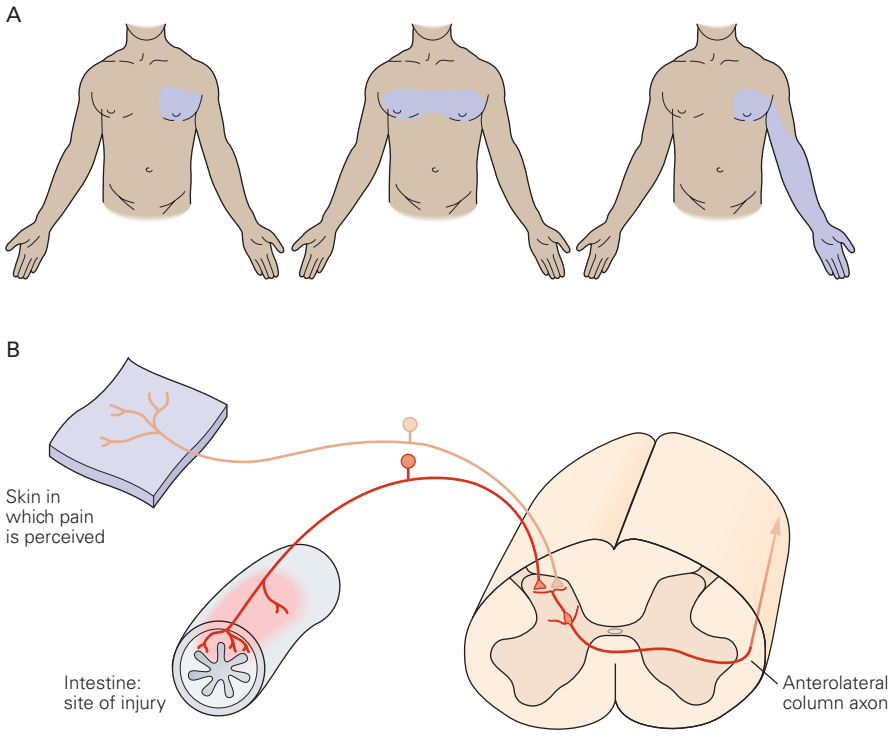


Figure 20–4 Signals from nociceptors in the viscera can be felt as "referred pain" elsewhere in the body.

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.

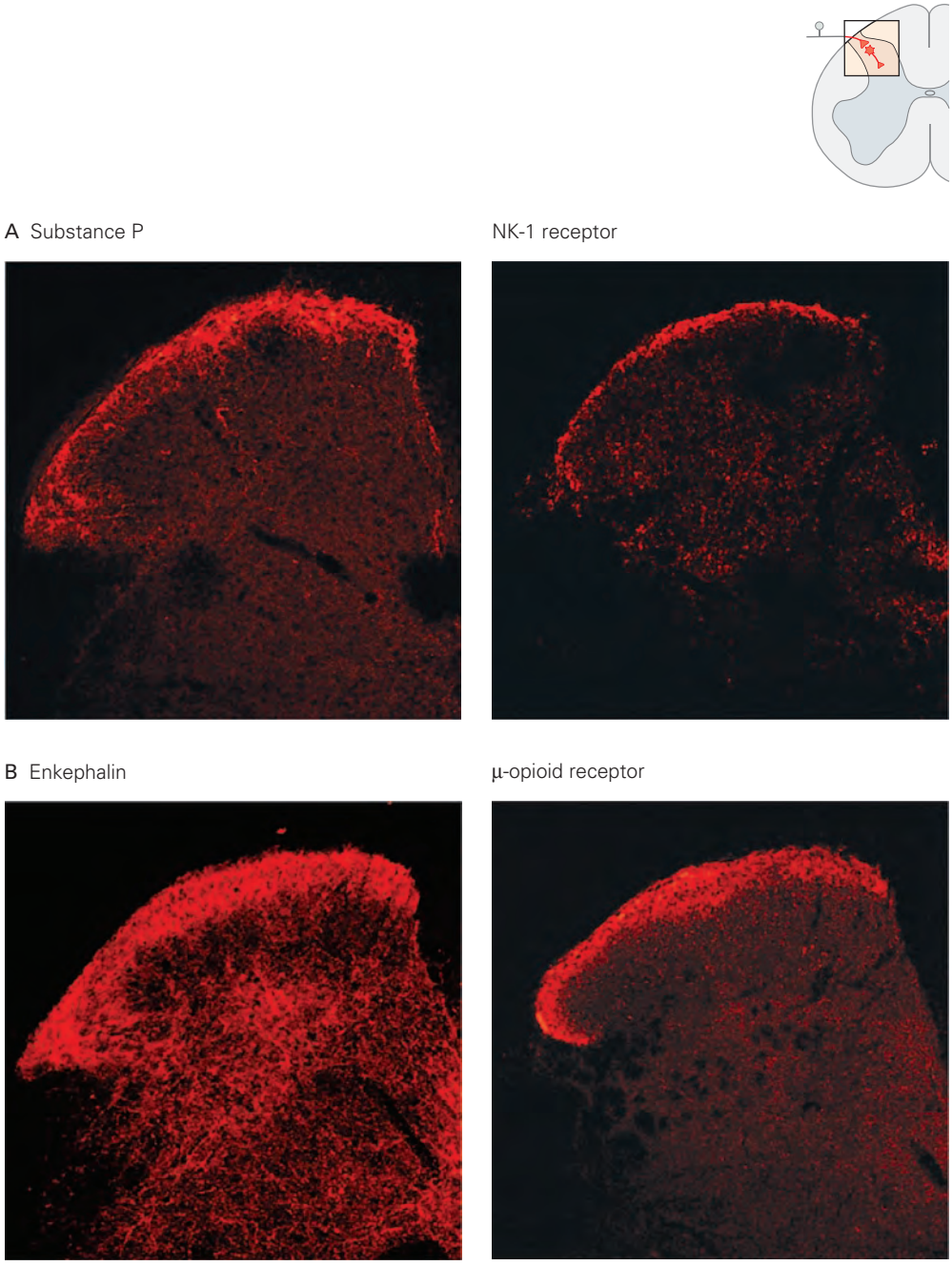


Figure 20–5 Neuropeptides and their receptors in the superficial dorsal horn of the rat spinal cord. (Images reproduced, with permission, from A. Basbaum.)

A. The terminals of unmyelinated primary sensory neurons are a major source of substance P in the superficial dorsal horn. Substance P activates the neurokinin-1 (**NK1**) receptor, which is expressed by neurons in the superficial dorsal horn, the majority of which are projection neurons.

B. Enkephalin is localized in interneurons and found in the same region of the dorsal horn as terminals containing substance P. The μ-opioid receptor, which is targeted by enkephalins, is expressed by neurons in the superficial dorsal horn and also, presynaptically, on the terminals of sensory neurons.

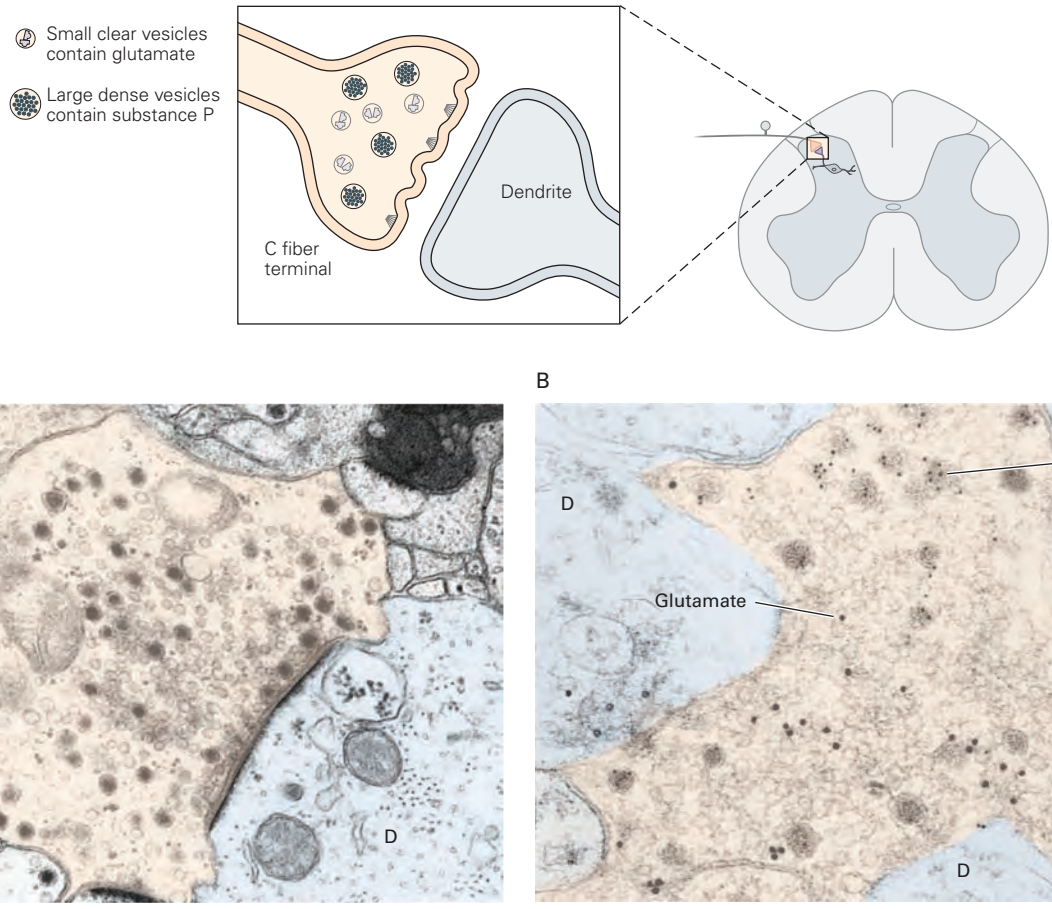


Figure 20–6 Transmitter storage in the synaptic terminals of primary nociceptive neurons in the dorsal spinal cord.

A. The terminal of a C fiber on the dendrite (D) of a dorsal horn neuron has two classes of synaptic vesicles that contain different transmitters. Small electron-lucent vesicles contain glutamate, whereas large dense-cored vesicles store neuropeptides. (Image reproduced, with permission, from H. J. Ralston III.)

B. Glutamate and the peptide substance P (marked by large and small gold particles, respectively) are scattered in the axoplasm of a sensory neuron terminal in lamina II of the dorsal horn. Dense core vesicles also store calcitonin gene–related peptide (CGRP). (Reproduced, with permission, from De Biasi and Rustioni 1990.)

Where do these chemicals come from, and what exactly do they do? Histamine is released from mast cells after tissue injury and activates polymodal nociceptors. The lipid anandamide, an endogenous cannabinoid agonist, is released under conditions of inflammation, activates the TRPV1 channel, and may trigger pain associated with inflammation. ATP, acetylcholine, and serotonin are released from damaged endothelial cells and platelets; they act indirectly to sensitize nociceptors by triggering the release of chemical agents such as prostaglandins and bradykinin from peripheral cells.

Bradykinin is one of the most active pain-producing agents. Its potency stems in part from the fact that it directly activates Aδ and C nociceptors and increases the synthesis and release of prostaglandins from nearby cells. Prostaglandins are metabolites of arachidonic acid that are generated through the activity of cyclooxygenase (COX) enzymes that cleave arachidonic acid (Chapter 14). The COX-2 enzyme is preferentially induced under conditions of peripheral inflammation, contributing to enhanced pain sensitivity. The enzymatic pathways of prostaglandin synthesis are targets of commonly used analgesic drugs. Aspirin and other nonsteroidal anti-inflammatory analgesics, such as ibuprofen and naproxen, are effective in controlling pain because they block the activity of the COX enzymes, reducing prostaglandin synthesis.

Activity of peripheral nociceptors can also produce all of the cardinal signs of inflammation, including heat

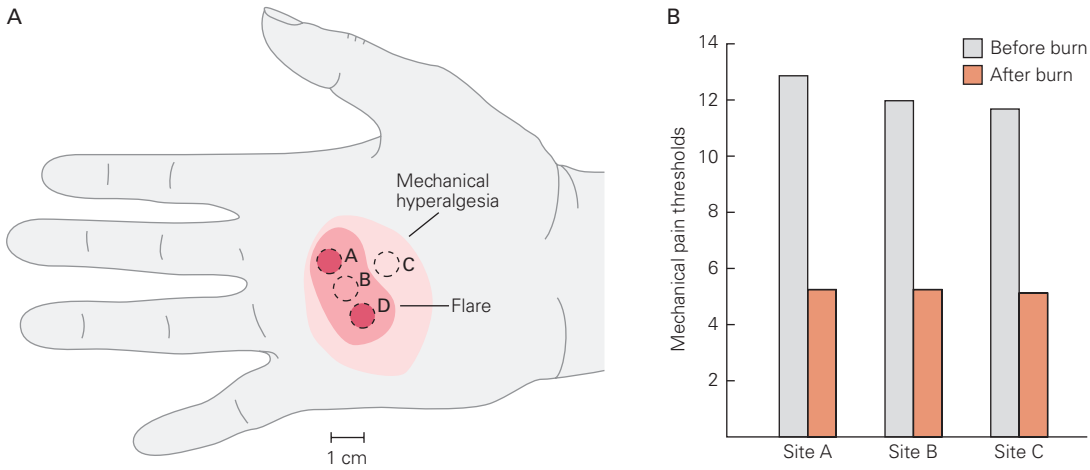


Figure 20–7 Hyperalgesia results from sensitization of nociceptors. (Reproduced, with permission, from Raja, Campbell, and Meyer 1984. Copyright © 1984, Oxford University Press.)

A. Mechanical thresholds for pain were recorded at sites A, B, and C before and after burns at sites A and D. The areas of reddening (flare) and mechanical hyperalgesia resulting from the burns are shown on the hand of one subject. In all subjects, the area of mechanical hyperalgesia was larger than the area of flare. Mechanical hyperalgesia was present even after the flare disappeared.

B. Mean mechanical pain thresholds before and after burns. The mechanical threshold for pain is significantly decreased after the burn.

(calor), redness (rubor), and swelling (tumor). Heat and redness result from the dilation of peripheral blood vessels, whereas swelling results from plasma extravasation, a process in which proteins, cells, and fluids are able to penetrate postcapillary venules. Release of the neuropeptides substance P and CGRP from the peripheral terminals of C fibers provokes plasma extravasation and vasodilation, respectively. Because this form of inflammation depends on neural activity, it has been termed *neurogenic inflammation* (Figure 20–8). Importantly, as profound peripheral vasodilation is a critical trigger of many migraine headaches, the development of antibodies to CGRP, which counteract the vasodilation by scavenging CGRP, offers significant hope for a new migraine therapy.

The release of substance P and CGRP from the peripheral terminals of sensory neurons is also responsible for the *axon reflex*, a physiological process characterized by vasodilation in the vicinity of a cutaneous injury. Pharmacological antagonists of substance P are able to block neurogenic inflammation and vasodilation in humans; this discovery illustrates how knowledge of nociceptive mechanisms can be applied in improving clinical therapies for pain.

In addition to these small molecules and peptides, neurotrophins are causative agents in pain. Nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) are particularly active in inflammatory pain states. The synthesis of BDNF is upregulated in many inflamed peripheral tissues (Figure 20–9). NGF-neutralizing molecules are effective analgesic agents in animal models of persistent pain. Indeed, inhibition of NGF function and signaling blocks pain sensation as effectively as COX inhibitors and opiates. Several promising clinical trials using antibodies to NGF for the management of knee osteoarthritis have been reported, once again demonstrating the translation of basic science to the clinic.

What accounts for the enhanced sensitivity of dorsal horn neurons to nociceptor signals? Under conditions of persistent injury, C fibers fire repetitively and the response of dorsal horn neurons increases progressively (Figure 20–10A). The gradual enhancement in the excitability of dorsal horn neurons has been termed "windup" and is thought to involve *N*-methyl-D-aspartate (NMDA)-type glutamate receptors (Figure 20–10B).

Repeated exposure to noxious stimuli therefore results in long-term changes in the response of dorsal horn neurons through mechanisms that are similar to those underlying the long-term potentiation of synaptic responses in many circuits in the brain. In essence, these prolonged changes in the excitability of dorsal horn neurons constitute a "memory" of the state of C-fiber input. This phenomenon has been termed *central sensitization* to distinguish it from sensitization at the peripheral terminals of the dorsal horn neurons, a process that involves activation of the enzymatic pathways of prostaglandin synthesis.

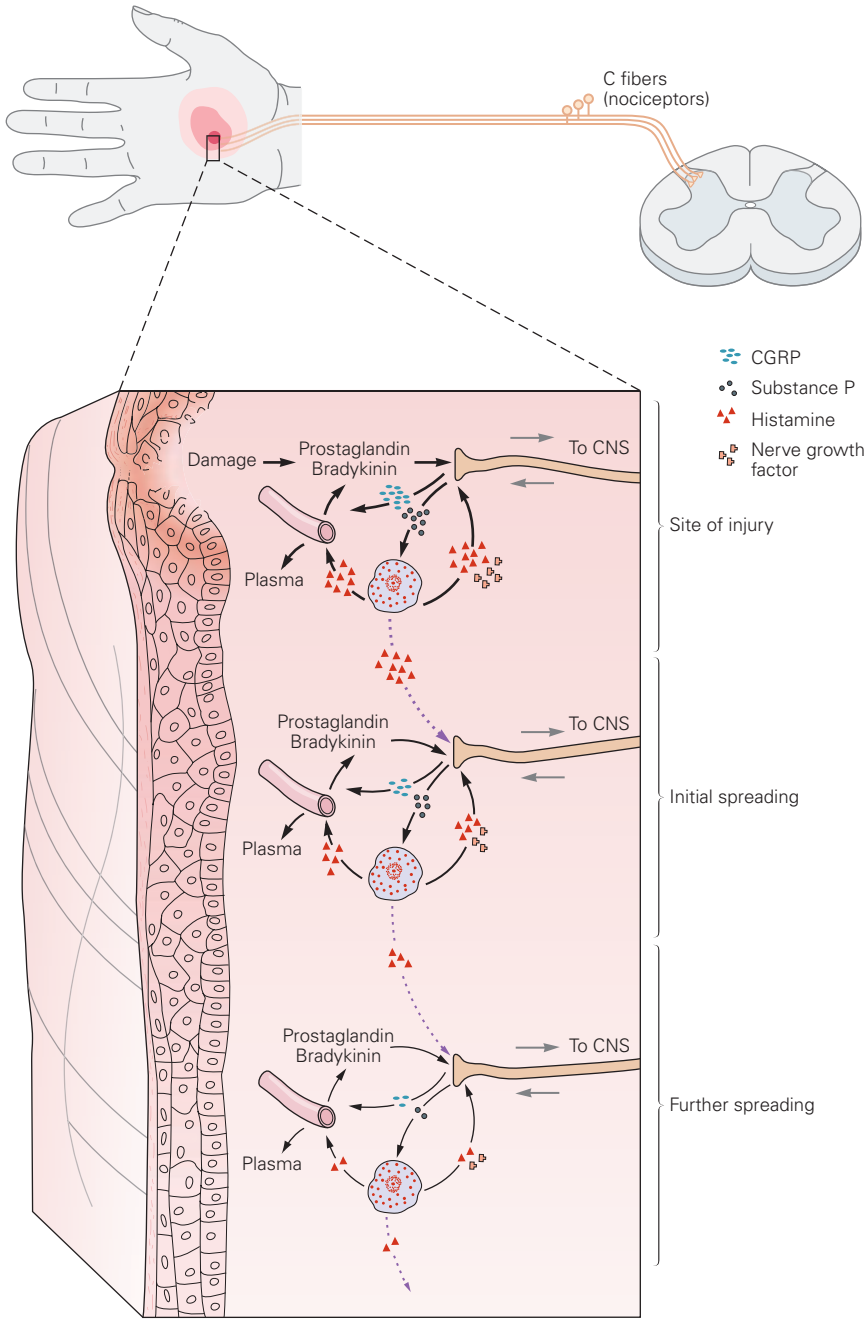
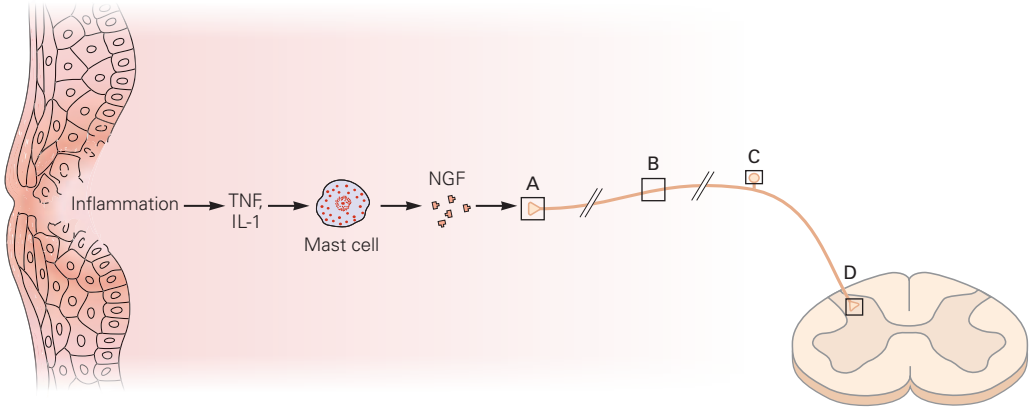


Figure 20–8 **Neurogenic inflammation.** Injury or tissue damage releases bradykinin and prostaglandins, which activate or sensitize nociceptors. Activation of nociceptors leads to the release of substance P and calcitonin gene–related peptide (**CGRP**). Substance P acts on mast cells (**light blue**) in the vicinity of sensory endings to evoke degranulation and the release of histamine, which directly excites nociceptors. Substance P also produces plasma extravasation and edema, and CGRP produces dilation of peripheral blood vessels (leading to reddening of the skin); the resultant inflammation causes additional liberation of bradykinin. These mechanisms also occur in healthy tissue, where they contribute to secondary or spreading hyperalgesia. (Abbreviation: **CNS**, central nervous system.)



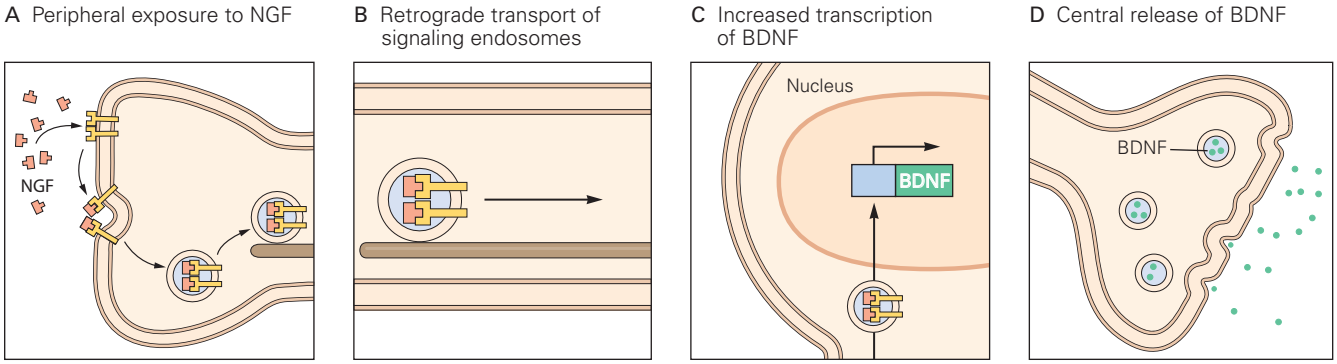


Figure 20–9 **Neurotrophins are pain mediators.** Local production of inflammatory cytokines such as interleukin-1 (**IL-1**) and tumor necrosis factor (**TNF**) promotes the synthesis and release of nerve growth factor (**NGF**) from several cell types in the periphery. Nerve growth factor binds to TrkA receptors on primary nociceptive terminals (**A**), triggering upregulation in expression of ion channels that increase nociceptor excitability. Retrograde transport of signaling endosomes to the cell body (**B**) results in enhanced expression of brain-derived neurotrophic factor (**BDNF**) (**C**), and its release from sensory terminals in the spinal cord (**D**) further increases excitability of dorsal horn neurons.

The sensitization of dorsal horn neurons also involves recruitment of second-messenger pathways and activation of protein kinases that have been implicated in memory storage in other regions of the central nervous system. One consequence of this enzymatic cascade is the expression of immediate-early genes that encode transcription factors such as *c-fos*, which are thought to activate effector proteins that sensitize dorsal horn neurons to sensory inputs. Most importantly, central sensitization of "pain" transmission circuitry in the dorsal horn is the process that can decrease pain thresholds (allodynia) and lead to *spontaneous pain* (ie, ongoing pain in the absence of peripheral stimulation).

Central sensitization is also a major contributor to neuropathic pain due to nerve injury. Here again, there is increased excitability of dorsal horn circuits mediated by NMDA receptors. There is also loss of inhibitory controls in the dorsal horn. Under normal conditions, GABAergic inhibitory interneurons in the dorsal horn are not only tonically active but are also turned on by activity of large-diameter, nonnociceptive Aβ fibers (Figure 20–11A). Peripheral nerve damage decreases the GABAergic controls, thus exacerbating the hyperactivity of these nociceptive pathways (Figure 20–11B). Recent studies also implicate nerve injury–induced activation of microglia and consequent reduced GABAergic inhibition in the central sensitization process (Figures 20–11C and 20–12). Together, these changes contribute to *mechanical allodynia* (ie, pain provoked by normally innocuous mechanical stimulation). Mechanical allodynia can also develop because of an inappropriate engagement of dorsal horn nociceptive pathway circuits by the Aβ myelinated afferents. In fact, spread of pain (secondary hyperalgesia) can occur because uninjured Aβ afferents outside of

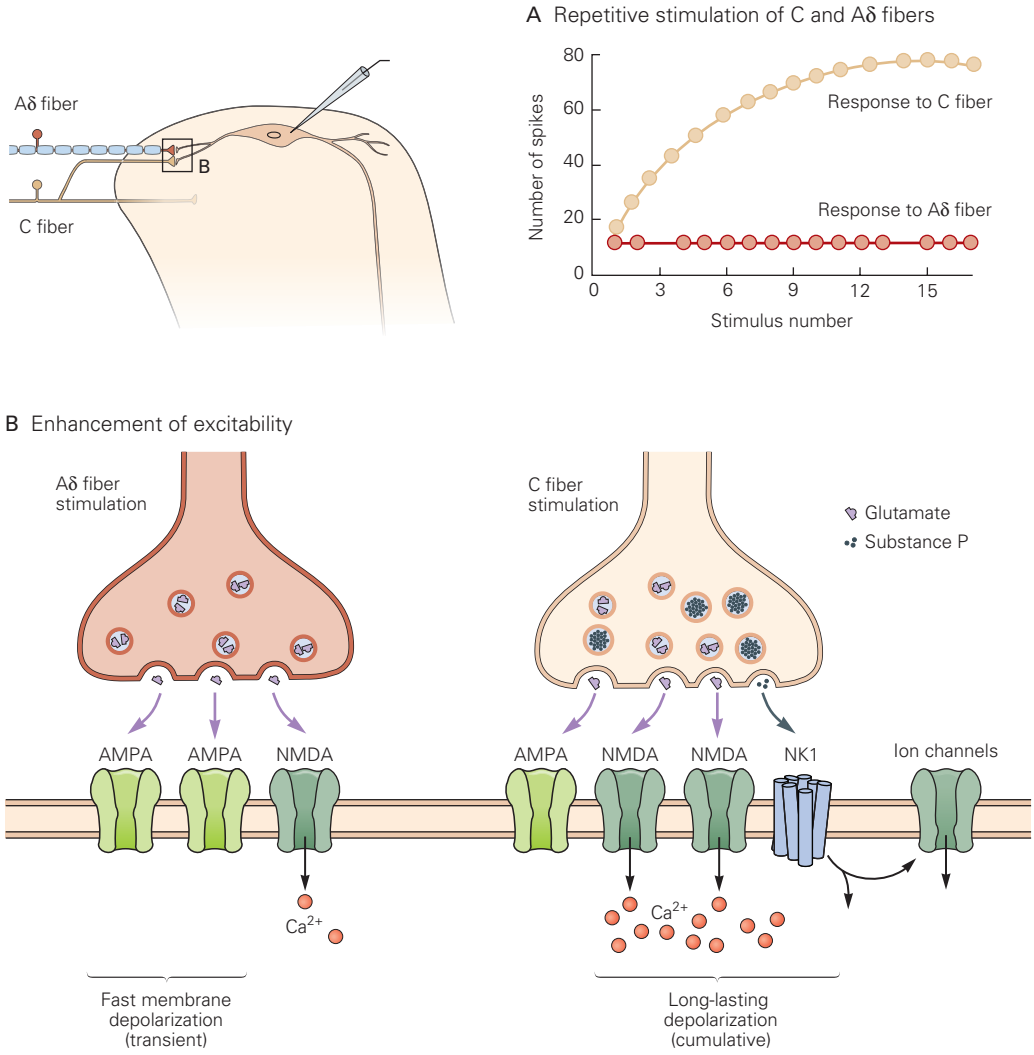


Figure 20–10 Mechanisms for enhanced excitability of dorsal horn neurons.

A. Typical responses of a dorsal horn neuron in the rat to electrical stimuli delivered transcutaneously at a frequency of 1 Hz. With repetitive stimulation, the long-latency component evoked by a C fiber increases gradually, whereas the short-latency component evoked by an A fiber remains constant.

B. Dorsal horn neurons receive mono- and polysynaptic input from Aδ and C fiber nociceptors. Elevation of residual Ca^{2+} in the presynaptic terminal leads to increased release of glutamate and substance P (and CGRP, not shown). *Left:* Activation of postsynaptic AMPA receptors by Aδ fibers causes a fast transient membrane depolarization, which relieves the Mg^{2+} block of the NMDA receptors. *Right*: Activation of the postsynaptic NMDA receptors and neurokinin-1 (**NK1**) receptors by C fibers generates a long-lasting cumulative depolarization. The cytosolic Ca^{2+} concentration in the dorsal horn neuron increases because of Ca^{2+} entry through the NMDA receptor channels and voltage-sensitive Ca^{2+} channels. The elevated Ca^{2+} and activation by NK1 receptors of second-messenger systems enhance the performance of the NMDA receptors. Activation of NK1 receptors, cumulative depolarization, elevated cytosolic Ca^{2+}, and other factors regulate the behavior of voltage-gated ion channels responsible for action potentials, resulting in enhanced excitability, all of which contribute to the process of central sensitization. (Abbreviations: **AMPA**, α-amino-3-hydroxy-5-methylisoxazole-4-propionate; **NMDA**, *N*-methyl-D-aspartate)

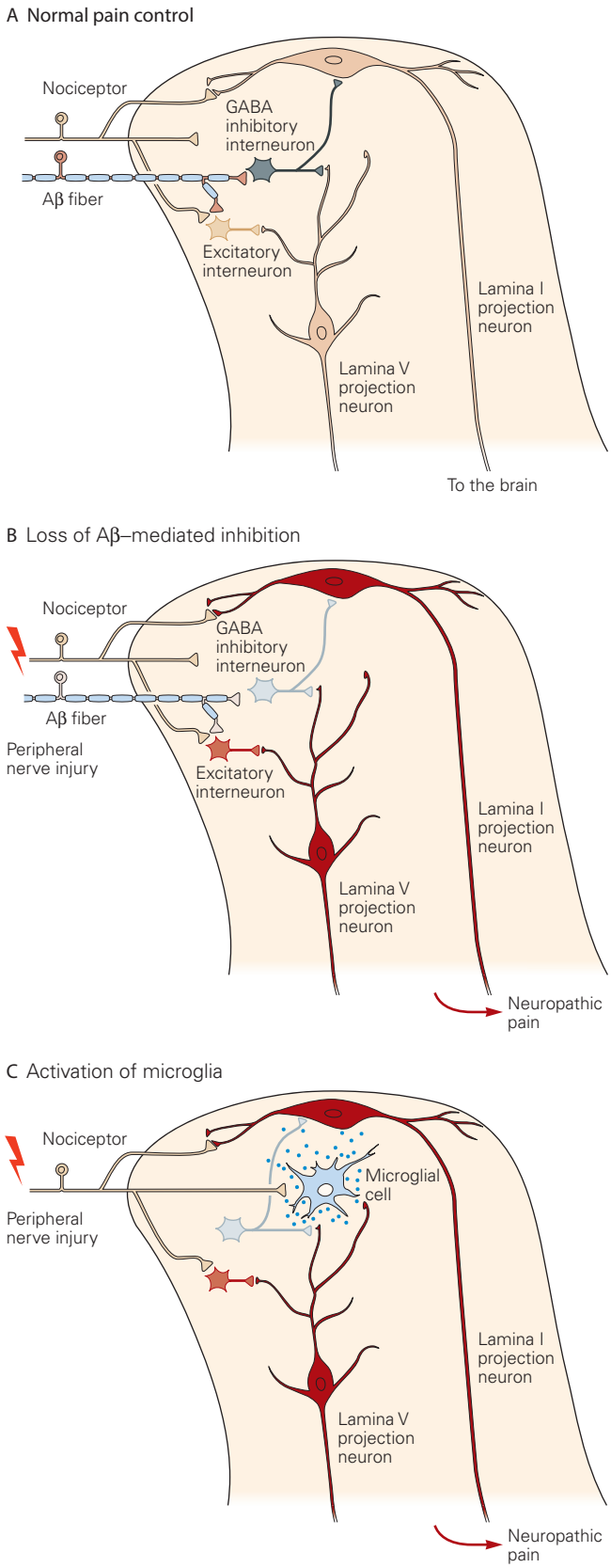


Figure 20–11 Nerve injury triggers multiple dorsal horn central sensitization mechanisms that contribute to neuropathic pain.

A. Under normal conditions, nociceptors engage dorsal horn pain transmission circuits, via both monosynaptic and polysynaptic (excitatory) inputs to projection neurons of laminae I and V that transmit nociceptive information to the brainstem and thalamus. (See Figure 20–13.) The output of the projection neurons is regulated by GABAergic inhibitory interneurons, which can be activated by nonnociceptive, large-diameter, myelinated Aβ afferent fibers.

B. Peripheral nerve injury can result in a loss of the inhibitory control exerted by the Aβ afferents, via loss of GABAergic interneurons, reduced production of GABA, or reduced expression of GABAergic receptors by the projection neurons. Pathophysiological sprouting of Aβ afferents may also permit nonnociceptive inputs to directly engage the projection neurons (not shown), resulting in the condition of Aβ-mediated mechanical hypersensitivity/allodynia, a hallmark of neuropathic pain.

C. Peripheral nerve injury not only activates dorsal horn neurons directly but also activates microglia, which in turn release a host of mediators that enhance neuronal excitability and reduce the inhibitory controls exerted by GABAergic interneurons. Thus, targeting the mediators released from microglia introduces yet another potential approach to the pharmacotherapy of chronic pain.

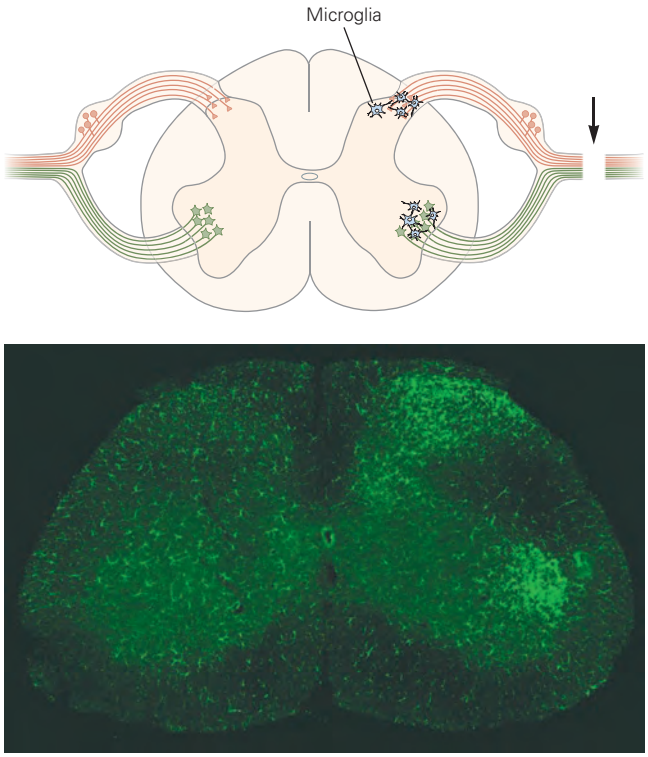


Figure 20–12 Peripheral nerve injury activates microglia in the dorsal and ventral horns. Schematic drawing and photomicrograph illustrate the location where microglia are activated after peripheral nerve injury. Activation of microglia in the dorsal horn results from damage (**arrow**) to the peripheral branch of primary sensory neurons (**orange cells**). Microglial activation around motor neuron cell bodies in the ventral horn occurs because the same injury damages efferent axons of the motor neurons (**green cells**). (Micrograph reproduced, with permission, from Julia Kuhn.)

the area of injury can inappropriately activate dorsal horn circuits that have undergone central sensitization.

Four Major Ascending Pathways Convey Nociceptive Information From the Spinal Cord to the Brain

Four major ascending pathways—the spinothalamic, spinoreticular, spinoparabrachial, and spinohypothalamic tracts—contribute sensory information to the central processes that generate pain.

The *spinothalamic tract* is the most prominent ascending nociceptive pathway in the spinal cord. It includes the axons of nociceptive-specific, thermosensitive, and wide-dynamic-range neurons in laminae I and V through VII of the dorsal horn. These axons cross the midline of the spinal cord near their segment of origin and ascend in the anterolateral white matter before terminating in thalamic nuclei (Figure 20–13). The spinothalamic tract has a crucial role in the transmission of nociceptive information. Cells at the origin of this tract typically have discrete, unilateral receptive fields that underlie our ability to localize painful stimuli. Not surprisingly, electrical stimulation of the tract is sufficient to elicit the sensation of pain; conversely, lesioning this tract (anterolateral cordotomy), a procedure that is generally only used for intractable pain in terminal cancer patients, can result in a marked reduction in pain sensation on the side of the body contralateral to that of the lesion.

The *spinoreticular tract* contains the axons of projection neurons in laminae VII and VIII. This tract ascends in the anterolateral quadrant of the spinal cord with spinothalamic tract axons, and terminates in both the reticular formation and the thalamus. As neurons at the origin of the spinoreticular tract generally have large, often bilateral receptive fields, this pathway has been implicated more in the processing of diffuse, poorly localized pains.

The *spinoparabrachial tract* contains the axons of projection neurons in laminae I and V. Information transmitted along this tract is thought to contribute to the affective component of pain. This tract projects in the anterolateral quadrant of the spinal cord to the parabrachial nucleus at the level of the pons (Figure 20–13). This pathway has extensive collaterals to the mesencephalic reticular formation and periaqueductal gray matter. Parabrachial neurons project to the amygdala, a critical nucleus of the limbic system, which regulates emotional states (Chapter 42).

The *spinohypothalamic tract* contains the axons of neurons found in spinal cord laminae I, V, VII, and VIII. These axons project to hypothalamic nuclei that serve as autonomic control centers involved in the regulation of the neuroendocrine and cardiovascular responses that accompany pain syndromes (Chapter 41).

Several Thalamic Nuclei Relay Nociceptive Information to the Cerebral Cortex

The thalamus contains several relay nuclei that participate in the central processing of nociceptive information. Two of the most important regions of the thalamus are the lateral and medial nuclear groups. The *lateral nuclear group* comprises the ventroposterolateral (VPL), ventroposteromedial (VPM) and posterior/pulvinar nuclei. The VPL and VPM, respectively, receive inputs via the spinothalamic tract from nociception-specific and wide-dynamic-range neurons in laminae I and V of the dorsal horn and via the trigeminothalamic tract