ESSENTIALS OF PAIN MEDICINE

FOURTH EDITION

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Scott M. Fishman • Spencer S. Liu
Steven P. Cohen

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To my wife and best friend, Geetha: Thanks for your constant support, immense sacrifice, and enthusiastic encouragement of my educational activities.

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Khalid Malik

To my wife, Carol, for her continued support, encouragement, and understanding;

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To my sister, Rita, who keeps reminding me to be strong and assertive.

Philip Peng

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PREFACE

The fourth edition of this book reflects the continuing advances in our subspecialty. All the chapters have been revamped and new chapters have been added including cannabinoids, TNF-alpha inhibitors, tai chi, dorsal root ganglion stimulation, ultrasound-guided pain procedures, and risk of infection in interventional procedures. Dr. Samer Narouze exited as an Associate Editor, and we thank him for his past and ongoing contributions. Dr. Philip Peng, our new Associate Editor, assisted with the chapters on ultrasound and nontraditional treatments of pain. We hope that this edition continues the outstanding quality of the previous editions, which is a reflection of the hard work of our contributors and editor, Ms. Angie Breckon.

The completion of any medical text has become more challenging, and this book is no exception. Given the growing number of textbooks devoted to pain medicine, writing book chapters does not have the allure it once had and at many institutions, chapters do not count towards academic promotion. However, the feedback of this textbook sets it apart from other books in this field, which has enabled us to continue to recruit an exceptional cadre of authors. Collectively, we believe that books will continue to play a role in the education of trainees and the continuing education of clinicians globally. We therefore thank the contributors who, in spite of their busy schedules, submitted authoritative and up-to-date reviews of their topics.

This is the last edition in which Drs. Benzon and Raja will serve as Editors. In 1998, Dr. Benzon recruited Drs. Srinivasa Raja, David Borsook, Robert Molloy, and Gary Strichartz as co-editors and persuaded Mr. Michael Houston, now an Executive Content Strategist of Elsevier, to have Churchill-Livingstone publish the book. When this book originally came out in 1999, it was the first one of its kind in pain medicine. It then went through subsequent revisions in 2005 and 2011. The third edition was translated into a Chinese version, which enabled us to expand its outreach to a much larger audience. The next edition will be under the tutelage of Dr. Steven P. Cohen. The remarkable quality of this book, and its continued availability as an authoritative reference to future residents, fellows, and clinicians, is therefore assured.

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SECTION I

Basic Considerations

SECTION OUTLINE HEAD

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CHAPTER 1

Anatomy and Physiology of the Pain Signaling Process

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Pain is a physiologic consequence of tissue injury and serves a vital protective function. For example, clinical observations of patients with congenital insensitivity to pain and patients with leprosy have clearly demonstrated that the absence of pain results in repeated injuries and disabilities. However, pain can become a disease when it occurs or persists in the absence of tissue damage or following appropriate healing of injured tissues. This chronic pain is disabling, has considerable negative impact on quality of life of the individual, and has profound economic impact on the family and society.

The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."[1] This definition acknowledges that pain is not only a sensory experience but may be associated with affective and cognitive responses. The definition also recognizes that the intensity of pain and the severity of tissue damage are not necessarily correlated. Thus, an understanding of the anatomic substrates and physiologic mechanisms by which noxious and nonnoxious stimuli are perceived provides the essential background to apprehend the mechanisms of acute and chronic pain and the sites of action of pharmacologic therapies for pain.

SOMATOSENSATION, NOCICEPTION, AND PAIN

Somatosensation is the physiologic process by which neural substrates are activated by physical stimuli resulting in the perception of what we describe as touch, pressure, and pain. Nociception is the physiologic process of activation of neural pathways by stimuli that are potentially or currently damaging to tissue. A stimulus is considered nociceptive when it induces behavioral avoidance or escape response in animals and humans or when the stimulus evokes activity in specialized groups of afferent fibers (i.e., nociceptors). Clinically, the degree of nociception is inferred by overt evidence of tissue damage. In contrast to nociception, pain is a conscious experience. Although the stimulus-induced activation of afferent neural pathways plays an important role, other factors such as alterations in somatosensory processing after injury to tissues and/or nerves and psychosocial factors may influence the overall perception of pain. The experience of pain, particularly chronic pain, often results in suffering. Suffering results from a multitude of factors that includes loss of physical function, social isolation, family distress, and a sense of inadequacy or spiritual loss. This chapter briefly reviews the basic anatomy and physiology of the neural pathways that respond to somatosensory stimuli, especially nociceptive stimuli, and emphasizes the plasticity in this system following an injury. This knowledge is fundamental in the evaluation and subsequent management of patients with painful disorders.

The sequence of events by which a stimulus is perceived involves four processes: (1) transduction, (2) transmission, (3) modulation, and (4) perception (Fig. 1.1). *Transduction* occurs in the peripheral terminals of primary afferent neurons, where different modes of stimuli (e.g., mechanical, heat, chemical, or cold) induce a generator potential through activation of transduction channels expressed on the axonal membrane. If the generator potential is sufficient, it will generate action potentials that are then transmitted through the nervous system. There are three major components of the transmission system. The peripheral sensory neurons with their cell bodies residing in the dorsal root ganglia transmit impulses from the site of transduction at their peripheral terminal to the spinal cord where the central terminals synapse with second-order neurons. The spinal neurons are the *second* component in the transmission network. These cells send projections to the thalamus and various brainstem and diencephalic structures. Finally, neurons of the brainstem and diencephalon form the *third* component of the transmission network as they project to various cortical sites. Modulation is the process whereby neural activity may be altered along the pain transmission pathway. A major site of modulation occurs within the dorsal horn of the spinal cord. *Modulation* at this level of processing involves a multitude of neurotransmitter systems that will be discussed in Chapter 2. Activation of pain modulation systems usually results in less activity in the pain transmission pathway after a noxious stimulus. Examples of activation of this process include stress-induced analgesia. However, in some circumstances, modulation can also result in an enhancement of pain signaling. *Perception* is the final stage of the nociceptive process by which neural activity in the somatosensory transmission pathway results in a subjective sensation of pain. It is presumed that this process results from the concerted activation of primary and secondary somatosensory and limbic cortices.

PERIPHERAL MECHANISMS

In general, somatosensation begins with activation of primary afferent neurons. These neurons are part of the peripheral nervous system, with cell bodies located in the dorsal root ganglia, from which the neurons project with a peripheral axon into the target tissue (skin, muscles, joints) and a central axon into the spinal cord. Primary afferent fibers are classified based on their conduction velocity and the stimuli by which they are activated. Much of our knowledge about the physiology of primary afferents including nociceptors originates from studies on cutaneous afferents (i.e., those that innervate the skin). Many of the principal

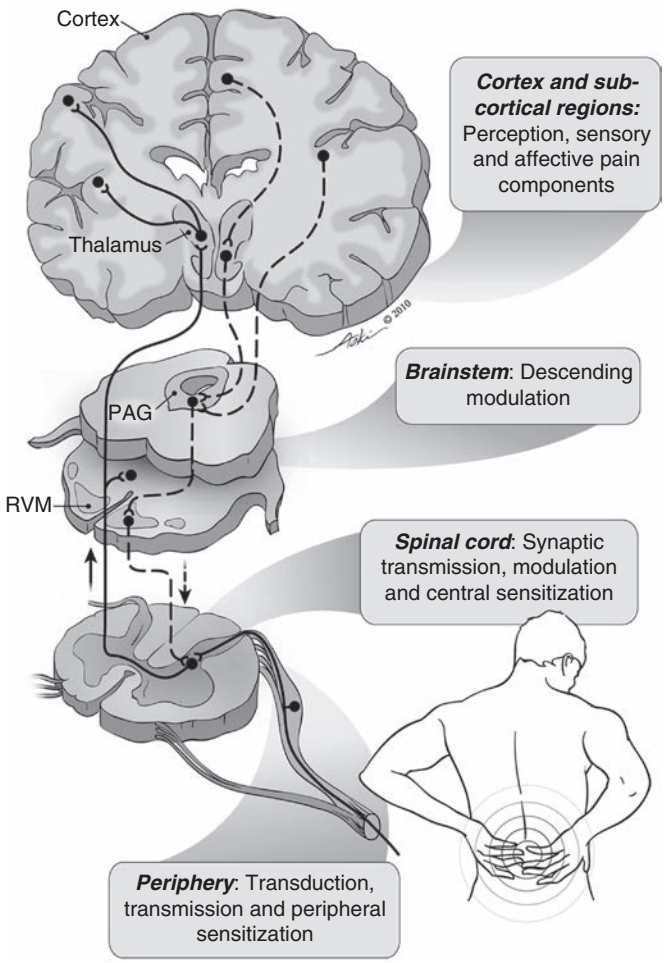

FIG. 1.1 Schematic of pain-signaling mechanisms involved in transduction, transmission, modulation, and perception of pain. Ascending afferent and descending modulatory pathways are shown. *PAG*, Periaqueductal gray; *RVM*, rostral ventromedial medulla.

findings made on cutaneous afferents extend to primary afferents innervating other peripheral tissues. Among cutaneous afferents, three classes of primary afferent fibers can be differentiated.[2,3] The fastest-conducting fibers (>20 m/s) are the large-diameter myelinated A beta (Aβ) fibers. These afferents are activated by nonnociceptive stimuli that evoke the sensation of light touch, pressure, or hair movement. The axons of nociceptive neurons are generally thinly myelinated A delta (Aδ) fibers or unmyelinated C fibers, which conduct between 2 and 20 m/s and less than 2 m/s, respectively. Many nociceptors have the capacity to respond to intense heat, cold, mechanical, and chemical stimuli (i.e., they respond to different stimulus modalities and are therefore "polymodal"). The functional role of the Aδ- and C-fiber nociceptors may be different. The C fibers are the predominant (75%) type of afferent fiber in peripheral nerves. Recordings from C fibers in humans suggest that C-fiber activity is associated with a prolonged burning sensation. In contrast, activation of faster-conducting Aδ fibers evokes a sharp, intense, tingling sensation. The combined activation of these two groups of afferents, such as by an intense brief heat stimulus, results in a dual-pain sensation as Aδ fibers convey the rapid-onset *first pain* sensation, a pricking pain, whereas C fibers mediate the slower-onset, burning *second pain* sensation that follows brief intense heat stimulation to the skin.[4] Combined, Aδ- and C-fiber nociceptors encode and transmit information to the central nervous system (CNS) concerning the intensity, location, and duration of noxious stimuli. Although polymodal nociceptors are the most common type, a functionally distinct and important subgroup of nociceptors is insensitive to mechanical stimuli. These mechanically insensitive nociceptors ("MIAs") likely act as chemonociceptors, and input from these afferents is thought to be crucial for the induction and maintenance of central sensitization.

Nociceptive afferents are further subclassified based on the molecules expressed on their cell surface (e.g., receptors, glycoconjugates), based on the molecules they store and release (e.g., peptides), and based on the enzymes they contain. Although none of these cell markers is completely specific for the peripheral target tissue innervated, the percentage of dorsal root ganglion cells positive for a given marker differs significantly among target tissues. For example, almost all visceral afferents are peptidergic, but only approximately half of the afferents projecting to the skin are,[5] and only a small percentage of the nonpeptidergic afferents, characterized by binding the plant isolectin B4 (IB4) from *Griffonia simplicifolia*,[6] project to muscle.[7,8] Similarly, the central projection areas of peptidergic and nonpeptidergic afferents differ, with peptidergic fibers mainly projecting to lamina I and lamina II outer, and IB4 binding (nonpeptidergic) afferents projecting preferably to lamina II inner (e.g., Silverman and Kruger,[6] but see also Woodbury et al.[9]). Most peptidergic neurons express the tyrosine kinase receptor A (trk A), suggesting that they depend on nerve growth factor (NGF) for survival.[10–12] In contrast, most IB4-positive dorsal root ganglion cells do not express trk A but express one of the glial cell-derived neurotrophic factor (GDNF) family receptors (GDNFRa1–4) together with receptor tyrosine kinase Ret.[13,14] Peptidergic and nonpeptidergic neurons also express different patterns of receptors involved in signal transduction, and they may therefore display different sensitivities to a given stimulus. Thus the P2X3 receptor, which mediates nociceptor excitation by ATP, is primarily expressed in IB4-positive neurons.[15] In contrast, the vanilloid receptor 1 (VR1/TRPV1), which mediates responses to heat, capsaicin, and protons, is expressed in only a minority of IB4-positive cells in mice,[16] and IB4-positive neurons are less responsive to these stimuli than their IB4-negative counterparts.[16–18] The role of these various peptides and receptors, in addition to others, in pain transmission is discussed in greater detail in Chapter 2. Another class of receptors primarily expressed in small primary afferent neurons are mas-related G protein–coupled receptors (Mrgprs). In mice, different Mrgprs are expressed in nonoverlapping neuronal populations, some of which have been linked to mediating specific behavior. For example, MrgprD neurons are thought to mediate nociceptive behavior to mechanical stimuli, whereas neural activity in neurons expressing MrgprA3 induces scratching behavior in response to itch-producing stimuli. In primary afferent nerve fibers, including nociceptors, information on the intensity of a given stimulus is coded by the number of action potentials in a population of primary afferents, with a generally monotonic relationship between the stimulus intensity and the number of impulses generated by afferent

fibers. The sensitivity of nociceptors to different stimuli is not fixed but can change considerably under pathologic conditions. For example, mediators released during inflammation can dramatically decrease the threshold for activation and increase responses to suprathreshold stimuli. This peripheral sensitization of nociceptive afferents is a major contributor to increased pain that can be elicited from a site of injury. In addition to this *primary hyperalgesia* from the injury site, increased pain responses may also be elicited from the surrounding area. This so-called *secondary hyperalgesia* involves mechanisms residing in the CNS and leads to the sensitization of central neurons (i.e., central sensitization).

Voltage-gated sodium channels are crucial for the generation and conduction of action potentials in central and peripheral neurons. The different channel isoforms ($Na_V1.1$-1.9) are broadly classified as tetrodotoxin (TTX) sensitive and TTX insensitive. Among these channels, the TTX-sensitive $Na_V1.7$ isoform and the TTX-insensitive isoforms ($Na_V1.8$, $Na_V1.9$) are of major interest in nociception and pain. Thus loss-of-function mutations in the gene *(SCN9A)* that encodes $Na_V1.7$ lead to congenital insensitivity to pain (CIP)[19] and anosmia.[20] Conversely, gain-of-function mutations in the same gene can lead to severe spontaneous pain episodes in patients, for example, with inherited erythromelalgia (IEM) or extreme paroxysmal pain disorder (for review see Dib-Hajj et al. [21]). Gain-of-function mutations of $Na_V1.7$ have also been observed in patients with small fiber neuropathy.[22] In contrast to $Na_V1.7$, which, in addition to primary afferent fibers, is also expressed in sympathetic nerve fibers and olfactory epithelium, the TTX-insensitive isoforms $Na_V1.8$ and $Na_V1.9$ appear to be selectively expressed in nociceptive afferents. Similar to $Na_V1.7$, gain-of-function mutations in $Na_V1.8$ have been found to contribute to painful peripheral neuropathy,[23] and a gain-of-function mutation for $Na_V1.9$ leads, paradoxically, to CIP.[24] It should be noted that $Na_V1.7$, $Na_V1.8$, and $Na_V1.9$ differ significantly in channel properties, and they contribute differently to cell excitability and action potential generation (for review see Dib-Hajj et al.[25]).

SPINAL MECHANISMS

The first synapse in somatosensory processing of information from the body surface occurs at either the spinal dorsal horn or in the dorsal column nuclei at the spinal cord–brainstem junction.[26] Somatosensory processing for information from the face is similarly processed either in the spinal trigeminal nucleus (pain and temperature) or in the chief sensory nucleus of the trigeminal nerve located in the mid-pons region of the brainstem. Both nociceptive and nonnociceptive fibers provide inputs to both of these initial targets. However, under normal circumstances the dorsal column nuclei and the chief sensory nucleus can be considered to selectively process inputs from large myelinated Aβ fibers related to light touch, whereas the spinal dorsal horn and spinal trigeminal nucleus process inputs of nociceptive Aδ and C fibers. This separation of modalities in the somatosensory system is the basis for the localization of neural lesions through neurologic examination in patients.

Nociceptive primary afferent fibers terminate in a highly ordered way in the spinal dorsal horn on the same side of the body of their origin.[27,28] The dorsal horn is anatomically organized in the form of layers or laminae, as first recognized by Rexed in the cat (Fig. 1.2).[29] The unmyelinated C fibers terminate primarily in the most superficial lamina (I and II outer), whereas the thinly myelinated Aδ fibers end in lamina I, and in laminae III to V. Collaterals of the large myelinated fibers (Aβ) terminate in laminae III to V of the dorsal horn. Lamina I is also known as the *marginal nucleus* and lamina II as the *substantia gelatinosa* of Rolando.

Two predominant types of second-order nociceptive spinal and spinal trigeminal projection neurons have been identified: wide dynamic range (WDR) neurons and nociceptive-specific (NS) neurons. WDR cells are especially concentrated in the deeper laminae of the dorsal horn (III to V), where they receive input from both low-threshold Aβ and nociceptive Aδ and C fibers, and hence are activated by both innocuous and noxious stimuli. However, the responses of WDR cells to these stimuli are graded such that the noxious stimuli evoke a greater response than nonnoxious stimuli. WDR spinal projection neurons (i.e., neurons whose axons terminate in supraspinal targets) have a spontaneous discharge (average rate of approximately 11 Hz in monkeys), and their activity is increased by innocuous cutaneous (average rate of approximately 25 Hz after brushing skin with a hair brush), and noxious mechanical stimulation (approximately 50 Hz after a small arterial clip is applied to the skin) (Fig. 1.3).

In contrast to WDR cells, NS projection cells respond only to noxious stimuli under physiologic conditions. The majority of NS cells are found in the superficial laminae of the dorsal horn (I and outer II). These cells have a lower rate of spontaneous activity than do WDR cells, averaging approximately 3 to 5 Hz. The discharge rates to the noxious stimuli of NS cells are comparable to those of WDR cells, averaging approximately 50 Hz (Fig. 1.4).

The axons of both the WDR and NS second-order neurons cross the midline near the level of the cell body, gather into bundles of ascending fibers in the contralateral, anterolateral spinal region, and then ascend toward targets in the brainstem and diencephalon (Fig. 1.5). The conduction velocity of the WDR cells is usually faster than that of the NS cells (approximately 30 m/s vs. 12 m/s). In addition, the axons of the NS cells that largely arise from laminae I of the dorsal horn and those of the WDR cells arising primarily from laminae III to V tend to run in slightly different positions in the anterolateral spinal funiculus. In the anterolateral spinal column, the NS cell axons are found in the dorsal medial region, whereas axons of WDR cells are more concentrated in the ventral lateral region.

SPINAL MODULATION

The concept of modulation of noxious inputs at spinal levels was highlighted by the gate control theory of Melzack and Wall.[30] This theory suggested that input along low-threshold (Aβ) fibers inhibits the responses of WDR cells to nociceptive input. The theory was offered as an explanation for the efficacy of transcutaneous electrical stimulation for pain relief. Subsequent studies have identified intrinsic spinal neurons that release a plethora of neurotransmitters in the spinal cord that play a role in the modulation of nociceptive impulses. Furthermore, a number of inputs

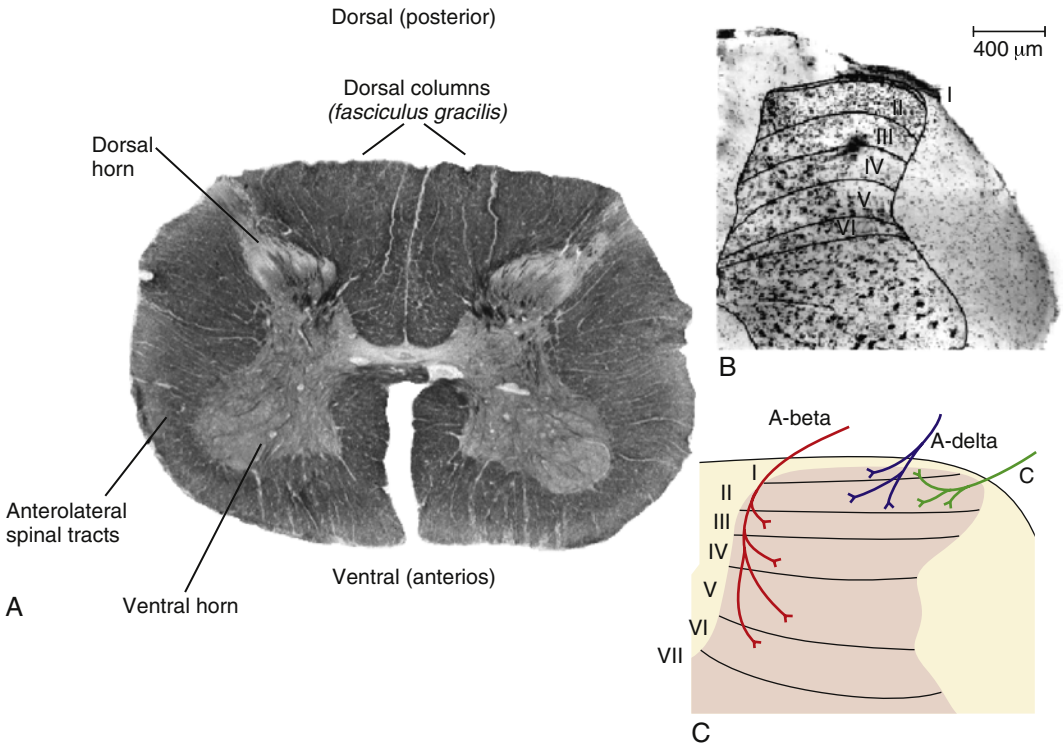

FIG. 1.2 Histologic sections and schematic diagrams of the spinal dorsal horn. (A) Human lumbar spinal cord is labeled to show the relationship between the major spinal somatosensory structures. (B) From rat spinal cord. The outer heavy lines show the boundary of the spinal gray matter, and the inner heavy lines show the boundaries of Rexed laminae. These boundaries are established by the histologic characteristics of each zone, and the layers are identified by the numerals at the right of the dorsal horn boundary. (C) Pattern of primary afferent innervation to the nonhuman primate spinal dorsal horn. The large myelinated (Aβ) fibers segregate to the dorsal aspect of an entering rootlet and then course medially in the dorsal horn and terminate in layers III to V. The small myelinated (Aδ) fibers and C fibers, which carry nociceptive information, segregate ventrally in the entering roots, course laterally in the dorsal horn, and then largely terminate in the more superficial layers (I and II) of the dorsal horn.

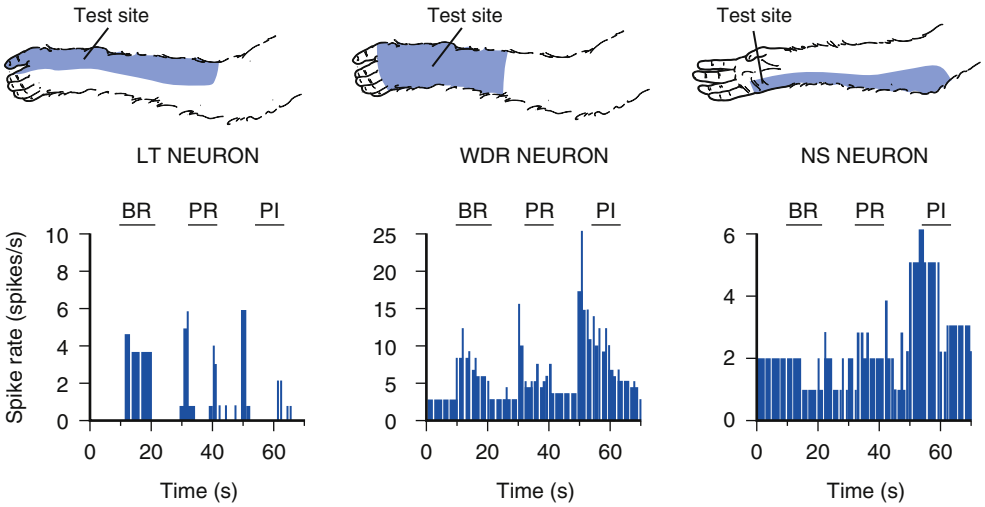

FIG. 1.3 Rate histograms show responses of primate spinothalamic tract neurons representative of low threshold (LT), wide dynamic range (WDR), and nociceptive-specific (NS) classes. The responses of these cells were evoked by application of a series of mechanical stimuli of graded intensity to multiple sites across the receptive field for each cell. The times and sites of each stimulus application are indicated by the lines and labels at the top of each histogram. The brush stimulus (BR) was provided by a soft, camel-hair brush, whereas a large arterial clip was used to produce innocuous pressure (PR), and a small arterial clip was used to produce a noxious pinch (PI) sensation. The WDR cell in the center shows responses that are graded with the intensity of the stimuli. The NS neuron at the right shows no significant responses to any stimuli but the most intense, whereas the LT neuron on the left responds to innocuous brushing of the skin alone (the transient responses with the application and removal of the arterial clips are due to the touch stimuli provided at contact). The diagrams of the hind limbs show the receptive field locations of each neuron *(shaded region)* and the site on the skin where each of the mechanical stimuli was applied (test site).

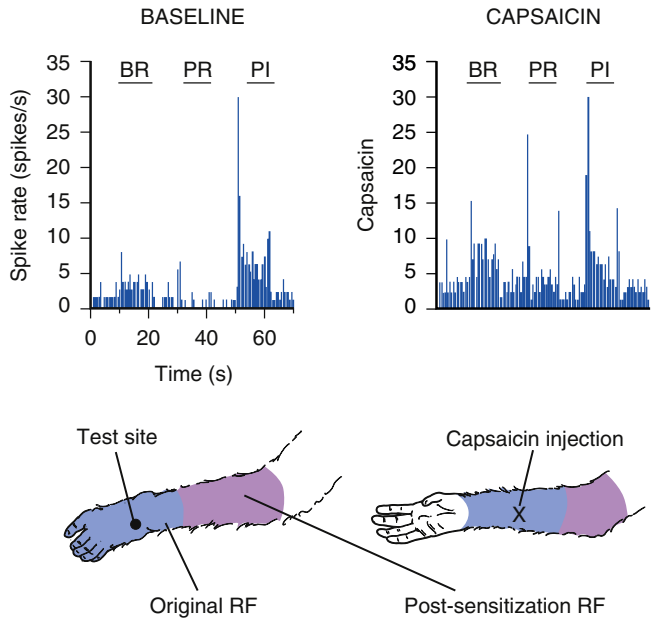

FIG. 1.4 Rate histograms show the background activity and responses of a representative wide dynamic range, spinothalamic tract neuron to mechanical stimulation of the hind limb before and after sensitization by an intradermal injection of capsaicin. The baseline responses to the mechanical stimuli are shown on the left, and the matching records after capsaicin are shown on the right. The mechanical stimuli were applied to the spot shown on the drawing of the leg at the bottom. The *X* shows the site at which capsaicin was delivered. The *blue area* shows the receptive field during the baseline recordings, whereas the *purple area* shows the expansion in the receptive field induced by capsaicin. *BR*, Brush stimulus; *PI*, pinch; *PR*, pressure; *RF*, receptive field.

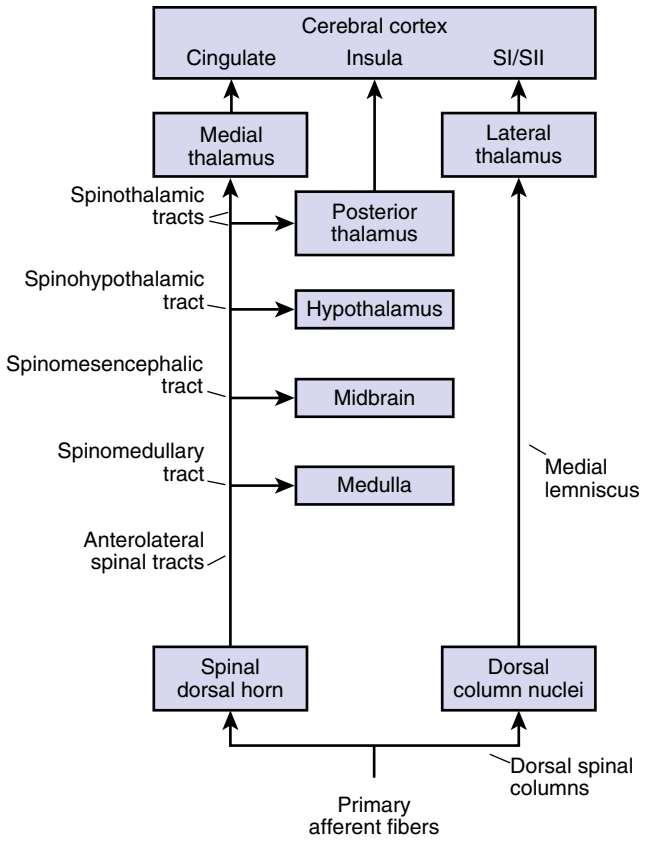

FIG. 1.5 Schematic diagram summarizing the central nociceptive pathways. Each box represents the discrete anatomic locations at which noxious stimuli are processed and/or registered. The lines indicate the neural pathways that interconnect each of the anatomic locations.

to the dorsal horn from various brainstem sites have been shown to also modulate peripheral inputs, as well as outputs, of intrinsic cells.[31,32] Both types of modulation, that arising in the local network of cells at the spinal levels as well as that from the descending inputs, can result in either augmented or inhibited output from spinal cord nociceptive neurons. It is the combined effects of spinal excitatory and inhibitory systems that determine what messages are delivered to the higher levels of the CNS.

A special type of spinal modulation that is observed under certain circumstances is known as *central sensitization*.[33] In this phenomenon, the capacity for transmission in the nociceptive system is changed or shows neuronal plasticity. The result of this plasticity is that after a noxious stimulus of sufficient intensity and duration, such as a surgical incision, the coding of pain-signaling neurons for a given stimulus may be increased. One example of central plasticity is the phenomenon of *wind-up*, whereby repeated stimulation of C fibers at intervals of 0.5 to 1 Hz results in a progressive increase in the number of discharges evoked by each volley.[34] In addition to an increase in discharges evoked by a given stimulus, sensitized spinal neurons also show an expansion of receptive field size and an increase in spontaneous discharge rate. WDR cells tend to become sensitized more readily than NS cells. However, in circumstances in which NS cells do show sensitization, they often acquire novel responsiveness to innocuous stimuli and hence could be recategorized as WDR neurons. The neurochemistry of central sensitization is discussed in Chapter 2. Better understanding of the pharmacology of this and other types of plasticity will have profound consequences in the development of new analgesic pharmacotherapies.

A different form of spinal modulation is exerted by glial cells (microglia, astrocytes, and oligodendrocytes). Microglia, the macrophages of the CNS, and astrocytes become activated after different insults including nerve injury, inflammation, or chronic opioid therapy. Upon activation, these cells can release a number of substances, including cytokines, inflammatory mediators, and growth factors, which then can affect neuronal function in multiple ways (for review see Ji et al.[35] and Tiwari et al.[36]). After nerve injury, for example, activated microglia release brain-derived neurotrophic factor (BDNF), which leads to the downregulation of potassium-chloride cotransporter KCC2 in lamina I neurons. As a consequence, a shift in transmembrane anion gradient can occur such that normally inhibitory input becomes excitatory.[37] Although animal studies have provided substantial evidence for a role of glia in chronic pain, it should be noted that the contribution and role of glia in chronic pain states in humans are less clear.

SUPRASPINAL MECHANISMS

Supraspinal structures involved in somatosensory processing include brainstem, diencephalic, and cortical sites.[38] There are two sets of somatosensory inputs to the brainstem and diencephalon. First, many axons and axon collaterals of the spinal projection neurons that ascend in the anterolateral spinal quadrant depart this ascending tract to terminate in a number of nuclei of the brainstem and midbrain (see Figs. 1.5 and 1.6). These target sites include

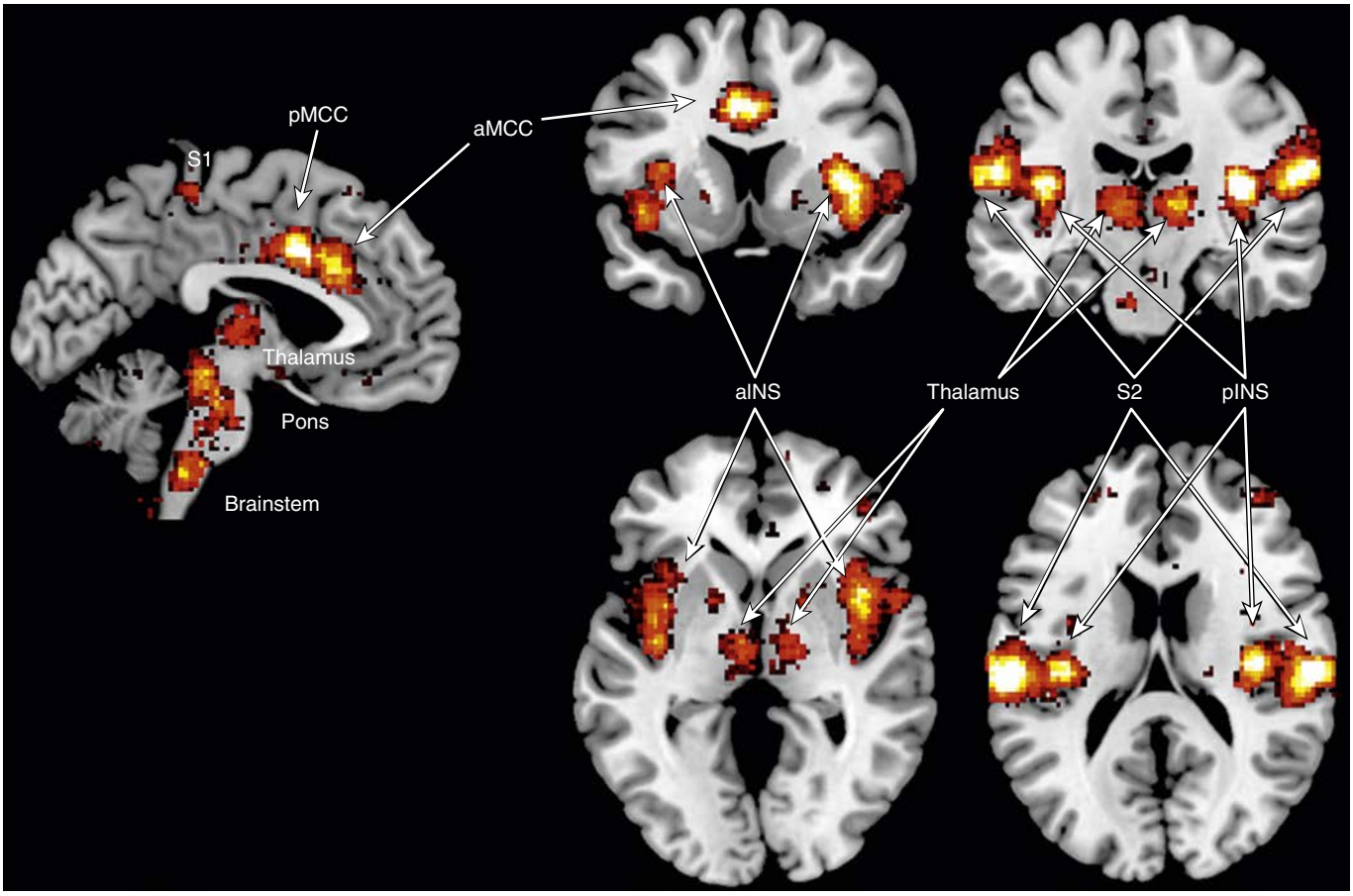

FIG. 1.6 Brain regions involved in pain signaling, based on imaging studies. Meta-analytic reverse inference statistical map of 420 fMRI studies with the term "pain" created on Neurosynth.org. *a/pINS*, Anterior/posterior insula; *a/pMCC*, anterior/posterior midcingulate cortex; *PAG*, periaqueductal gray; *S1/2*, primary/secondary somatosensory cortex. *(Courtesy of Dr. David A. Seminowicz.)*

brainstem autonomic regulatory sites that influence cardiovascular and respiratory functions, whereas in the midbrain there are multiple inputs to centers from which both descending and ascending (e.g., to thalamus) modulation of somatosensory processing is evoked. The remainder of the so-called anterolateral system fibers continue through the brainstem and midbrain to terminate in diencephalic structures, including the hypothalamus and posterior, lateral, and medial regions of the thalamus (see Figs. 1.5 and 1.6).

The second set of somatosensory inputs to the brainstem includes those primary afferent fibers that ascend in the dorsal (posterior) columns of the spinal cord to form their first synapse at the dorsal column nuclei. These inputs are organized so that the fibers from the lower extremities synapse most medially in the nucleus gracilis and inputs from the upper extremities synapse laterally in the nucleus cuneatus. The trunk is represented in regions of both nuclei. Comparative inputs from the face are processed in the chief sensory nucleus of the trigeminal nerve located at the origin site of cranial nerve five in the midpons of the brainstem. The axons of the second-order cells in the dorsal column nuclei cross the midline and form the medial lemniscus on the contralateral side of the brainstem. These fibers then ascend through the brainstem and midbrain, acquiring the functionally related fibers from the trigeminal nerve as they pass and continue on to provide the second somatosensory input to the diencephalon as they terminate in the ventral posterior lateral (VPL) nucleus (inputs from the body) and ventral posterior medial (VPM) nucleus (inputs from the face) of the thalamus.

The somatosensory inputs to the cortex include the third-order projections from thalamic somatosensory relay neurons of VPL and VPM as well as third- (and higher-) order neurons projecting from brainstem and midbrain relay neurons.[39,40] Some of these projections are highly organized and quite specific. For example, the cells in the core of VPL that receive inputs from the dorsal column–medial lemniscus fibers project to cortical areas SI and SII. The neurons in the posterior region of the lateral thalamus that receive inputs from the anterolateral system project to SII and the retroinsular areas of cortex, whereas medial thalamic nuclei ultimately project to the anterior cingulate cortex. Similarly, somatosensory relay neurons of the midbrain parabrachial nucleus project specifically to the amygdaloid nucleus of the neocortex. On the other hand, other third-order projections into cortex are quite diffuse. Outputs from cells of the brainstem reticular activating system that receive somatosensory inputs from the spinoreticular tract, for example, project throughout the neocortex.

In addition to peripheral and spinal mechanisms of nociceptive processing and modulation, there are several cortical regions that consistently have been shown to be involved

in acute and chronic pain states. Although the exact brain areas included in what has been coined the "pain matrix" have been the focus of debate, the primary and secondary somatosensory cortices, insula, anterior cingulate cortex, prefrontal cortex, and several nuclei of the thalamus have consistently been shown to be active in imaging studies of acute and chronic pain states (see Fig. 1.6). In addition, pharmacologically induced analgesia has been shown to have effects in these brain regions. The "pain matrix" has further been categorized as comprising the lateral pathway, which encodes for the sensory-discriminative aspect of pain perception, and the medial pathway, which encodes for the affective component of pain perception. Brain structures involved in the affective component of pain processing are required for encoding the unpleasant and aversive aspects of pain, which is critical for self-preservation. A case study of several patients with unilateral ischemic damage to the insular cortex exhibited pain *asymbolia*, as evidenced by a lack of or inappropriate emotional response to multiple painful stimuli applied over the entire body. Moreover, these patients failed to learn appropriate escape or protective responses in response to the painful stimuli.[41] Another example of the role of cortical structures in the experience of pain is the placebo analgesic effect. Previous studies have shown that the placebo effect is at least partially mediated by activation of the endogenous opioid system, and μ-opioid receptors are highly localized within structures of the pain matrix.[42,43] Studies using positron emission tomography and the selective μ-opioid radiotracer[11] [^{11}C] carfentanil have shown that the placebo-mediated activation of the endogenous opioid system is predominantly located in the pain matrix structures, such as the anterior cingulate, prefrontal cortex, insula, medial thalamus, amygdala, and periaqueductal gray (PAG).[44,45]

SUPRASPINAL MODULATION OF NOCICEPTION

Several lines of research have clearly indicated that plasticity and modulation of somatosensory signaling occur at brainstem, midbrain, and diencephalic levels. Examples of plasticity of responses of dorsal column neurons after intradermal injection of the irritant capsaicin have been documented in the rat and monkey. Similarly, with the development of acute inflammation and after deafferentation, neurons of the thalamus alter their patterns of spontaneous discharge so that a large increase in bursting of these cells is observed. Ascending modulation from the brainstem dorsal raphe nucleus also influences signaling of thalamic neurons.

Descending modulation of nociception at the supraspinal level is a well-established phenomenon that can have both inhibitory and facilitatory effects on neurons in the dorsal horn. This modulation is important for the attenuation of acute pain, and the facilitatory aspect has been implicated in the establishment and maintenance of chronic pain states. There are many different sites and pathways involved in descending modulation. Highlighting the complexity of this phenomenon, the vast majority of these anatomic sites have been shown to have inhibitory and facilitatory effects. The best characterized pathway is the PAG and rostral ventromedial medulla (RVM) pathway. The PAG and RVM receive descending projections from a variety of cortical and limbic sites known to be involved in the affective component of pain processing, such as the anterior cingulate cortex, amygdala, and prefrontal cortex. Activation of these structures results in pronociceptive or antinociceptive effects and requires the PAG and RVM.[46,47] The PAG has few direct projections to the spinal cord and instead projects to the RVM, which sends either inhibitory or excitatory impulses to nociceptive projection and WDR neurons in the superficial and deep layers of the dorsal horn of the spinal cord.

It is hypothesized that the RVM is able to facilitate both inhibitory and facilitatory effects on the dorsal horn via different types of neurons termed "ON" and "OFF" cells.[48] These contrasting cell types have distinctly different functional characteristics. OFF cells are tonically active except during nociceptive input and activated by known analgesics, such as morphine. In contrast, ON cells become more active during nociceptive input and are inhibited by morphine.[48–50] It is generally accepted that OFF cells are required for descending inhibition.

Although the evidence supporting the role of ON cells in descending facilitation is mixed, several studies have shown that activation of ON cells within the RVM induces hyperalgesia. For example, the peptide cholecystokinin (CCK) induces mechanical and thermal hyperalgesia when directly injected into the RVM, and this direct CCK administration has been shown to preferentially activate ON cells.[51,52] In addition, ON cells are activated and OFF cells suppressed in models of chronic pain.[53,54] Descending facilitation via ON cell activation is thought to induce hyperalgesia by upregulating spinal dynorphin, which is linked to the increased release of excitatory neurotransmitters from primary afferent neurons, which can lead to central sensitization and chronic pain.[55] ON cells activation and the subsequent cascade of facilitatory effects in the spinal cord are also implicated in opioid-induced hyperalgesia resulting from chronic opioid exposure.[56,57]

Studies indicate that in addition to functional changes in neurons, microglia and astrocytes may also play an important role in the central sensitization process. Other central neuroplastic changes that may contribute to neuropathic pain states include deafferentation hyperactivity that may occur following spinal cord or avulsion injuries, loss of large-fiber afferent inhibition, reorganization of central connections of primary afferent fibers, and excitatory descending modulatory mechanisms. Central and, to a lesser extent, peripheral sensitization are considered to be the prime culprits responsible for pain induced by innocuous stimuli *(allodynia)* and increased pain to normally noxious stimuli *(hyperalgesia)*, which are commonly observed in neuropathic pain states.

KEY POINTS

- The processes resulting in a noxious stimulus-inducing pain are transduction, transmission, modulation, and perception.
- Nociceptors in the periphery respond to intense heat, cold, mechanical, or chemical stimuli and encode the intensity, location, and duration of noxious stimuli.
- The dorsal horn is anatomically organized in laminae. Unmyelinated C fibers terminate in Rexed laminae I and II, and large myelinated fibers terminate in laminae III to V.

- Two types of second-order nociceptive spinal and spinal trigeminal projection neurons are wide dynamic range (WDR) and nociceptive specific (NS). WDR cells receive input from both Aβ and nociceptive (C and Aδ) fibers.
- The somatosensory system is composed of two main signaling channels. The anterolateral system is the primary pain-signaling channel. In contrast, the dorsal column–medial lemniscal system is primarily a high-speed, very discrete signaling channel for innocuous stimuli.
- Several cortical regions, referred to as the "pain matrix," have been shown to be involved in acute and chronic pain states. These regions include the primary and secondary somatosensory cortices, insula, anterior cingulate cortex prefrontal cortex, amygdala, and several nuclei of the thalamus.
- Descending modulation of nociception from supraspinal level sites can have both inhibitory and facilitatory effects on spinal dorsal horn neuronal activity. Descending modulation may be important for the attenuation of acute pain. However, descending facilitatory activity has been implicated in the establishment and maintenance of chronic pain states.
- Derangements can occur in both the ascending and descending signaling systems at any and all levels that result in the generation of chronic pain.

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