achieved by hypersensitizing the injured area (primary hyperalgesia) as well as the surrounding tissues (secondary hyperalgesia) to all types of stimuli such that contact with any external stimulus is avoided and the reparative process can proceed undisturbed.[108] This realization is not, however, a license to allow patients to suffer needlessly in the postoperative period. By

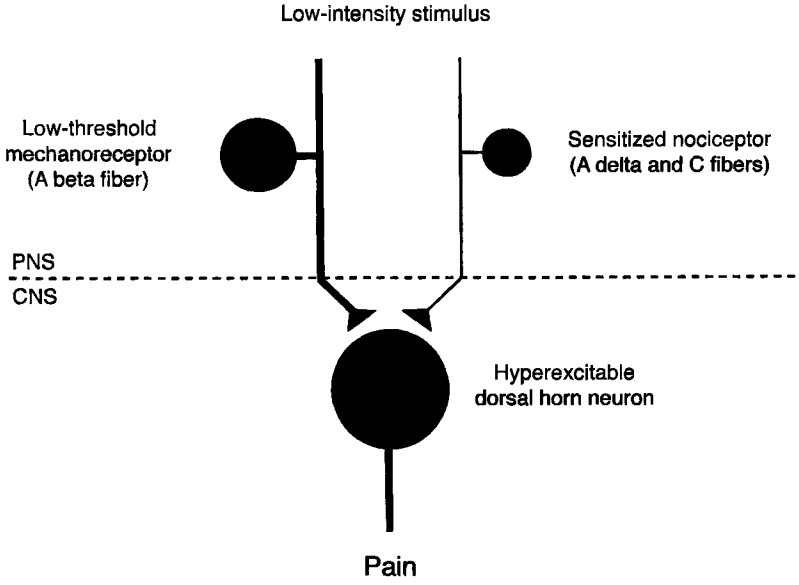

Figure 5. Pathologic pain (or clinical pain) results from abnormal excitability in the nervous system. This involves both central and peripheral changes, and the net result is that a low-intensity stimulus can elicit pain. PNS = peripheral nervous system; CNS = central nervous system. (*From* Woolf CJ, Chong MS: Preemptive analgesia—treating postoperative pain by preventing the establishment of central sensitization. Anesth Analg 77:363–379, 1993; with permission.)

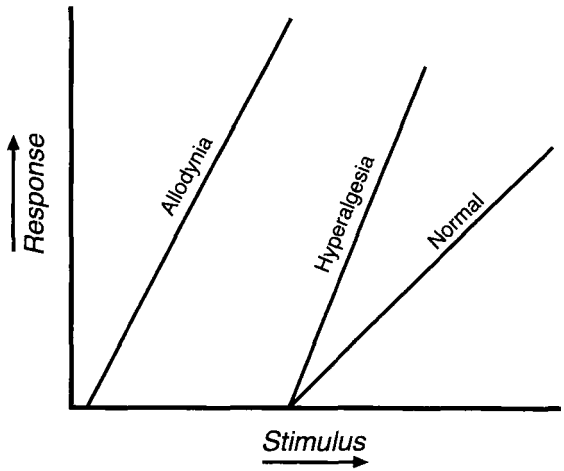

Figure 6. Nociceptive stimulus–response characteristics. Hyperalgesia is characterized by an increased response to a noxious stimulus, without a change in nociceptor threshold (i.e., the slope of the stimulus–response curve is greater than normal). Allodynia is characterized by a decrease in the nociceptor threshold required to produce a response (i.e., the stimulus–response curve is shifted to the left).

having an appreciation of the underlying functional basis of such pain, the practitioner is able to initiate appropriate pain management strategies while taking steps to optimize wound healing.

Chronic Pain

Chronic pain persists beyond the expected time frame for a given disease process or injury and has been arbitrarily defined as having a duration greater than 3 to 6 months.[37, 68, 98] Such pain may arise as a result of sustained noxious input such as ongoing inflammation, or it may be autonomous, with no temporal relation to the inciting cause. Chronic pain may manifest itself spontaneously, or it may be provoked by various external stimuli. The response is typically exaggerated in duration or amplitude, or both.[108] In recognition of the multifactorial nature of this type of pain, the International Association for the Study of Pain has incorporated more than 200 clinical syndromes in their classification of chronic pain,[68] with cancer pain, osteoarthritic pain, and postamputation phantom limb pain among the most relevant to the veterinary practitioner. In all cases, chronic pain is maladaptive and offers no useful biologic function or survival advantage, with the nervous system itself actually becoming the focus of the pathology and contributing to patient morbidity.[68, 111] Therefore, chronic pain implies more than just duration—it is a debilitating affliction that has a significant impact on a patient's quality of life and is often characterized by a dismal response to conventional analgesic treatments. In the future, an understanding of the altered neuromechanisms underlying this state of heightened neural sensitivity may pave the way to more effective chronic pain management strategies.

NERVOUS SYSTEM PLASTICITY

Hypersensitivity is a cardinal feature of acute and chronic pathologic pain. This phenomenon occurs as a direct result of dramatically altered nervous system function, with dynamic changes seen peripherally as a reduction in the threshold of nociceptor activation at the site of injury and centrally as an increased responsiveness of spinal neurons to sensory input.

Peripheral Sensitization

Under normal physiologic circumstances, mechanical, thermal, and chemical stimuli activate high threshold nociceptors associated with Aδ and C fibers to signal a noxious insult. In the clinical setting, however, even relatively benign noxious stimuli are often associated with a degree of tissue inflammation that initiates a cascade of sensitizing cellular and subcellular events. Damaged cells and primary afferent fibers release a number of chemical mediators, including substance P, neurokinin A, and calcitonin gene–related peptide, that have direct effects on the excitability of sensory and sympathetic fibers.[31, 58, 84, 93, 95, 105, 107] These mediators also promote vasodilation with extravasation of plasma proteins and the recruitment of inflammatory cells (Fig. 7). Mast cells, macrophages, lymphocytes, and platelets contribute to the scenario such that a complex milieu of inflammatory mediators, including hydrogen ions, norepinephrine, bradykinin, histamine, potassium ions, cytokines, serotonin, nerve growth factor, nitric oxide, and products from the cyclo-oxygenase and lipoxygenase pathways of arachidonic acid metabolism, is produced.[31, 58, 93, 94] It seems that these molecules act synergistically rather than individually, generating what is often referred to as a *sensitizing soup* that effectively lowers the response threshold for Aδ and

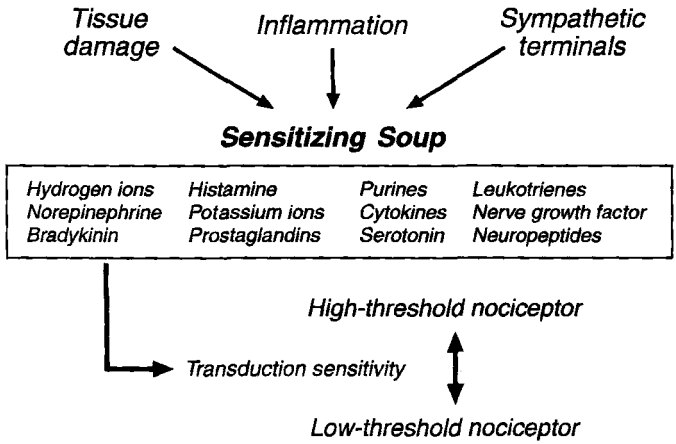

Figure 7. Transduction sensitivity of high-threshold nociceptors can be modified in the periphery by a combination of chemicals that act synergistically as a *sensitizing soup*. These chemicals are produced by damaged tissue as part of the inflammatory reaction and by sympathetic nerve terminals. (*From* Woolf CJ, Chong MS: Preemptive analgesia—treating postoperative pain by preventing the establishment of central sensitization. Anesth Analg 77:363–379, 1993; with permission.)

C fiber activation.[103, 108] Although changes in the afferent transduction threshold characterizing peripheral sensitization are responsible for the zone of primary hyperalgesia surrounding the site of tissue injury, they cannot explain all the behavioral aspects of pain hypersensitivity seen in the clinical setting.[93, 108] Furthermore, the identification of a subpopulation of afferent nerve terminals called "silent" nociceptors has also contributed to our understanding of the phenomenon of peripheral sensitization.[89] These nociceptors are a class of unmyelinated polymodal C fibers that demonstrate little if any activity even when subjected to extreme stimulation; however, they are exquisitely sensitive to the effects of local inflammation and may discharge vigorously under such conditions.[94] Although they apparently exist in a variety of tissue types and species, the significance of these silent nociceptors in clinical pain syndromes has not yet been elucidated.

Central Sensitization

In addition to primary hyperalgesia associated with damaged tissue, clinical or pathologic pain also invokes a heightened sensitivity in neighboring areas not subjected to injury (called the *zone of secondary hyperalgesia*) as well a responsiveness to normally innocuous mechanical stimuli (allodynia).[93, 108] It is now recognized that these clinical hypersensitivities are a result of dynamic changes in dorsal norn neuron excitability, which modifies their receptive field properties (Fig. 8).[21, 112] The first stage is related to the duration of the slow synaptic action potentials generated by Aδ and C fibers that have an impact on dorsal horn neurons. These synaptic potentials may last up to 20 seconds, and this results in a summation of potentials during low-frequency repeated nociceptor inputs, creating a progressively increasing and long-lasting depolarization in dorsal horn neurons.[94, 108, 112] Just a few seconds of C-fiber input can generate several minutes of postsynaptic depolarization. This so-called "windup" of spinal neurons is mediated by *N*-methyl-D-aspartate (NMDA) receptors, which

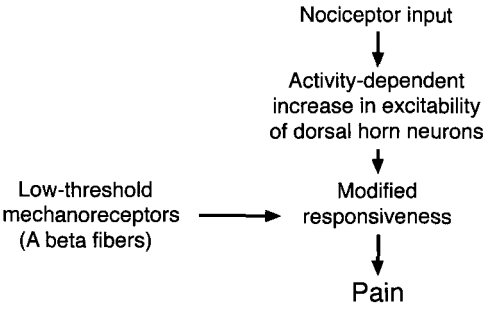

Figure 8. Central sensitization represents a modification in sensory processing within the central nervous system, such that innocuous sensations elicited by low-threshold primary sensory neurons can become painful. Nociceptor input not only has the capacity to produce pain directly, but in producing hyperexcitability in the spinal cord, can produce pain indirectly by changing the response to inputs that do not normally produce pain. (*From* Woolf CJ, Chong MS: Preemptive analgesia—treating postoperative pain by preventing the establishment of central sensitization. Anesth Analg 77:363–379, 1993; with permission.)

bind glutamate, and tachykinin receptors, which bind substance P and neurokinin A.[74, 108, 112] The activation of NMDA receptors results in an influx of calcium and activation of protein kinase C, which structurally modifies the NMDA channel to increase its sensitivity to glutamate (Fig. 9).[74, 108, 109, 112] Windup thus contributes to the overall state of increased membrane excitability in dorsal horn neurons commonly referred to as central sensitization, although the two terms are not, strictly speaking, synonomous.[59, 109]

Central sensitization is manifested at the cellular level as a change in receptive field properties with a reduction in threshold, an increase in responsiveness and spatial extent, and the recruitment of novel inputs.[20, 109] Specifically, Aβ fibers, which are large myelinated primary sensory neurons associated with highly specialized low-threshold peripheral mechanoreceptors, are recruited. Under normal circumstances, they are the peripheral sensory fibers responsible for generating innocuous sensations. Activation of Aβ afferents typically elicits unitary sensations of pressure, flutter, or vibration depending on the rate of adaptation of the fiber, but it never elicits pain even when high-frequency stimuli are applied.[20, 111] Once the dorsal horn has been sensitized by nociceptive input,

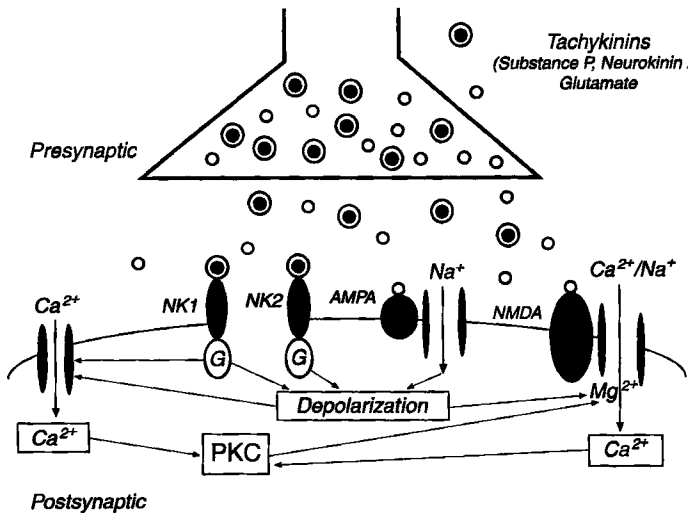

Figure 9. The transmitter and cellular mechanisms that produce central sensitization. C-fiber terminals release both the excitatory amino acid glutamate and neuropeptides such as the tachykinins in the dorsal horn of the spinal cord. Glutamate acts at *N*-methyl-D-aspartate (NMDA) receptors on postsynaptic membranes on dorsal horn neurons. Normally, the ion channel linked to the NMDA receptor is blocked by a magnesium ion, but the block can be removed by a depolarization of the cell leading to an influx of calcium and sodium ions, which leads to a further depolarization. The tachykinins bind to neurokinin receptors NK1 and NK2, leading (via G-protein activation) to depolarization and to changes in second messengers. The former will directly act on the NMDA ion channel, but the latter acts indirectly via protein kinase C (PKC) activation. Therefore, there are a number of postsynaptic mechanisms that lead to positive feedforward and feedback changes that increase excitability. Changes in second messengers can also modify immediate early gene expression, potentially producing very prolonged alterations in function. (*From* Woolf CJ, Chong MS: Preemptive analgesia—treating postoperative pain by preventing the establishment of central sensitization. Anesth Analg 77:363–379, 1993; with permission.)

however, activation of Aβ fiber mechanoreceptors by previously nonpainful tactile stimuli actually contributes to the pain response.[108, 111] The secondary hyperalgesia and mechanical allodynia manifested clinically can be explained in terms of a misinterpretation of normal inputs that are not part of the physiologic pain system and would never normally generate pain but arise as a direct consequence of central sensitization.[108, 111] Thus, the pathophysiology of postinjury pain hypersensitivity involves dynamic changes occurring in the periphery, which enable low-intensity stimuli to produce pain by activating sensitized Aδ and C fibers, while input in low-threshold Aβ sensory fibers generates pain as a result of altered central processing in the dorsal horn of the spinal cord (see Fig. 8).

VISCERAL PAIN

Pain emanating from deep visceral structures obviously poses a significant clinical challenge for both human and veterinary practitioners. Until recently, most experimental work on pain physiology and pathophysiology has focused entirely on pain originating from superficial cutaneous stimulation. In the past, it was assumed that the ideas derived from a somatic model of inflammatory pain could simply be applied directly to visceral pain. It has become increasingly apparent, however, that the neural mechanisms involved in generating these two types of pain differ markedly.

It is easy to appreciate the protective and biologically adaptive function of physiologic pain as it relates to cutaneous noxious input; however, it is less clear in the context of deep visceral pain. The skin is subject to an almost constant array of external perturbations, and nociceptive processing is vital in initiating necessary behavioral avoidance strategies. Viscera are rarely exposed to comparable external insults but are more commonly the targets of disease processes, and the protective function of the ensuing pain response in this situation is not as obvious.[67, 75] In addition, the concept of nociceptive afferents activated by stimuli that pose a direct threat to tissue homeostasis is difficult to transfer to visceral types of pain. Clinically, several major life-threatening forms of tissue destruction, including perforation of a hollow organ or visceral neoplastic processes, are frequently not painful, and, conversely, various experimental stimuli that are perceived as painful such as distention of a hollow viscous are not necessarily tissue damaging.[67] The nature of the pain itself originating from visceral verses somatic tissues is significantly different, with visceral pain possessing several distinguishing characteristics.

The sensitivity of visceral tissue to traditional types of mechanical, thermal, or chemical stimuli differs profoundly. Viscera seem most sensitive to distention of hollow muscular-walled organs (including the gastrointestinal tract, the urinary tract, and the gallbladder), ischemia (notably the myocardium in human patients), and inflammation (such as in cystitis or pancreatitis).[64, 67] Furthermore, the area over which a stimulus is applied may be a crucial determinant of threshold in visceral types of pain, with spatial summation having the potential to drastically lower the effective threshold, which may explain the inability of most localized mechanical stimuli to produce a pain response.[67] Visceral pain also differs from somatic pain with regard to localization. Visceral pain is typically perceived as being extensive and diffuse and is often associated with a sense of nausea and malaise. Referred pain, whereby the pain response is localized to distant structures, is another hallmark of visceral pain. The mechanisms of this phenomenon remain a matter of considerable debate. Finally, although cutaneous hypersensitivity (primary and secondary hyperalgesia, allo-

dynia) has been well characterized and repeatedly documented, few reports of similar changes occurring in viscera are available, although it does seem that inflammatory states in particular may predispose to visceral hypersensitivity.[67]

NEUROPATHIC PAIN

Neuropathic pain is produced as a consequence of damage to the nervous system. Like inflammatory pain states, neuropathic pain is characterized by altered sensory processing of stimuli and results in several distinct and unique manifestations of hypersensitivity.[108] Patients suffering from neuropathic pain typically experience persistent burning sensations, partial or focal loss of sensitivity, allodynia, and hyperresponsiveness to multiple stimuli (hyperpathia).[106] Multiple mechanisms are undoubtedly at work here, but two general categories of pathologic changes seem to contribute to neuropathic pain: abnormal peripheral input and abnormal central processing.[106, 108]

Abnormal peripheral input may arise from an acute injury discharge in axotomized afferent fibers.[104] This discharge persists for a period of 10 or more seconds, and the collective effects generate a massive and aberrant input to the central nervous system. In addition to producing intense and excruciating pain, this input seems to produce long-lasting NMDA receptor–mediated windup in dorsal horn neurons.[90, 106] Several days after this acute injury discharge, a second form of abnormal peripheral input develops, with ectopic activity originating from injured axons, the proximal axonal stump (neuroma), and cell bodies in the dorsal root ganglion.[25, 106] This ectopic discharge is chronic and may reflect the development of abnormal sensitivity to mechanical, thermal, or chemical stimuli. The potential also exists for cross-excitation between different types of sensory fibers or between postganglionic sympathetic fibers and sensory fibers.[106]

The phenomenon of central sensitization also contributes to the persistence and hypersensitivity associated with neuropathic pain. Afferent fiber input may arise from chronic ectopic discharge in sensory neurons as described previously, or it may be driven by sympathetic neurons exciting C fibers that have developed an adrenergic sensitivity secondary to axotomy (sympathetically maintained pain).[14] An additional form of altered central processing is observed in neuropathic pain states and involves structural reorganization in the cell bodies of injured axons in the dorsal root ganglion.[106] Studies have demonstrated that axotomized Aβ fibers sprout from their normal site of termination in the deeper laminae of the dorsal horn into the superficial laminae I and II, which are normally occupied by Aδ and C fibers.[100, 113] Nerve injury also stimulates sympathetic fibers to sprout around large dorsal root ganglion cells, providing another mechanism whereby postaxotomy sympathetic activity may activate nociceptive afferents.[66] Sympathetically maintained pain is an important and therapeutically challenging component of neuropathic pain in human patients and presumably occurs, in varying degrees, in veterinary patients as well. Abnormal central processing as a result of a persistent state of central sensitization or dorsal horn structural reorganization may provide a unifying explanation for neuropathic pain mediated by sympathetic and Aβ fibers.[106]

THE NEUROMATRIX THEORY OF PAIN

It is generally accepted that future avenues in the study of pain will focus on understanding the role of the brain. In a recent editorial by Melzack,[67a] he

proposes a new theory that challenges conventional views that the brain functions passively to detect and analyze nociceptive input from the periphery. The neuromatrix theory of pain proposes that pain is a multidimensional experience produced from characteristic "neurosignature" patterns arising from nerve impulses generated by a widely distributed neural network, the "body-self neuromatrix," located in the brain. Although these neurosignatures may be triggered by somatosensory inputs (i.e., according to nociceptive processing), they may also be generated independently of them. Thus, the neuromatrix theory of brain function breaks the Cartesian psychophysical link between injury and pain and suggests that nociceptive input is not, in fact, a prerequisite for the experience of pain. Sensory inputs merely modulate that experience; they do not directly cause it. Although sculpted by sensory input, the neuromatrix is genetically predetermined, and so provides an attractive explanation for phantom limb pain and other examples in which the perceived level of pain is poorly correlated with pathology.[67a] This new insight into the complexity of the brain's role in modulating the experience of the body as a whole points to a new and exciting future in the understanding of pain and its management.

SYSTEMIC RESPONSES TO PAIN AND INJURY

The nervous system is the principal target of nociceptive information and provides the vehicle by which an organism can react to such input. The ensuing pain response, however, is diverse and by no means confined solely to the nervous system. Pain induces segmental and suprasegmental reflex responses that result in increased sympathetic tone, vasoconstriction, increased systemic vascular resistance, increased cardiac output through increases in stroke volume and heart rate, increased myocardial work through increases in metabolic rate and oxygen consumption, decreased gastrointestinal and urinary tone, and increased skeletal muscle tone.[102, 114] Endocrine responses include increased secretion of corticotropin, cortisol, antidiuretic hormone, growth hormone, cyclic adenosine monophosphate, catecholamines, renin, angiotensin II, aldosterone, glucagon, and interleukin 1, with concomitant decreases in insulin and testosterone secretion.[114] Metabolically, this translates into a catabolic state characterized by hyperglycemia, increased protein catabolism and lipolysis, renal retention of water and sodium with increased potassium excretion, and decreased glomerular filtration rate.[114] Nociceptive stimulation of brainstem centers causes increased respiratory drive, although segmental hypoventilation may occur as a result of splinting or bronchospasm. At the diencephalic and cortical levels, intense anxiety and fear greatly enhance the reflex sympathetic responses outlined previously and contribute to increased blood viscosity, prolonged clotting time, fibrinolysis, and platelet aggregation.[102, 114]

These effects constitute the classic "stress response," the magnitude and duration of which parallel the degree of tissue damage, which often persists for days or more.[6, 102] The stress response is an evolutionary adaptation designed to optimize survival in the immediate postinjury period; however, its persistence in a clinical setting can be deleterious and have an impact on patient morbidity. In many patients with severe posttraumatic or postsurgical pain, the ensuing neuroendocrine responses are sufficient to initiate and maintain a state of shock.[86] Therefore, attenuation of the stress response is an important component of any pain management strategy. Indeed, the presence or absence of stress-related physiologic changes forms the foundation of most pain assessment schemes currently used in animal patients.

New Markers of Pain-Induced Stress

Suppression of the classic adrenal–pituitary axis stress hormone response has long been regarded as the best objective gauge of optimal pain management. The recognition of intracellular markers of stress has fueled renewed interest in this area. These markers are generated within dorsal horn neurons of the spinal cord and are believed to contribute to phenotypic changes in peripheral sensory neurons.[108] The following are just a few of the currently studied intracellular markers:

1. Expression of immediate-early genes (e.g., c-*fos*) that code for protein products involved in initiating long-term neuronal excitability[15, 73]
2. Activation of enzymes (e.g., protein kinase C and nitric oxide synthase) that play important roles in central sensitization and development of opioid tolerance[3, 15, 28]
3. Secretion of nerve growth factor and neuropoietic cytokines that have widespread effects, contributing to both peripheral and central sensitization[1, 108]

As a more thorough understanding of dorsal horn physiology evolves, it is likely that these markers of pain-related stress may prove useful in assessing pain states and the efficacy of pharmacologic interventions.

IMPLICATIONS FOR PAIN MANAGEMENT

Most clinical pain syndromes are complex and often involve more than one type of pain. It can be difficult to predict the mechanisms mediating pain associated with multiple tissue and neuronal perturbations in a given animal. Pain associated with intervertebral disk disease or invasive soft tissue neoplasias likely has inflammatory and neuropathic components. In addition, acute and chronic pain states may occur simultaneously. An animal with osteosarcoma may present with classic symptoms of chronic inflammatory pain and hypersensitivity, although surgery to amputate the affected limb may generate pain sensation typical of acute tissue injury. Amputation may also initiate neuropathic pain associated with large nerve transection. It should not be surprising then that a single drug administered at a "standard" dose for various pain syndromes is not an effective strategy for managing pain in all patients. The clinical objective should be to minimize debilitating pathologic pain while maintaining the protective and adaptive aspects associated with physiologic pain. With this in mind, various strategies can be employed to maximize the success of therapeutic interventions.

The first of these strategies is the concept of preemptive analgesia (Fig. 10). The plasticity of the nervous system in response to noxious input has been well established. Initiating treatment before acute insult is believed to inhibit peripheral and central sensitization processes.[112] The second strategy involves combining analgesic drugs and techniques to achieve beneficial additive or synergistic analgesic effects (multimodal or balanced analgesia). With this approach, lower doses can usually be used, thereby reducing potential undesirable side effects.[8, 54] The following is a brief review of the major classes of analgesic agents commonly used to obtund the nociceptive processes of transduction, transmission, and modulation and thus the perception of pain.

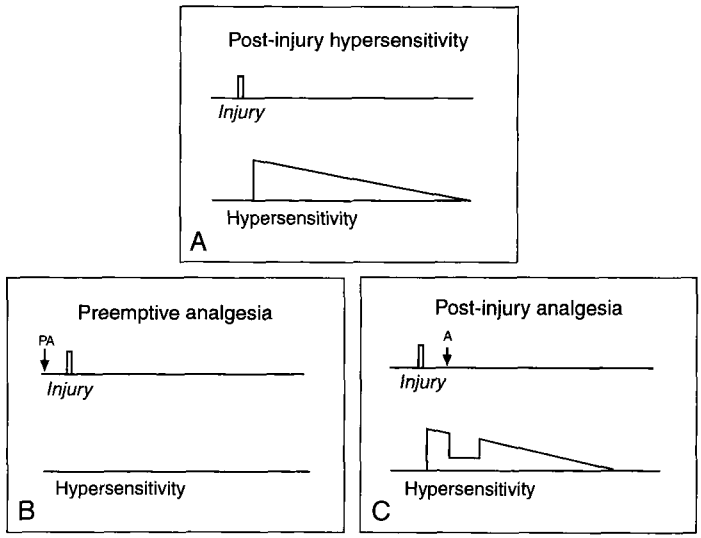

Figure 10. A simple model of the rationale behind single-treatment preemptive analgesia. Injury triggers central sensitization, leading to a prolonged hypersensitivity state *(A)*. A preemptive analgesic (PA) prevents the induction of central sensitization, preempting the postinjury hypersensitivity *(B)*. Postinjury analgesia (A) has a much diminished effect on an established state of hypersensitivity *(C)*. (*From* Woolf CJ, Chong MS: Preemptive analgesia—treating postoperative pain by preventing the establishment of central sensitization. Anesth Analg 77:363–369, 1993; with permission.)

Analgesic Agents

Opioids are a diverse group of natural and synthetic drugs used extensively in the management of postoperative and cancer-related pain in human beings and animals.[45, 60] The endogenous opioid system provides the site of action for exogenously administered opioids. Specific opioid receptors are located in the periphery,[35, 42, 44, 53, 58] spinal cord,[15, 28, 53, 115] and supraspinal structures,[44, 49, 53, 61, 83] with the μ and κ receptors being the most clinically important with regard to analgesia. Opioids have been classified as agonists, partial agonists, or agonist-antagonists depending on the dose–response relation of the drug at the various opioid receptors.[34, 40, 45] The traditional view that a given drug always behaves as either an agonist or an antagonist at a particular receptor is a gross oversimplification, and recent studies have demonstrated that a number of variables contribute to the efficacy of various opioids in the clinical setting. Dosage, species, stimulus intensity, character, and duration can all alter the overall analgesic effect of an opioid.[7, 11, 72]

Opioids dampen peripheral and central afferent nociceptive transmission and thus are extremely effective in treating acute inflammatory pain (Fig. 11). They are not, however, equally efficacious in managing all types of pain. Neuropathic pain syndromes are often characterized by a poor or short-lived response to opioids.[17, 26] There are several clinical methods of opioid administration, including (1) systemic administration—orally, subcutaneously, intramuscularly, or intravenously (as a bolus or a constant-rate infusion), (2) epidural or spinal

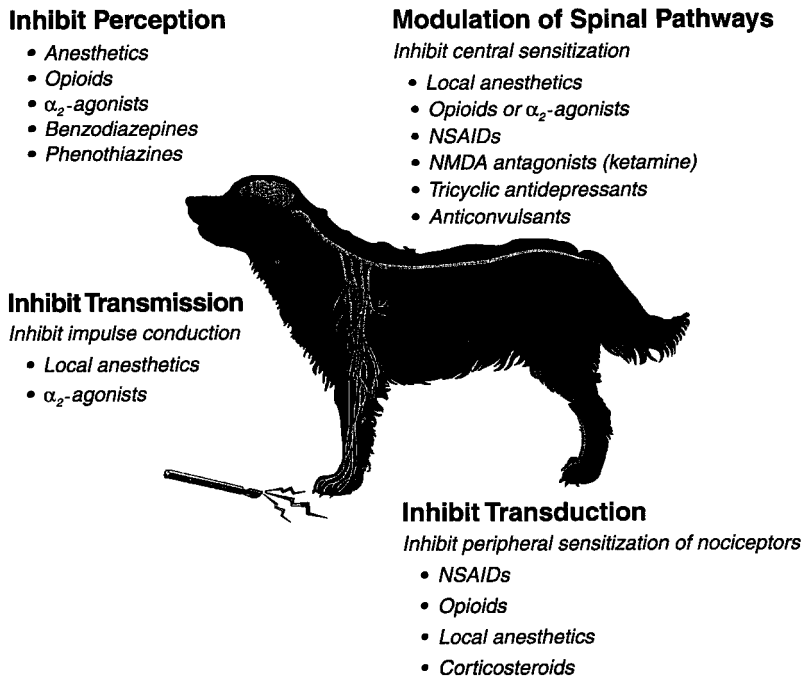

Figure 11. The sites of action of the major classes of analgesics as they affect transduction, transmission, and modulation of nociceptive input and the perception of pain. NSAIDs = nonsteroidal anti-inflammatory drugs; NMDA = *N*-methyl-D-aspartate.

injection, (3) transdermal application,[33, 43, 57] (4) intra-articular injection,[51, 79, 85] and (5) local administration at the site of injury.[48]

Local anesthetics act either by blocking sodium channels, which prevents nerve impulse transmission and nociceptor excitation, or by inhibiting modulatory nociceptive processing when administered centrally. In addition to their well-known topical, local, and regional effects,[33, 45, 79] recent studies have documented the efficacy of low-dose intravenous lidocaine infusions in the management of hyperalgesia and neuropathic pain states.[39, 56, 78]

Nonsteroidal anti-inflammatory drugs (NSAIDs) continue to be the mainstay of chronic pain management in both human and veterinary patients. The recent development of more selective agents has generated considerable interest in their use for postoperative pain as well.[63] Traditionally, it has been believed that the analgesic effects of NSAIDs are related to their ability to inhibit cyclooxygenase and lipoxygenase activity and to prevent prostaglandin synthesis and peripheral nociceptor sensitization.[23, 63] There is considerable evidence that at least some NSAIDs have a central spinal site of action, however, and may act synergistically with other analgesic compounds.[2, 46] Typically, NSAIDs are administered systemically (orally, subcutaneously, intramuscularly, or intravenously), although one recent study has shown that analgesia may be achieved by administering the NSAID locally at the surgical site. Local administration helps to maximize drug levels at the site of inflammation while minimizing overall systemic tissue exposure and the potential for adverse side effects.[30]

α_2-Adrenergic agonists bind to α_2-receptors located in the dorsal horn of the spinal cord, modulating the release of substance P, calcitonin gene–related peptide, and various other neurotransmitters involved in rostral transmission of nociceptive information.[19] Opioids likely exert their analgesic action through similar modulatory pathways, and coadministration may result in additive or synergistic drug interactions. α_2-Agonists are used as "rescue" therapy when opioid tolerance has developed.[77] The analgesic drug tramadol has both opioid and α_2-agonist–like actions and has been used to treat a variety of pain syndromes in human patients.[13] α_2-Receptors are also located supraspinally in the locus coeruleus, thalamus, and cerebral cortex, where when activated, they inhibit norepinephrine release, resulting in profound sedation that diminishes the conscious perception of pain.[19] Although α_2-receptors are notably lacking on the axons of peripheral nerves, α_2-agonists are apparently capable of producing some degree of C-fiber conduction blockade. This action may underlie their enhancement of sensory nerve blockade when combined with local anesthetics.[12, 32, 38] Thus, α_2-agonists have been administered systemically, epidurally,[71] or peripherally to prolong sensory nerve blockade achieved by local anesthetics.[32, 65, 95]

Traditionally, ketamine has been classified as a dissociative anesthetic, but more recently, it has been recognized as an NMDA antagonist as well.[55, 95] Although there are multiple binding sites, it is the NMDA receptor blockade that accounts for most of the analgesic, amnestic, psychomimetic, and neuroprotective effects of ketamine.[55] At low doses, ketamine can enhance analgesia by preventing NMDA receptor–mediated windup and subsequent sensitization of dorsal horn neurons. It may even abolish hypersensitivity once it is already established[28, 55, 110]; therefore, the spinal cord modulatory effects of ketamine make it particularly useful in the management of chronic neuropathic types of pain that typically respond poorly to opioid treatment.[27, 28, 76, 80] Analgesic effects of ketamine may be achieved by systemic administration (either intramuscularly or intravenously as a bolus or constant-rate infusion), epidural administration, or topical application to burn injuries.

General anesthetics are not, strictly speaking, analgesics. They do, however, inhibit the perception of pain by rendering the cortex unaware of incoming nociceptive information (unconsciousness). Although a patient at a surgical plane of anesthesia is unaware of pain, it is still beneficial to inhibit peripheral transduction and transmission while enhancing spinal modulation processes so as to prevent intense noxious input from sensitizing the nervous system. For this reason, the concepts of preemptive and multimodal analgesia are relevant in this context and should be incorporated into the overall anesthetic plan when general anesthesia for surgical trauma is anticipated.

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