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20

Pain

According to the International Association for the Study of Pain, pain is an unpleasant sensation and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. Pricking, burning, aching, stinging, and soreness are among the most distinctive of all the sensory modalities. As with the other somatosensory modalities—touch, pressure, and position sense—pain serves an important protective function, alerting us to injuries that require evasion or treatment. In children born with insensitivity to pain, severe injuries often go unnoticed and can lead to permanent tissue damage. Yet pain is unlike other somatosensory modalities, or vision, hearing, and smell, in that it has an urgent and primitive quality, possessing a powerful emotional component.

The perception of pain is subjective and is influenced by many factors. An identical sensory stimulus can elicit quite distinct responses in the same individual under different conditions. Many wounded soldiers, for example, do not feel pain until they have been removed from the battlefield; injured athletes are often not aware of pain until a game is over. Simply put, there are no purely "painful" stimuli, sensory stimuli that invariably elicit the perception of pain in all individuals. The variability of the perception of pain is yet another example of a principle that we have encountered in earlier chapters: Pain is not the direct expression of a sensory event but rather the product of elaborate processing in the brain of a variety of neural signals.

When pain is experienced, it can be acute, persistent, or, in extreme cases, chronic. Persistent pain characterizes many clinical conditions and is usually the reason that patients seek medical attention. In contrast, chronic pain appears to have no useful purpose; it only makes patients miserable. Pain's highly individual and subjective nature is one of the factors that make it so difficult to define objectively and to treat clinically.

In this chapter, we discuss the neural processes that underlie the perception of pain in normal individuals and explain the origins of some of the abnormal pain states that are encountered clinically.

Noxious Insults Activate Thermal, Mechanical, and Polymodal Nociceptors

Many organs in the periphery, including skin and subcutaneous structures such as joints and muscles, possess specialized sensory receptors that are activated by noxious insults. Unlike the specialized somatosensory receptors for light touch and pressure, most of these *nociceptors* are simply the free nerve endings of primary sensory neurons. There are three main classes of nociceptors—thermal, mechanical, and polymodal—as well as a more enigmatic fourth class, termed silent nociceptors.

Thermal nociceptors are activated by extremes in temperature, typically greater than 45°C (115°F) or less than 5°C (41°F). They include the peripheral endings of small-diameter, thinly myelinated Aδ axons that conduct action potentials at speeds of 5 to 30 m/s and unmyelinated C-fiber axons that conduct at speeds less than 1.0 m/s (Figure 20–1A). *Mechanical nociceptors* are activated optimally by intense pressure applied to the skin; they too are the endings of thinly myelinated Aδ axons. *Polymodal nociceptors* can be activated by high-intensity mechanical, chemical, or thermal (both hot and cold) stimuli. This class of nociceptors consists predominantly of unmyelinated C fibers (Figure 20–1A).

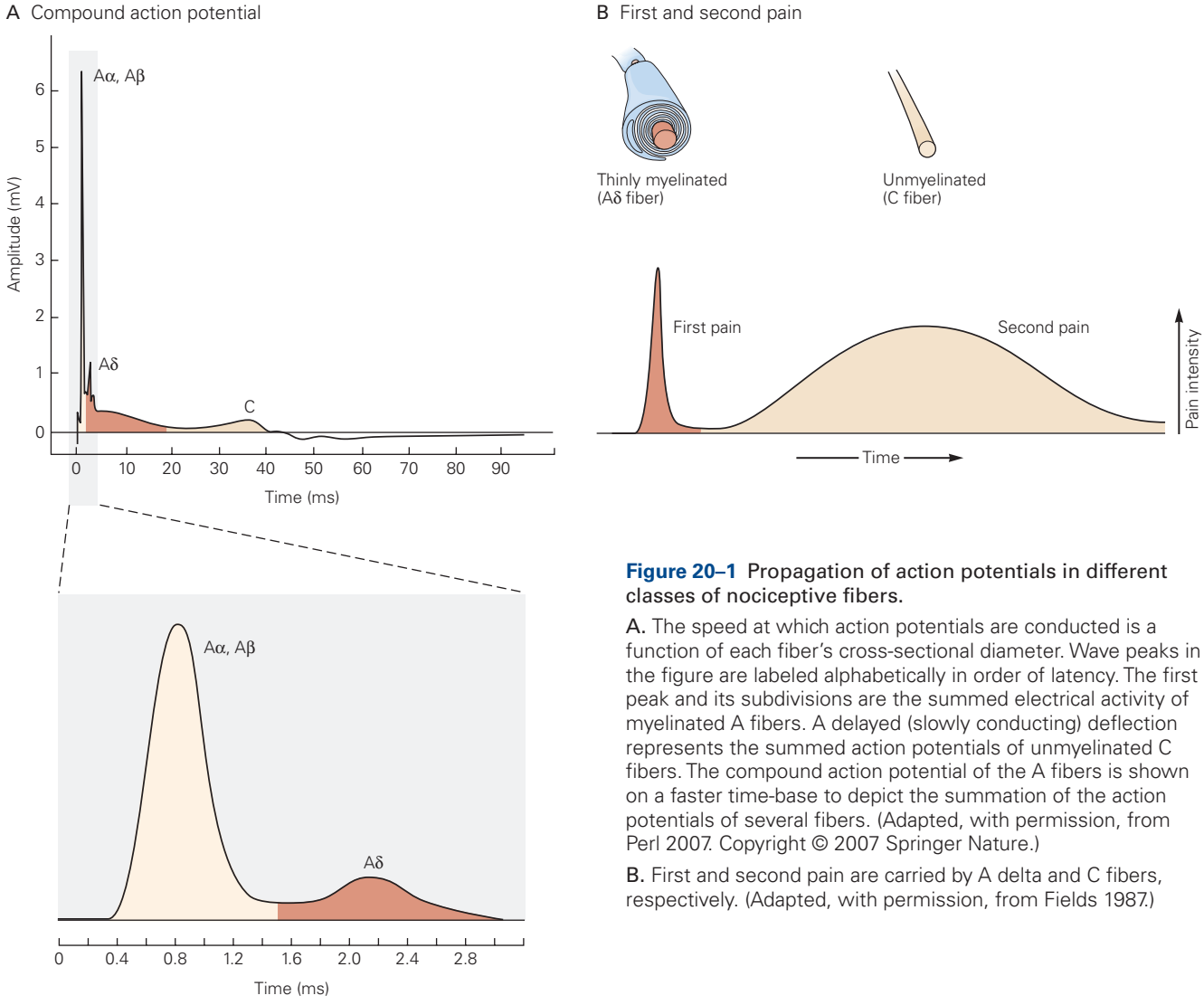

Figure 20–1 Propagation of action potentials in different classes of nociceptive fibers.

A. The speed at which action potentials are conducted is a function of each fiber's cross-sectional diameter. Wave peaks in the figure are labeled alphabetically in order of latency. The first peak and its subdivisions are the summed electrical activity of myelinated A fibers. A delayed (slowly conducting) deflection represents the summed action potentials of unmyelinated C fibers. The compound action potential of the A fibers is shown on a faster time-base to depict the summation of the action potentials of several fibers. (Adapted, with permission, from Perl 2007. Copyright © 2007 Springer Nature.)

B. First and second pain are carried by A delta and C fibers, respectively. (Adapted, with permission, from Fields 1987.)

These three classes of nociceptors are widely distributed in skin and deep tissues and are often co-activated. When a hammer hits your thumb, you initially feel a sharp pain ("first pain") followed by a more prolonged aching and sometimes burning pain ("second pain") (Figure 20–1B). The fast sharp pain is transmitted by Aδ fibers that carry information from damaged thermal and mechanical nociceptors. The slow dull pain is transmitted by C fibers that convey signals from polymodal nociceptors.

Silent nociceptors are found in the viscera. This class of receptors is not normally activated by noxious stimulation; instead, inflammation and various chemical agents dramatically reduce their firing threshold. Their activation is thought to contribute to the emergence of secondary hyperalgesia and central sensitization, two prominent features of chronic pain.

Noxious stimuli depolarize the bare nerve endings of afferent axons and generate action potentials that are propagated centrally. How is this achieved? The membrane of the nociceptor contains receptors that convert the thermal, mechanical, or chemical energy of noxious stimuli into a depolarizing electrical potential. One such protein is a member of a large family of so-called transient receptor potential (TRP) ion channels. This receptor-channel, TRPV1, is expressed selectively by nociceptive neurons and mediates the pain-producing actions of capsaicin, the active ingredient of hot peppers and many other pungent chemicals. The TRPV1 channel is also activated by noxious thermal stimuli, with a threshold for activation around 45°C, the temperature that provokes heat pain. Importantly, TRPV1-mediated membrane currents are enhanced by a reduction in pH, a characteristic of the chemical milieu of inflammation.

Other receptor-channels of the TRP channel family are expressed by nociceptors and underlie the perception of a wide range of temperatures, from cold to intense heat. Of particular interest is TRPM8, a menthol-responsive and cold-sensing channel that likely mediates the extreme cold hypersensitivity produced by many chemotherapeutic drugs (such as oxaliplatin). TRPA1 responds to a variety of irritants, from mustard oil to garlic and even air pollutants (Figure 20–2). Very recently, a family of mechanical transducers (Piezo1 and Piezo2) was described (Chapter 18). These channels may be important contributors to the mechanical hypersensitivity that is a prominent feature of many chronic pain conditions.

In addition to this constellation of TRP channels, sensory neurons express many other receptors and ion channels involved in the transduction of peripheral stimuli. Nociceptors selectively express many different voltage-gated Na^{2+} channels, which are the target of local anesthetics that so effectively block pain. (Think of the dentist who can completely eliminate tooth pain.) Nociceptors express Na^{2+} channels that are sensitive or resistant to tetrodotoxin (TTX). One type of TTX-sensitive channel, Nav1.7, is a key molecular mechanism in the perception of pain in humans, as revealed in the rare individuals who have a loss-of-function mutation in the corresponding *SCN9A* gene. These individuals are insensitive to pain but are otherwise healthy and exhibit normal sensory responses to touch, temperature, proprioception, tickle, and pressure. A second class of mutations in the *SCN9A* gene result in hyperexcitability of nociceptors; individuals with these mutations exhibit an inherited condition called erythromelalgia, in which there is intense, ongoing burning pain of the extremities, accompanied by profound redness (vasodilation). Since Nav1.7, unlike many other voltage-gated Na^{+} channels, is not found in the central nervous system, pharmaceutical companies are developing antagonists that will hopefully provide a novel approach to regulating pain processing without the adverse side effects that can occur with systemic administration of lidocaine, which blocks all subtypes of voltage-gated Na^{+} channels.

Nociceptors also express an ionotropic purinergic receptor, PTX3, which is activated by adenosine triphosphate (ATP) released from peripheral cells after tissue damage. In addition, they express members of the Mas-related G protein–coupled receptor (Mrg) family, which are activated by peptide ligands and serve to sensitize nociceptors to other chemicals released in their local environment (see Figure 20–7). Subsets of these unmyelinated afferents also include receptor-channels that respond to a variety of itch-provoking substances, including the pruritogens histamine and chloroquine. It follows that these receptors and channels are attractive targets for the development of drugs selective for sensory neurons responsive to pain and itch-provoking stimuli.

Uncontrolled activation of nociceptors is associated with several pathological conditions. Two common pain states that result from alterations in nociceptor activity are allodynia and hyperalgesia. Patients with *allodynia* feel pain in response to stimuli that are normally innocuous: a light stroking of sunburned skin, the movement of joints in patients with rheumatoid arthritis, and even the act of getting out of bed in the morning after a vigorous workout. Nevertheless, patients with allodynia do not feel pain constantly; in the absence of a peripheral stimulus, there is no pain. In contrast, patients with *hyperalgesia*—an exaggerated

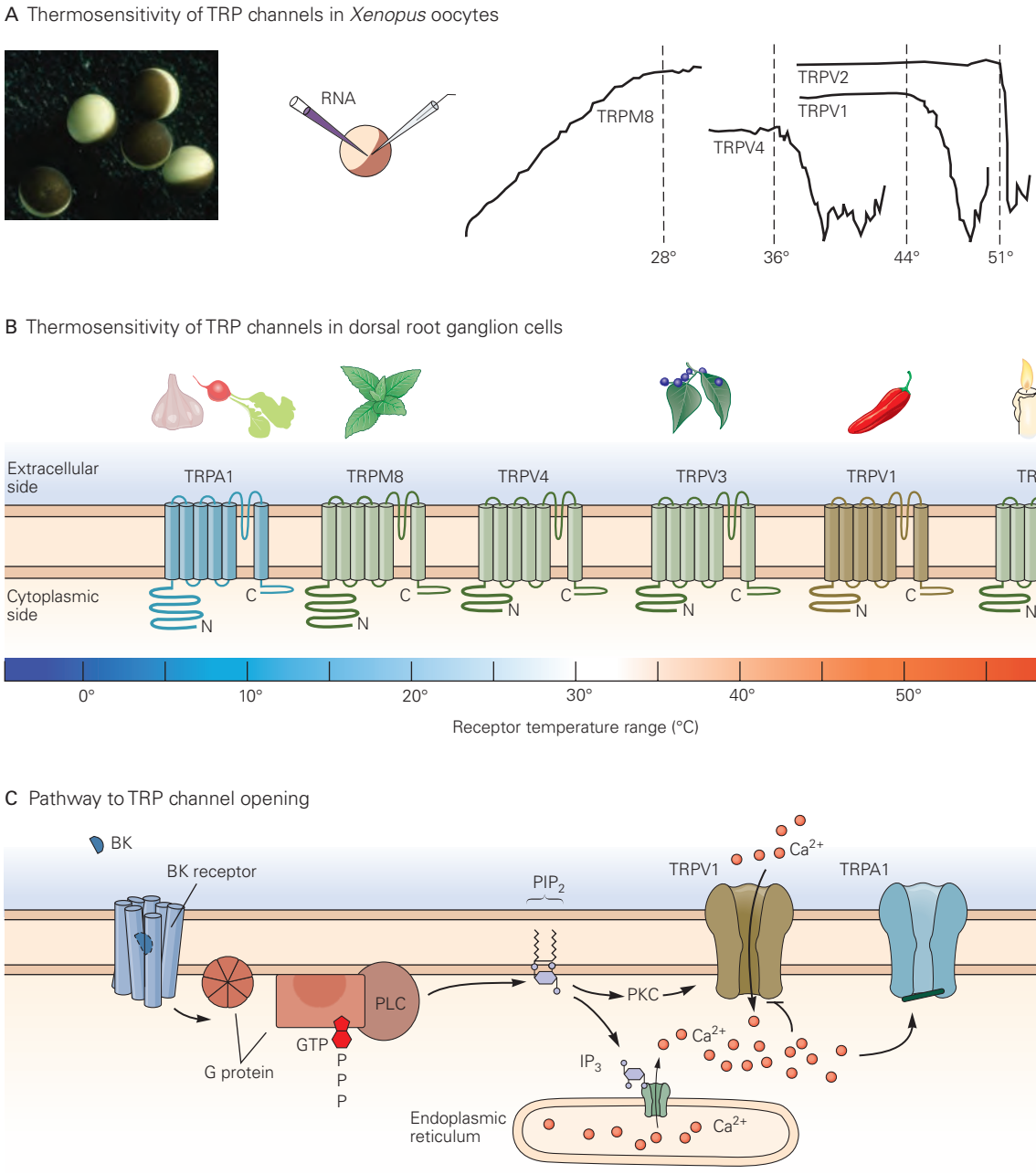

Figure 20–2 Transient receptor potential ion channels in nociceptive neurons.

A. Recordings from *Xenopus* oocytes injected with mRNA encoding transient receptor potential (**TRP**) channels reveal the thermosensitivity of the channels. The temperature (centigrade) at which a specific TRP channel is activated is shown by the downward deflection of the recording. (Photograph on left reproduced, with permission, from Erwin Siegel 1987; traces on the right reproduced, with permission, from Tominaga and Caterina 2004.)

B. Temperature response profiles of different TRP channels expressed by dorsal root ganglion neurons. (Adapted, with permission, from Jordt, McKemy, and Julius 2003; Dhaka, Viswanath, and Patapoutian 2006.)

C. Bradykinin (**BK**) binds to G protein–coupled receptors on the surface of primary afferent neurons to activate phospholipase C (**PLC**), leading to the hydrolysis of membrane phosphatidylinositol bisphosphate (PIP_2), the production of inositol 1,4,5-trisphosphate (IP_3), and the release of Ca^{2+} from intracellular stores. Activation of protein kinase C (**PKC**) regulates TRP channel activity. The TRPV1 channel is sensitized, leading to channel opening and Ca^{2+} influx. (Source: Bautista et al. 2006.)

response to noxious stimuli—typically report persistent pain in the absence of sensory stimulation.

Persistent pain can be subdivided into two broad classes, nociceptive and neuropathic. *Nociceptive pain* results from the activation of nociceptors in the skin or soft tissue in response to tissue injury, and it usually occurs with inflammation. Sprains and strains produce mild forms of nociceptive pain, whereas arthritis or a tumor that invades soft tissue produce a much more severe nociceptive pain. Typically, nociceptive pain is treated with nonsteroidal anti-inflammatory drugs (NSAIDS; see later discussion) or, when severe, with opiates such as morphine.

Neuropathic pain results from direct injury to nerves in the peripheral or central nervous system, and is often accompanied by a burning or electric sensation. Neuropathic pains include complex regional pain syndrome, which can follow even very minor damage to a limb peripheral nerve; post-herpetic neuralgia, the severe pain experienced by many patients after a bout of shingles; or trigeminal neuralgia, an intense, shooting pain in the face that results from an as yet unknown pathology of the trigeminal nerve. Other neuropathic pains include phantom limb pain, which can occur after limb amputation (see Figure 20–14). In some instances, spontaneous, ongoing, often burning pain can even occur without a peripheral stimulus, a phenomenon termed *anesthesia dolorosa*. This syndrome can be triggered following attempts to treat trigeminal neuralgia by ablating trigeminal sensory neurons. Neuropathic pains do not respond to NSAIDS and are generally poorly responsive to opiates. Finally, lesions of the central nervous system, for example, in multiple sclerosis, after stroke, or after spinal cord injury, can also result in central neuropathic pain states. Since loss of inhibitory controls (as occurs in epilepsy) is an important contributor to neuropathic pain, the first-line therapy for neuropathic pain, not surprisingly, involves anticonvulsants, notably the gabapentinoids. (The reference to γ-aminobutyric acid [GABA] was based on a structural similarity of gabapentin to GABA. However, gabapentin in fact exerts its action by binding to the $\alpha_2\delta$-subunit of voltage-gated Ca^{2+} channels, ultimately decreasing neurotransmitter release.)

Signals From Nociceptors Are Conveyed to Neurons in the Dorsal Horn of the Spinal Cord

The sensation of noxious stimuli arises from signals in the peripheral axonal branches of nociceptive sensory neurons whose cell bodies are located in dorsal root ganglia. The central branches of these neurons terminate in the spinal cord in a highly orderly manner. Most terminate in the dorsal horn. Primary afferent neurons that convey distinct sensory modalities terminate in different laminae (Figure 20–3B) such that there is a tight link between the anatomical organization of dorsal horn neurons, their receptive properties, and their function in sensory processing.

Many neurons in the most superficial lamina of the dorsal horn, termed *lamina I* or the *marginal layer*, respond to noxious stimuli conveyed by Aδ and C fibers. Because they respond selectively to noxious stimulation, they have been called *nociceptive-specific neurons*. This set of neurons projects to the midbrain and thalamus. A second class of lamina I neurons receives input from C fibers that are activated selectively by cool stimuli. Other classes of lamina I neurons respond in a graded fashion to both innocuous and noxious mechanical stimulation and thus are termed *wide dynamic range neurons*.

Lamina II, the substantia gelatinosa, is a densely packed layer that contains many different classes of local interneurons, some excitatory and others inhibitory. Some of these interneurons respond selectively to pain-provoking inputs, whereas others are selectively activated by itch-provoking stimuli. Laminae III and IV contain a mixture of local interneurons and supraspinal projection neurons. Many of these neurons receive input from Aβ afferent fibers that respond to innocuous cutaneous stimuli, such as deflection of hairs and light pressure. Lamina V contains neurons that respond to a wide variety of noxious stimuli and project to the brain stem and thalamus. These neurons receive direct inputs from Aβ and Aδ fibers and, because their dendrites extend into lamina II, are also innervated by C-fiber nociceptors (Figure 20–3B).

Neurons in lamina V also receive input from nociceptors in visceral tissues. The convergence of somatic and visceral nociceptive inputs onto individual lamina V neurons provides one explanation for a phenomenon called "referred pain," a condition in which pain from injury to a visceral tissue is perceived as originating from a region of the body surface. Patients with myocardial infarction, for example, frequently report pain from the left arm as well as the chest (Figure 20–4). This phenomenon occurs because a single lamina V neuron receives sensory input from both regions, and thus a signal from this neuron does not inform higher brain centers about the source of the input. As a consequence, the brain often incorrectly attributes the pain to the skin, possibly because cutaneous inputs predominate. Another anatomical explanation for instances of referred pain is that the axons of nociceptive sensory

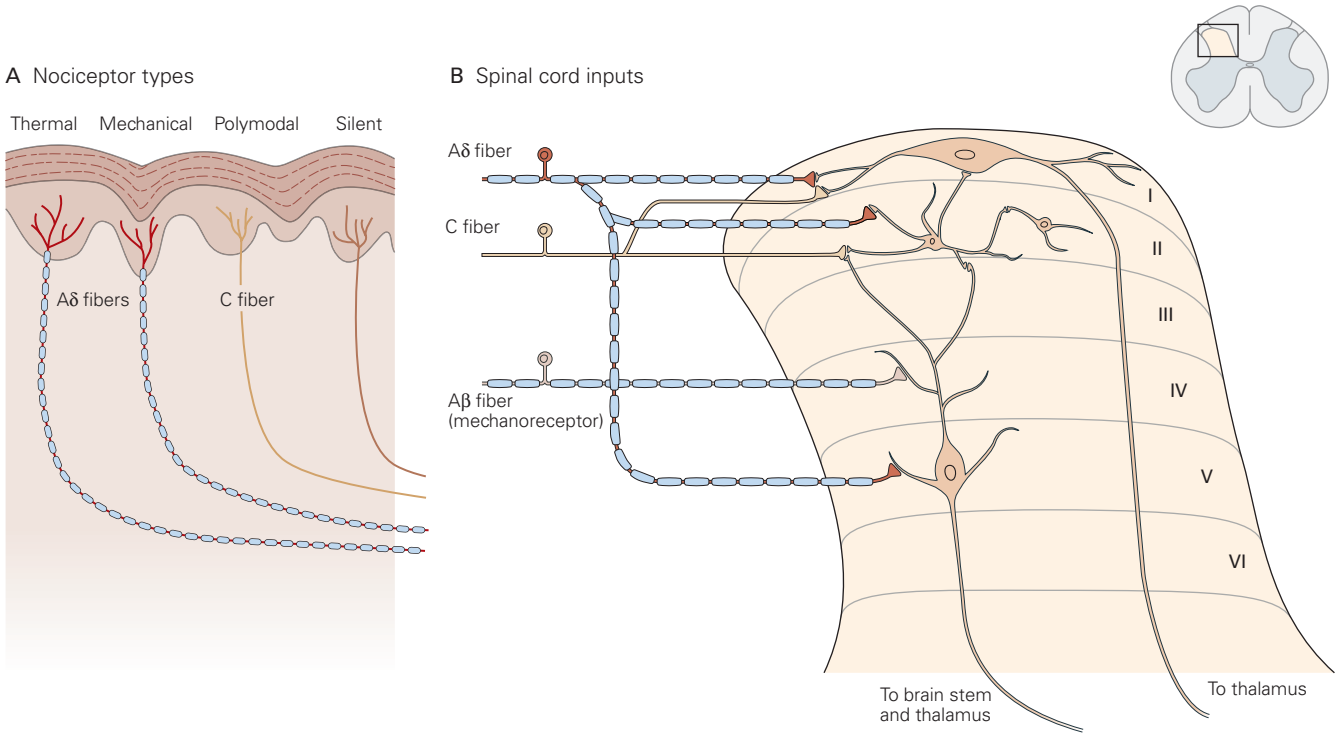

Figure 20–3 Nociceptive fibers terminate in different laminae of the dorsal horn of the spinal cord.

A. There are three main classes of peripheral nociceptor as well as the silent nociceptors, which are activated by inflammation and various chemical substances.

B. Neurons in lamina I of the dorsal horn receive direct input from myelinated (**Aδ**) nociceptive fibers and both direct and indirect input from unmyelinated (**C**) nociceptive fibers via interneurons in lamina II. Lamina V neurons receive low-threshold input from large-diameter myelinated Aβ mechanoreceptive fibers as well as inputs from nociceptive Aδ and C fibers. Lamina V neurons send dendrites to lamina IV, where they are contacted by the terminals of Aβ primary afferents. Axon terminals of lamina II interneurons can make contact with dendrites in lamina III that arise from cells in lamina V. Aα primary afferents contact motor neurons and interneurons in the ventral spinal cord (not shown). (Adapted, with permission, from Fields 1987.)

neurons branch in the periphery, innervating both skin and visceral targets.

Neurons in lamina VI receive inputs from large-diameter primary afferent fibers that innervate muscles and joints. These neurons are activated by innocuous joint movement and do not contribute to the transmission of nociceptive information. Many neurons in laminae VII and VIII, the intermediate and ventral regions of the spinal cord, do respond to noxious stimuli. These neurons typically have complex response properties because the inputs from nociceptors to these neurons are conveyed through many intervening synapses. Neurons in lamina VII often respond to stimulation of either side of the body, whereas most dorsal horn neurons receive unilateral input. The activation of lamina VII neurons is therefore thought to contribute to the diffuse quality of many pain conditions.

Nociceptive sensory neurons that activate neurons in the dorsal horn of the spinal cord release two major classes of neurotransmitters. Glutamate is the primary neurotransmitter of all primary sensory neurons, regardless of sensory modality. Neuropeptides are released as cotransmitters by many nociceptors with unmyelinated axons. These peptides include substance P, calcitonin gene–related peptide (CGRP), somatostatin, and galanin (Figure 20–5). Glutamate is stored in small, electron-lucent vesicles, whereas peptides are sequestered in large, dense-core vesicles at the central terminals of nociceptive sensory neurons (Figure 20–6). Separate storage sites permit these two classes of neurotransmitters to be selectively released under different physiological conditions.

Of the neuropeptide transmitters released by nociceptive sensory neurons, the actions of substance P, a member of the neurokinin peptide family, have been studied in most detail. Substance P is released from the central terminals of nociceptive afferents in response to tissue injury or after intense stimulation of peripheral

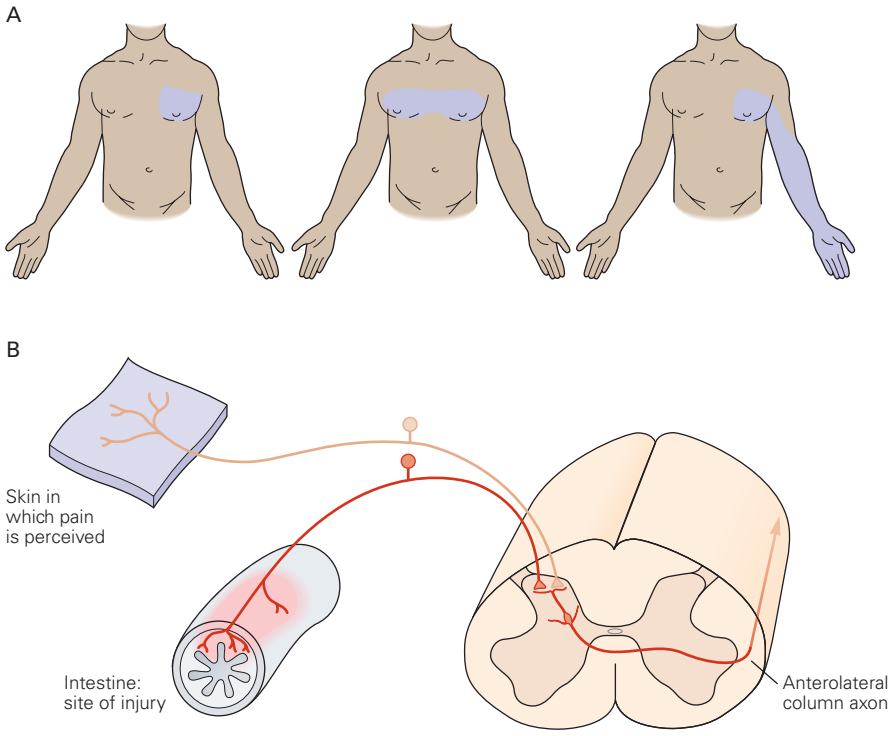

Figure 20–4 Signals from nociceptors in the viscera can be felt as "referred pain" elsewhere in the body.

A. Myocardial infarction and angina can be experienced as deep referred pain in the chest and left arm. The source of the pain cannot be readily predicted from the site of referred pain.

B. Convergence of visceral and somatic afferent fibers may account for referred pain. Nociceptive afferent fibers from the viscera and fibers from specific areas of the skin converge on the same projection neurons in the dorsal horn. The brain has no way of knowing the actual site of the noxious stimulus and mistakenly associates a signal from a visceral organ with an area of skin. (Adapted, with permission, from Fields 1987.)

nerves. Its interaction with neurokinin receptors on dorsal horn neurons elicits slow excitatory postsynaptic potentials that prolong the depolarization elicited by glutamate. Although the physiological actions of glutamate and neuropeptides on dorsal horn neurons are different, these transmitters act coordinately to regulate the firing properties of dorsal horn neurons.

Details of the interaction of neuropeptides with their receptors on dorsal horn neurons have suggested strategies for chronic pain regulation. Infusion of substance P coupled to a neurotoxin into the dorsal horn of experimental animals results in selective destruction of neurons that express neurokinin receptors. Animals treated in this way fail to develop the central sensitization that is normally associated with peripheral injury. This method of neuronal ablation is more selective than traditional surgical interventions such as partial spinal cord transection (anterolateral cordotomy) and is being considered as a treatment for patients suffering from otherwise intractable chronic pain.

Hyperalgesia Has Both Peripheral and Central Origins

Up to this point, we have considered the conveyance of noxious signals in the normal physiological state. But the normal process of sensory signaling can be dramatically altered when peripheral tissue is damaged, resulting in an increase in pain sensitivity or hyperalgesia. This condition can be elicited by sensitizing peripheral nociceptors through repetitive exposure to noxious stimuli (Figure 20–7).

The sensitization is triggered by a complex mix of chemicals released from damaged cells that accumulate at the site of tissue injury. This cocktail contains peptides and proteins such as bradykinin, substance P, and nerve growth factor, as well as molecules such as ATP, histamine, serotonin, prostaglandins, leukotrienes, and acetylcholine. Many of these chemical mediators are released from distinct cell types, but together they act to decrease the threshold of nociceptor activation.