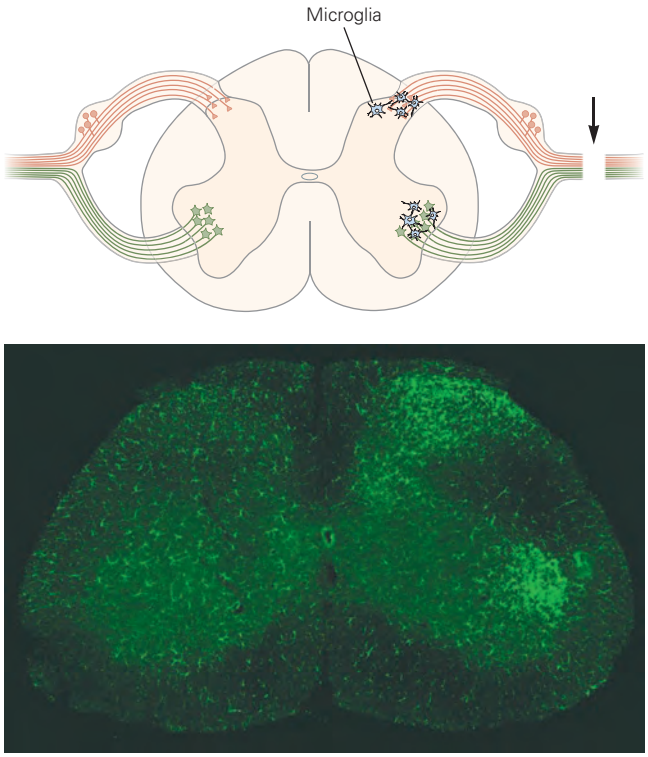

Figure 20–12 Peripheral nerve injury activates microglia in the dorsal and ventral horns. Schematic drawing and photomicrograph illustrate the location where microglia are activated after peripheral nerve injury. Activation of microglia in the dorsal horn results from damage (**arrow**) to the peripheral 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

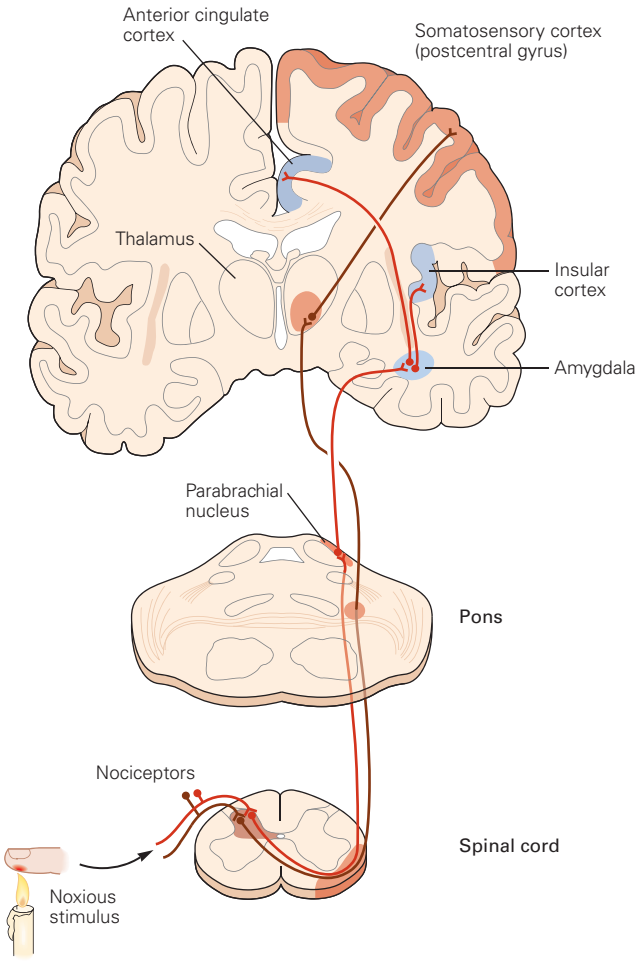

Figure 20–13 Major ascending pathways that transmit nociceptive information. Sensory discriminative features of the pain experience are transmitted from the spinal cord to the ventroposterolateral thalamus via the spinothalamic tract (**brown**). From there, information is transmitted predominantly to the somatosensory cortex. A second pathway, (the spinoparabrachial tract (**red**), carries information from the spinal cord to the parabrachial nucleus of the dorsolateral pons. These neurons in turn target limbic forebrain regions, including the insular and anterior cingulate cortex, which process emotional features of the pain experience.

from the trigeminal nucleus caudalis, the trigeminal homolog of the dorsal horn that processes nociceptive information from orofacial regions. The lateral thalamus processes information about the precise location of an injury, information usually conveyed to consciousness as acute pain. Consistent with this view, neurons in the lateral thalamic nuclei have small receptive fields, matching those of the presynaptic spinal neurons.

A cerebrovascular infarct that destroys the lateral thalamus can produce a central neuropathic pain condition called the Dejerine-Roussy (thalamic pain) syndrome. Patients with this syndrome experience spontaneous burning pain as well as abnormal sensations (called dysesthesias) contralateral to the infarct. Electrical stimulation of the thalamus can also result in intense pain. In one dramatic clinical case, electrical stimulation of the thalamus rekindled sensations of angina pectoris that were so realistic that the anesthesiologist thought the patient was experiencing a heart attack. This and other clinical observations suggest that in chronic neuropathic pain conditions there is a fundamental change in thalamic and cortical circuitry. This hypothesis is consistent with studies demonstrating that the topographic map of the body in the thalamus and somatosensory cortex is not fixed, but can change with use and disuse. Loss of a limb can lead to shrinking and even disappearance of the cortical representation of the limb. Abnormal reorganization likely contributes to the phantom limb pain (Figure 20–14).

The *medial nuclear group* of the thalamus comprises the medial dorsal and central lateral nucleus of the thalamus and the intralaminar complex. Its major input is from neurons in laminae VII and VIII of the dorsal horn. The pathway to the medial thalamus was the first spinothalamic projection evident in the evolution of mammals and is therefore known as the *paleospinothalamic tract.* It is also sometimes referred to as the spinoreticulothalamic tract because it includes indirect connections through the reticular formation of the brain stem. The projection from the lateral thalamus to the ventroposterior lateral and medial nuclei is most developed in primates, and thus is termed the *neospinothalamic tract.* Many neurons in the medial thalamus respond optimally to noxious stimuli and project to many regions of the limbic system, including the anterior cingulate cortex.

The Perception of Pain Arises From and Can Be Controlled by Cortical Mechanisms

Anterior Cingulate and Insular Cortex Are Associated With the Perception of Pain

Imaging studies now show that no single area of the cortex is responsible for pain perception. Rather, many regions are activated when an individual experiences pain. In the somatosensory cortex, neurons typically have small receptive fields and may not contribute greatly to the diffuse perception of aches and pains that characterize most clinical syndromes. The anterior cingulate gyrus and insular cortex also contain neurons that are activated strongly and selectively by noxious somatosensory stimuli (Box 20–1).

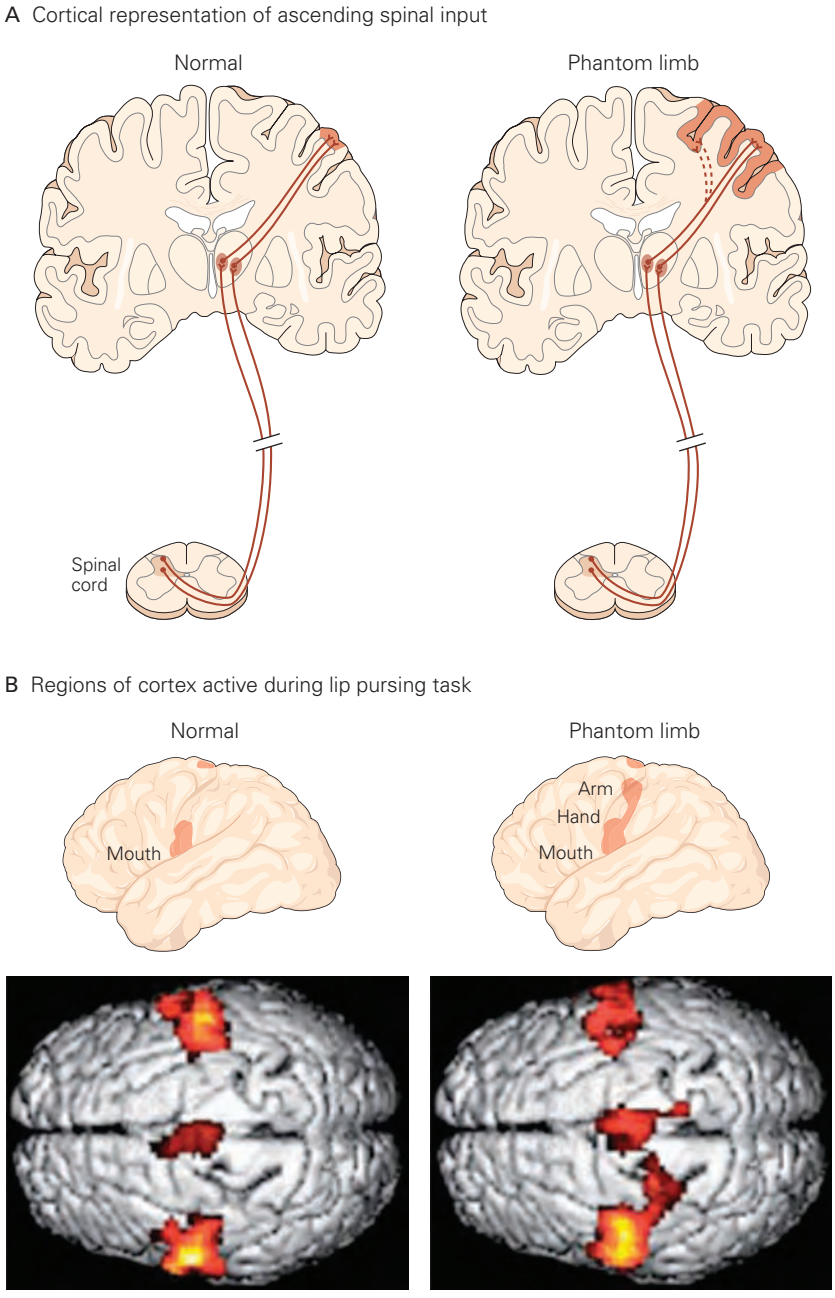

Figure 20–14 Changes in neural activation in phantom limb pain.

A. The domain of cerebral cortex activated by ascending spinal sensory inputs is expanded in patients with phantom limb pain.

B. Functional magnetic resonance imaging (fMRI) of patients with phantom limb pain and healthy controls during a lip-pursing task. In amputees with phantom limb pain, cortical representation of the mouth has extended into the regions of the hand and arm. In amputees without pain, the areas of primary somatosensory and motor cortices that are activated are similar to those in healthy controls (image not shown). (Adapted, with permission, from Flor, Nokolajsen, and Jensen 2006. Copyright © 2006 Springer Nature.)

The anterior cingulate gyrus is part of the limbic system and is involved in processing emotional states associated with pain. The insular cortex receives direct projections from the thalamus as well as from the amygdala. Neurons in the insular cortex process information about the internal state of the body and contribute to the autonomic component of pain responses. Importantly, neurosurgical procedures that ablate the cingulate cortex or the pathway from the frontal cortex to the cingulate cortex reduce the affective features of pain without eliminating the ability to recognize the intensity and location of the injury. Patients with lesions of the insular cortex present the striking syndrome of asymbolia for pain. They perceive noxious stimuli as painful and can distinguish sharp from dull pain but fail to display appropriate emotional responses. These observations implicate the insular cortex as an area in which

Box 20–1 Localizing Illusory Pain in the Cerebral Cortex

Thunberg's illusion, first demonstrated in 1896, is a strong, often painful heat felt after placing the hand on a grill of alternating warm and cool bars (Figure 20–15A).

One hypothesis proposes that this illusory sensation occurs as a result of differential grill responses of two classes of spinothalamic tract neurons, one sensitive to innocuous and another to noxious cold. This finding has led to a model of pain perception based on a central disinhibition or unmasking process in the cerebral cortex. The model predicts perceptual similarities between grill-evoked and cold-evoked pain, a prediction that has been verified psychophysically. The thalamocortical integration of pain and temperature stimuli may explain the burning sensation felt when nociceptors are activated by cold.

To identify the anatomical site of the unmasking phenomenon described above, positron emission tomography (PET) was used to compare the cortical areas activated by Thunberg's grill with those activated by cool, warm, noxious cold, and noxious heat stimuli separately. All thermal stimuli activate the insula and somatosensory cortices. The anterior cingulate cortex is activated by Thunberg's grill and by noxious heat and cold, but not by discrete warm and cool stimuli (Figure 20–15B).

A

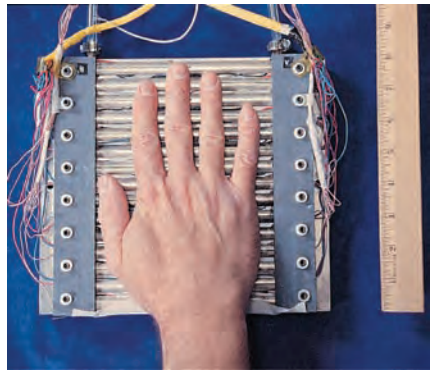

Figure 20–15A Thunberg's thermal grill. The stimulus surface (20 × 14 cm) is made of 15 sterling silver bars, each 1 cm wide, set approximately 3 mm apart. Underneath each bar are three longitudinally spaced thermoelectric (Peltier) elements (1 cm^2), and on top of each bar is a thermocouple. Alternate (even- and odd-numbered) bars can be controlled independently. (Adapted, with permission, from Craig and Bushnell 1994. Copyright © 1994 AAAS.)

B

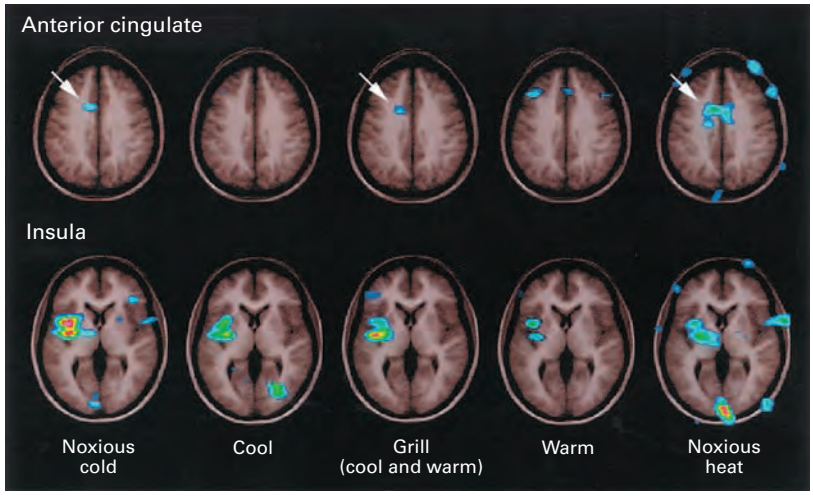

Figure 20–15B Cortical areas activated by Thunberg's grill. The anterior cingulate and insula regions of the cerebral cortex are activated when the hand is placed on the grill but not when warm and cool stimuli are applied separately. (Reproduced, with permission, from Craig AD, Reiman EM, Evans A, et al. 1996. Functional imaging of an illusion of pain. Nature 384:258–260. Copyright © 1996 Springer Nature.)

the sensory, affective, and cognitive components of pain are integrated.

Pain Perception Is Regulated by a Balance of Activity in Nociceptive and Nonnociceptive Afferent Fibers

Many projection neurons in the dorsal horn of the spinal cord respond selectively to noxious inputs, but others receive convergent inputs from both nociceptive and nonnociceptive afferents. The concept that the convergence of sensory inputs onto spinal projection neurons regulates pain processing first emerged in the 1960s.

Ronald Melzack and Patrick Wall proposed that the relative balance of activity in nociceptive and nonnociceptive afferents might influence the transmission and perception of pain. In particular, they proposed that activation of nonnociceptive sensory neurons, by engaging inhibitory interneurons in the dorsal horn, closes a "gate" for afferent transmission of nociceptive signals that can be opened by the activation of nociceptive sensory neurons. In the original and simplest form of this gate-control theory, the interaction between large and small fibers occurred at the first possible site of convergence on projection neurons in the dorsal horn of the spinal cord (Figure 20–16). We now know that such interactions can also occur at many supraspinal relay centers.

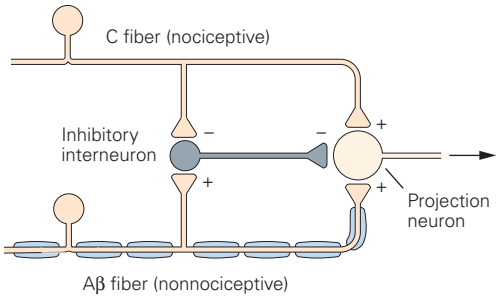

Figure 20–16 The gate control theory of pain. The gate-control hypothesis was proposed in the 1960s to account for the fact that activation of low-threshold primary afferent fibers can attenuate pain. The hypothesis focused on the interaction of neurons in the dorsal horn of the spinal cord: the nociceptive (**C**) and nonnociceptive (**Aβ**) sensory neurons, projection neurons, and inhibitory interneurons. In the original version of the model, as shown here, the projection neuron is excited by both classes of sensory neurons and inhibited by interneurons in the superficial dorsal horn. The two classes of sensory fibers also terminate on the inhibitory interneurons; the C fibers indirectly inhibit the interneurons, thus increasing the activity of the projection neurons (thereby "opening the gate"), whereas the Aβ fibers excite the interneurons, thus suppressing the output of the projection neurons (and "closing the gate").

The concept of convergence of different sensory modalities has provided an important basis for the design of new pain therapies. Viewed in its broadest sense, the convergence of high- and low-threshold inputs at spinal or supraspinal sites provided a plausible explanation for several empirical observations about the perception of pain. The shaking of the hand that follows a hammer blow or burn is a reflexive behavior and may alleviate pain by activating large-diameter afferent fibers that suppress the transmission of information about noxious stimuli.

The idea of convergence also helped to promote the use of transcutaneous electrical nerve stimulation (TENS) and spinal cord stimulation for the relief of pain. With TENS, stimulating electrodes placed at peripheral locations activate large-diameter afferent fibers that innervate areas that overlap but also surround the region of injury and pain. The region of the body in which pain is reduced maps to those segments of the spinal cord in which nociceptive and nonnociceptive afferents from that body region terminate. This makes intuitive sense: You do not shake your left leg to relieve pain in your right arm.

Electrical Stimulation of the Brain Produces Analgesia

Several sites of endogenous pain regulation are located in the brain. One effective means of suppressing nociception involves stimulation of the periaqueductal gray region, the area of the midbrain that surrounds the third ventricle and the cerebral aqueduct. In experimental animals, stimulation of this region elicits a profound and selective analgesia. This *stimulation-produced analgesia* is remarkably modality-specific; animals still respond to touch, pressure, and temperature within the body area that is not sensitive to pain. Stimulation-evoked analgesia has proved to be an effective way of relieving pain in a limited number of human pain conditions.

Stimulation of the periaqueductal gray matter blocks spinally mediated withdrawal reflexes that are normally evoked by noxious stimulation. Few of the neurons in the periaqueductal gray matter project directly to the dorsal horn of the spinal cord. Most make excitatory connections with neurons of the rostroventral medulla, including serotonergic neurons in a midline region called the nucleus raphe magnus. The axons of these serotonergic neurons project through the dorsal region of the lateral funiculus to the spinal cord, where they form inhibitory connections with neurons in laminae I, II, and V of the dorsal horn (Figure 20–17). Stimulation of the rostroventral

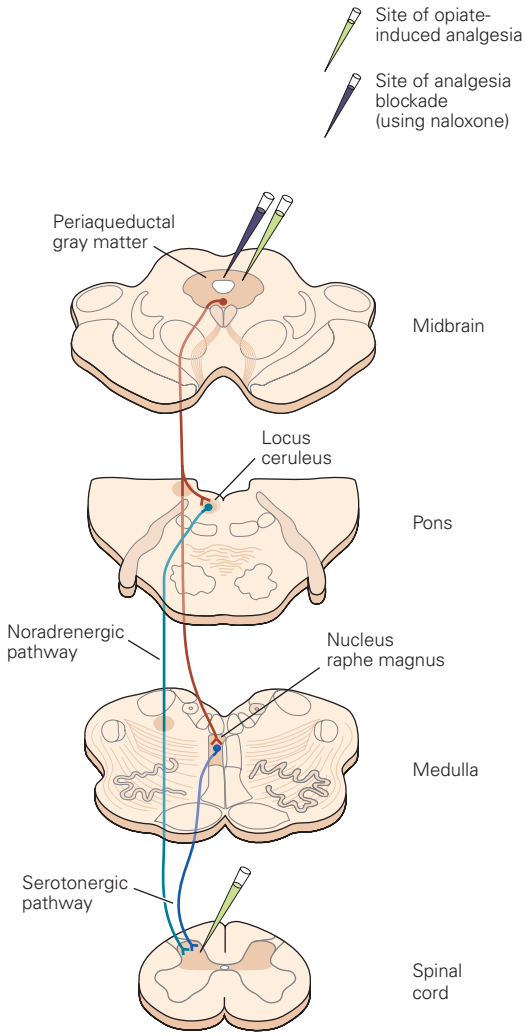

Figure 20–17 Descending monoaminergic pathways regulate nociceptive relay neurons in the spinal cord. A serotonergic pathway arises in the nucleus raphe magnus and projects through the dorsolateral funiculus to the dorsal horn of the spinal cord. A noradrenergic system arises in the locus ceruleus and other nuclei in the pons and medulla. (See Figure 40–11A for the locations and projections of monoaminergic neurons.) In the spinal cord, these descending pathways inhibit nociceptive projection neurons through direct connections as well as through interneurons in the superficial layers of the dorsal horn. Both the serotonergic nucleus raphe magnus and noradrenergic nuclei receive input from neurons in the periaqueductal gray region. Sites of opioid peptide expression and actions of exogenously administered opioids are shown.

medulla thus inhibits the firing of many classes of dorsal horn neurons, including projection neurons of the major ascending pathways that convey afferent nociceptive signals to the brain.

A second major monoaminergic descending system can also suppress the activity of nociceptive neurons in the dorsal horn. This noradrenergic system originates in the locus ceruleus and other nuclei of the medulla and pons (Figure 20–17). Through direct and indirect synaptic actions, these projections inhibit neurons in laminae I and V of the dorsal horn.

Opioid Peptides Contribute to Endogenous Pain Control

Since discovery of the opium poppy by the Sumerians in 3300 BC, the plant's active ingredients, opiates such as morphine and codeine, have been recognized as powerful analgesic agents. Over the past two decades, we have begun to understand many of the molecular mechanisms and neural circuits through which opiates exert their analgesic actions. In addition, we have come to realize that the neural networks involved in stimulation-produced and opiate-induced analgesia are intimately related.

Two key discoveries led to these advances. The first was the recognition that morphine and other opiates interact with specific receptors on neurons in the spinal cord and brain. The second was the isolation of endogenous neuropeptides with opiate-like activities at these receptors. The observation that the opiate antagonist, naloxone, blocks stimulation-produced analgesia provided the first clue that the brain contains endogenous opioids.

Endogenous Opioid Peptides and Their Receptors Are Distributed in Pain-Modulatory Systems

Opioid receptors fall into four major classes: mu (μ), delta (δ), kappa (κ), and orphanin FQ. The genes encoding each of these receptor types constitute a subfamily of G protein–coupled receptors. The μ receptors are particularly diverse; numerous μ receptor isoforms have been identified, many with different patterns of expression. This finding has prompted a search for analgesic drugs that target specific isoforms.

The opioid receptors were originally defined on the basis of the binding affinity of different agonist compounds. Morphine and other opioid alkaloids are potent agonists at μ receptors, and there is a tight correlation between the potency of an analgesic and its affinity of binding to μ receptors. Mice in which the gene for the μ receptor has been inactivated are insensitive to morphine and other opiate agonists. Many opiate antagonist drugs, such as naloxone, also bind to the μ receptor and compete with morphine for receptor occupancy without activating receptor signaling.

The μ receptors are highly concentrated in the superficial dorsal horn of the spinal cord, the ventral

Table 20–1 Four Major Classes of Endogenous Opioid Peptides

Propeptide	Peptide(s)	Preferential receptor
POMC	β-Endorphin	μ/δ
	Endomorphin-1	μ
	Endomorphin-2	μ
Proenkephalin	Met-enkephalin	δ
	Leu-enkephalin	δ
Prodynorphin	Dynorphin A	κ
	Dynorphin B	κ
Pro-orphanin FQ	Orphanin FQ	Orphan receptor

POMC, pro-opiomelanocortin.

medulla, and the periaqueductal gray matter—important anatomical sites for the regulation of pain. Nevertheless, like other classes of opioid receptors, they are also found at many other sites in the central and peripheral nervous systems. Their widespread distribution explains why systemically administered morphine influences many physiological processes in addition to the perception of pain.

The discovery of opioid receptors and their expression by neurons in the central and peripheral nervous systems led to the definition of four major classes of endogenous opioid peptides, each interacting with a specific class of opioid receptors (Table 20–1).

Three classes—the enkephalins, β-endorphins, and dynorphins—are the best characterized. These opioid peptides are formed from large polypeptide precursors by enzymatic cleavage (Figure 20–18) and encoded by distinct genes. Despite differences in amino acid sequence, each contains the sequence Tyr-Gly-Gly-Phe. β-Endorphin is a cleavage product of a precursor that also generates the active peptide adrenocorticotropic hormone (ACTH). Both β-endorphin and ACTH are synthesized by cells in the pituitary and are released into the bloodstream in response to stress. Dynorphins are derived from the polyprotein product of the *dynorphin* gene.

Members of the four classes of opioid peptides are distributed widely in the central nervous system, and individual peptides are located at sites associated with the processing or modulation of nociceptive information. Neuronal cell bodies and axon terminals containing enkephalin and dynorphin are found in the dorsal horn of the spinal cord, particularly in laminae I and II, as well as in the rostral ventral medulla and the periaqueductal gray matter. Neurons that synthesize β-endorphin are confined primarily to the hypothalamus; their axons terminate in the periaqueductal gray region and on noradrenergic neurons in the brain stem. Orphanin FQ appears to participate in a broad range of other physiological functions.

Morphine Controls Pain by Activating Opioid Receptors

Microinjection of low doses of morphine, other opiates, or opioid peptides directly into specific regions of the rat brain produces a powerful analgesia. The periaqueductal gray region is among the most sensitive sites, but local administration of morphine into other regions, including the spinal cord, also elicits a powerful analgesia.

Systemic morphine-induced analgesia can be blocked by injection of the opiate antagonist naloxone into the periaqueductal gray region or the nucleus raphe magnus (Figure 20–17). In addition, bilateral transection of the dorsal lateral funiculus in the spinal cord blocks analgesia induced by central administration of morphine. Thus, the central analgesic actions of morphine involve the activation of descending pathways to the spinal cord, the same descending pathways that mediate the analgesia produced by electrical brain stimulation and morphine.

In the spinal cord, as elsewhere, morphine acts by mimicking the actions of endogenous opioid peptides. The superficial dorsal horn of the spinal cord contains interneurons that express enkephalin and dynorphin, and the terminals of these neurons lie close to synapses formed by nociceptive sensory neurons and spinal projection neurons (Figure 20–19A). Moreover, the μ, δ, and κ receptors are located on the terminals of the nociceptive sensory neurons as well as on the dendrites of dorsal horn neurons that receive afferent nociceptive input, thus placing endogenous opioid peptides in a strategic position to regulate sensory input. The C-fiber nociceptors, which mediate slow persistent pain or "second pain," have more μ receptors than the Aδ nociceptors, which mediate fast and acute pain or "first pain" (Figure 20–1). This may help to explain why morphine is more effective in the treatment of persistent rather than acute pains.

Opioids (both opiates and opioid peptides) regulate nociceptive transmission at synapses in the dorsal horn through two main mechanisms. First, they increase membrane K^+ conductances in dorsal horn neurons, hyperpolarizing the neurons and increasing their threshold for activation. Second, by binding to receptors on presynaptic sensory terminals, opioids block voltage-gated Ca^{2+} channels, which reduces Ca^+

Figure 20–18 Four families of endogenous opioid peptides arise from large precursor polyproteins.

A. Proteolytic enzymes cleave each of the precursor proteins to generate shorter, biologically active peptides, some of which are shown in this diagram. The proenkephalin precursor protein contains multiple copies of methionine-enkephalin (**M**), leucine-enkephalin (**L**), and several extended enkephalins. Proopiomelanocortin (POMC) contains β-endorphin (**β-END**, melanocyte-stimulating hormone (**MSH**), adrenocorticotropic hormone (ACTH), and corticotropin-like intermediate-lobe peptide (**CLIP**). The prodynorphin precursor can produce dynorphin (**D**) and α-neoendorphin (**N**). The pro-orphanin precursor contains the orphanin FQ peptide (**O**), also called nociceptin. The **black domains** indicate a signal peptide.

B. Amino acid sequences of proteolytically processed bioactive peptides. The amino acid residues shown in **bold type** mediate interaction with opioid receptors. (Adapted, with permission, from Fields 1987.)

entry into the sensory nerve terminal (Figure 20–19B). This effect in turn inhibits the release of neurotransmitter and thereby decreases activation of postsynaptic dorsal horn neurons.

The wide distribution of opioid receptors within the brain and periphery accounts for the many side effects produced by opiates. Activation of opioid receptors expressed by muscles of the bowel and anal sphincter results in constipation. Similarly, opioid receptor–mediated inhibition of neuronal activity in the nucleus of the solitary tract underlies the respiratory depression and cardiovascular side effects. For this reason, direct spinal administration of opiates has significant advantages. Morphine injected into the cerebrospinal fluid of the spinal cord subarachnoid space interacts with opioid receptors in the dorsal horn to elicit a profound and prolonged analgesia. Spinal administration of morphine is now commonly used in the treatment of postoperative pain, notably the pain associated with cesarean section during childbirth. In addition to producing prolonged analgesia, intrathecal morphine has fewer side effects because the drug does not diffuse far from its site of injection. Continuous local infusion of morphine to the spinal cord has also been used for the treatment of certain cancer pains.

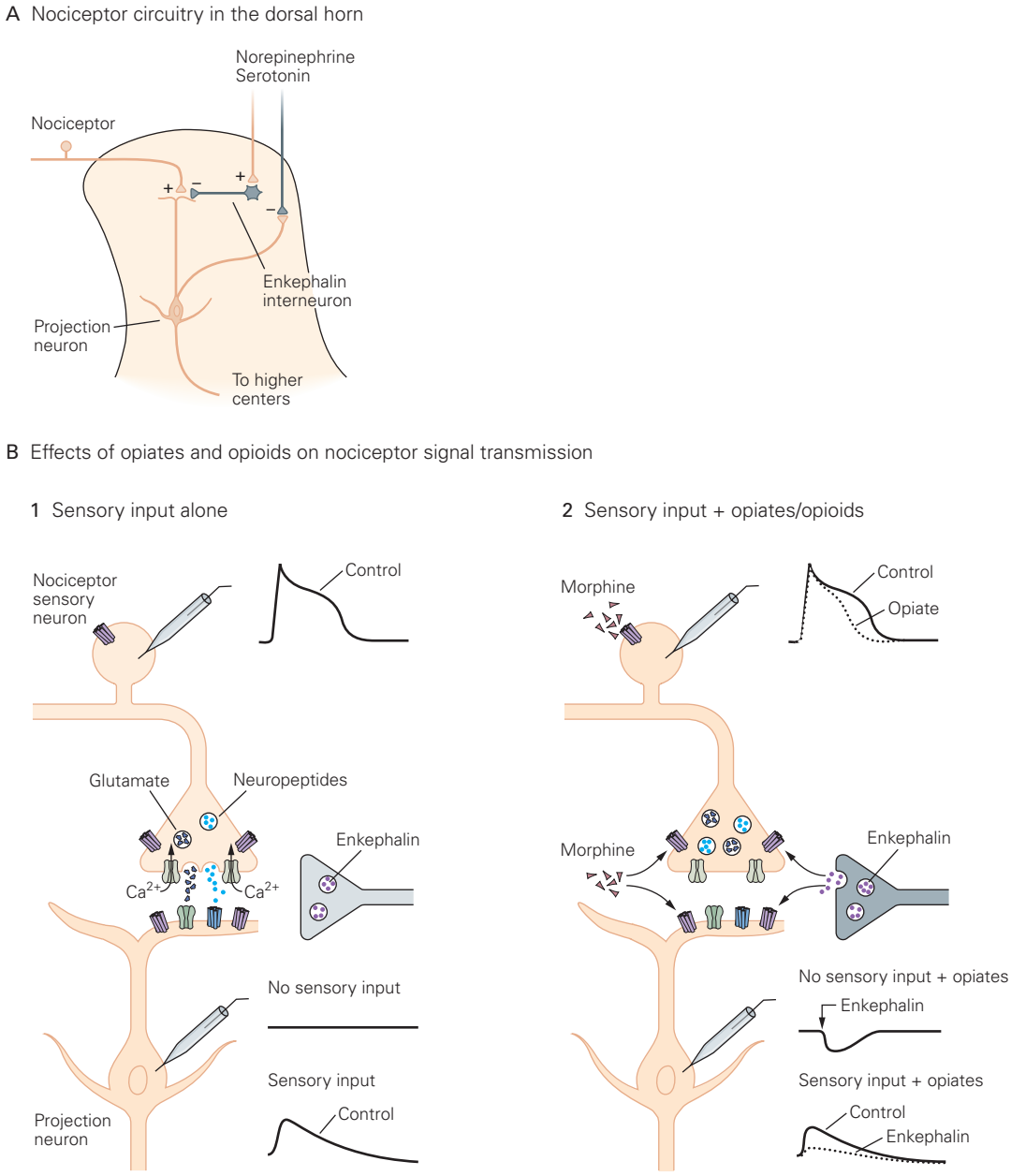

Figure 20–19 Local interneurons in the spinal cord integrate descending and afferent nociceptive pathways.

A. Nociceptive afferent fibers, local interneurons, and descending fibers interconnect in the dorsal horn of the spinal cord (see also Figure 20–3B). Nociceptive fibers terminate on second-order projection neurons. Local GABAergic and enkephalin-containing inhibitory interneurons exert both pre- and postsynaptic inhibitory actions at these synapses. Serotonergic and noradrenergic neurons in the brain stem activate the local interneurons and also suppress the activity of the projection neurons. Loss of these inhibitory controls contributes to ongoing pain and pain hypersensitivity.

B. Regulation of nociceptive signals at dorsal horn synapses. **1.** Activation of a nociceptor leads to the release of glutamate and neuropeptides from the primary sensory neuron, producing an excitatory postsynaptic potential in the projection neuron. **2.** Opiates decrease the duration of the postsynaptic potential, probably by reducing Ca^{2+} influx, and thus decrease the release of transmitter from the primary sensory terminals. In addition, opiates hyperpolarize the dorsal horn neurons by activating a K^+ conductance and thus decrease the amplitude of the postsynaptic potential in the dorsal horn neuron.