4 The Anatomy of Pain and Its Implications for Regional Anesthesiology Practice

Harry J. Gould III and Alan David Kaye

Introduction

In years past, the prevailing approach to providing pain control was focused on identifying underlying etiologies or pathologic syndromes, e.g., low back pain, trigeminal neuralgia, and cancer pain, that produce the pain. While treating the presumed source of the pain, attempts to improve the accompanying discomfort relied largely on the use of non-opioid medications and the limited use of opioid and adjuvant analgesics. Over the past 25 years, however, there has been a dramatic increase in our understanding of the nervous system and how stimuli associated with actual or potential tissue injury are transduced, transmitted, modulated, perceived, and interpreted to form the basis for initiating appropriate evasive or protective behavior, thereby avoiding or limiting injury. Our current bank of knowledge has led to the recognition that (1) pain in the chronic state is in itself a disease deserving consideration, assessment, and management; (2) pain is not a single entity but a complex, multifaceted experience that warrants detailed and comprehensive evaluation to elucidate symptoms that may reflect specific associated mechanisms amenable to targeted treatment [1, 2]; and (3) treatment modalities and management approaches not heretofore considered can be effective and can improve the quality of life for those suffering with pain. This chapter will provide a brief overview of the anatomy of pain that forms the basis for current practice.

Considerations of General Organization

The somatosensory system provides the means through which living organisms explore and monitor the body's external and internal environment in order to recognize changes that may be beneficial and embraced or detrimental to survival and avoided.

The peripheral elements of the nervous system are organized in a segmental fashion that is determined during the somatic stage of development when the embryo more closely resembles phylogenetically earlier stages of evolution (Figs. 4.1 and 4.2). Neural crest cells that are destined to become sensory neurons establish connections with local tissues of the developing somatic and lateral plate mesoderm and project centrally to connect with elements of the central nervous system close to the entry zone. At that stage of

H. J. Gould III, MD, PhD (✉)
Neurology and Neuroscience, Louisiana State University Health Sciences Center—New Orleans, New Orleans, LA, USA
e-mail: hgould@lsuhsc.edu

A. D. Kaye, MD, PhD
Department of Anesthesiology, Louisiana State University School of Medicine, New Orleans, LA, USA

A. D. Kaye et al. (eds.), *Essentials of Regional Anesthesia*,
https://doi.org/10.1007/978-3-319-74838-2_4

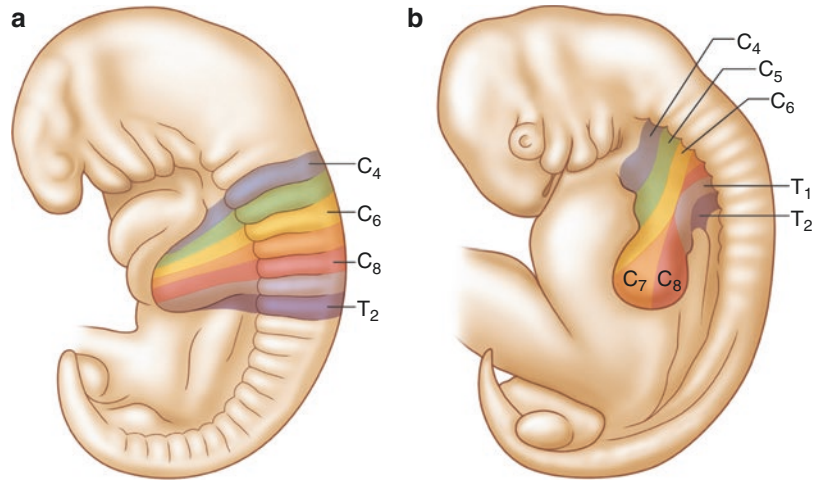


Fig. 4.1 Diagrams of the dermatomal pattern during early development of the pectoral limb bud at 5 weeks (**a**) and 6 weeks (**b**) of gestation

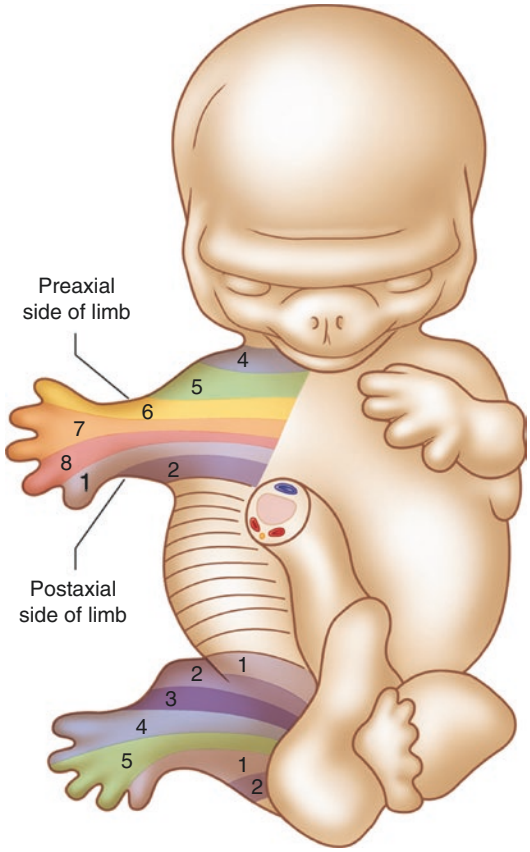


Fig. 4.2 Diagram of the ordered segmental distribution of peripheral afferents during an early stage of development

development, the pattern is clear. Sensory neurons from three levels are responsible for monitoring each region of the body to ensure redundancy of coverage and the integrity of the sensory monitoring system in the case of injury. Although the segmental relationship between the peripheral and central elements of the somatosensory nervous system remains and provides the basis for an ordered radicular or dermatomal pattern of innervation, the simple overlapping pattern is modified during later stages of development, resulting in a predictable increase in complexity of the basic dermatomal pattern (Fig. 4.3). The apparent change in distribution occurs during the process of differential growth and limb rotation through which the simple adult dermatomal pattern that is evident in the trunk is altered, leaving the inverted distribution of the segments of the trigeminal nerve in the head (Fig. 4.4), the autonomous regions of single root innervation in the limbs (Figs. 4.5 and 4.6), and the spiraling dermatomal pattern in the lower extremities (Fig. 4.6).

Axons that travel in close proximity to each other are packaged into nerve bundles that provide the conduits for neuronal traffic. Neurons innervating somatic derivatives of several dermatomal levels are packaged together and course through branches of spinal nerves that are distributed to the body wall and appendages (Figs. 4.7 and 4.8). The paths taken by neurons that innervate derivatives of the lateral plate mesoderm are less well defined in that they are variable and can course along blood vessels through elements of branches of the somatic nerves and through

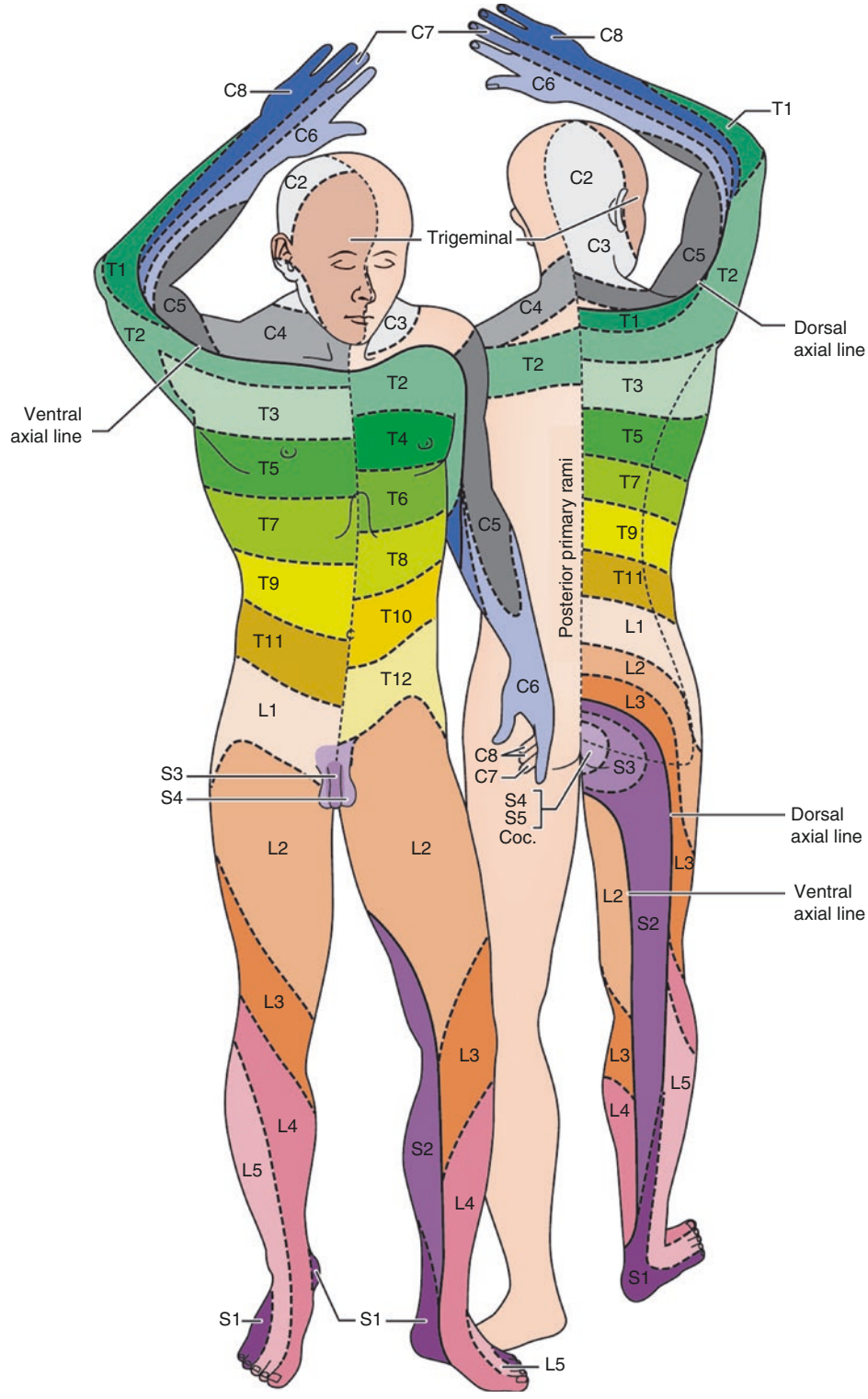


Fig. 4.3 Dermatomal distribution in the adult. Overlapping distribution of segments is indicated for the trunk (adapted from Lockhart RD, Hamilton GF, Fyfe FW. Anatomy of the Human Body. Philadelphia: J.B. Lippincott Company; 1972)

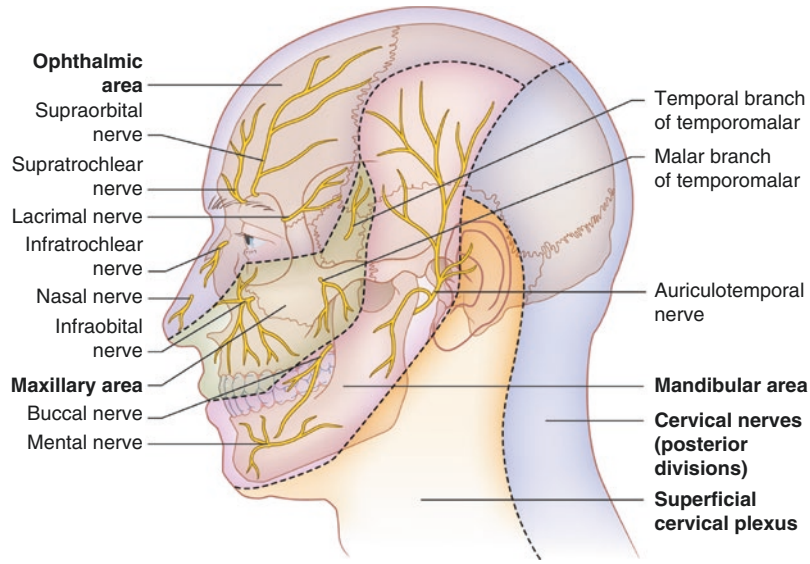


Fig. 4.4 Distribution of sensory nerves to the head (adapted from Gray's Anatomy, 1966)

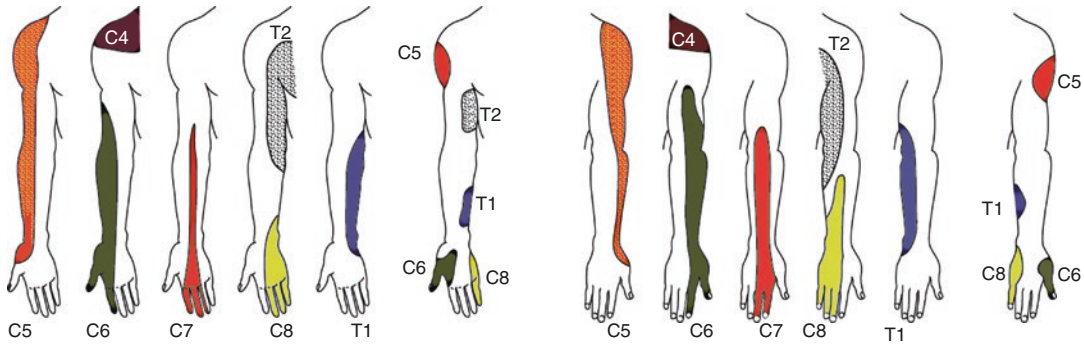


Fig. 4.5 Dermatomal distribution of the anterior (left) and posterior (right) upper extremity, showing areas supplied by only one segmental level (illustrations 6 and 12 from left) (adapted from Lockhart RD, Hamilton GF, Fyfe FW. Anatomy of the Human Body. Philadelphia: J.B. Lippincott Company; 1972)

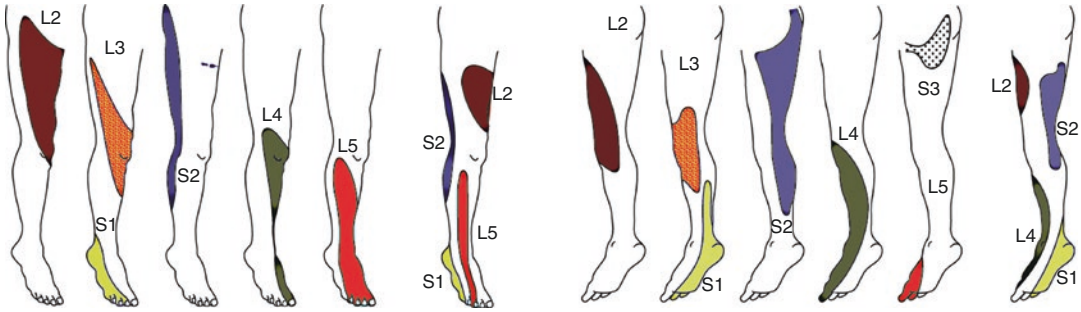


Fig. 4.6 Dermatomal distribution of the anterolateral (left) and posteromedial (right) lower extremity, showing areas supplied by only one segmental level (illustrations 6 and 12 from left) (adapted from Lockhart RD, Hamilton GF, Fyfe FW. Anatomy of the Human Body. Philadelphia: J.B. Lippincott Company; 1972)

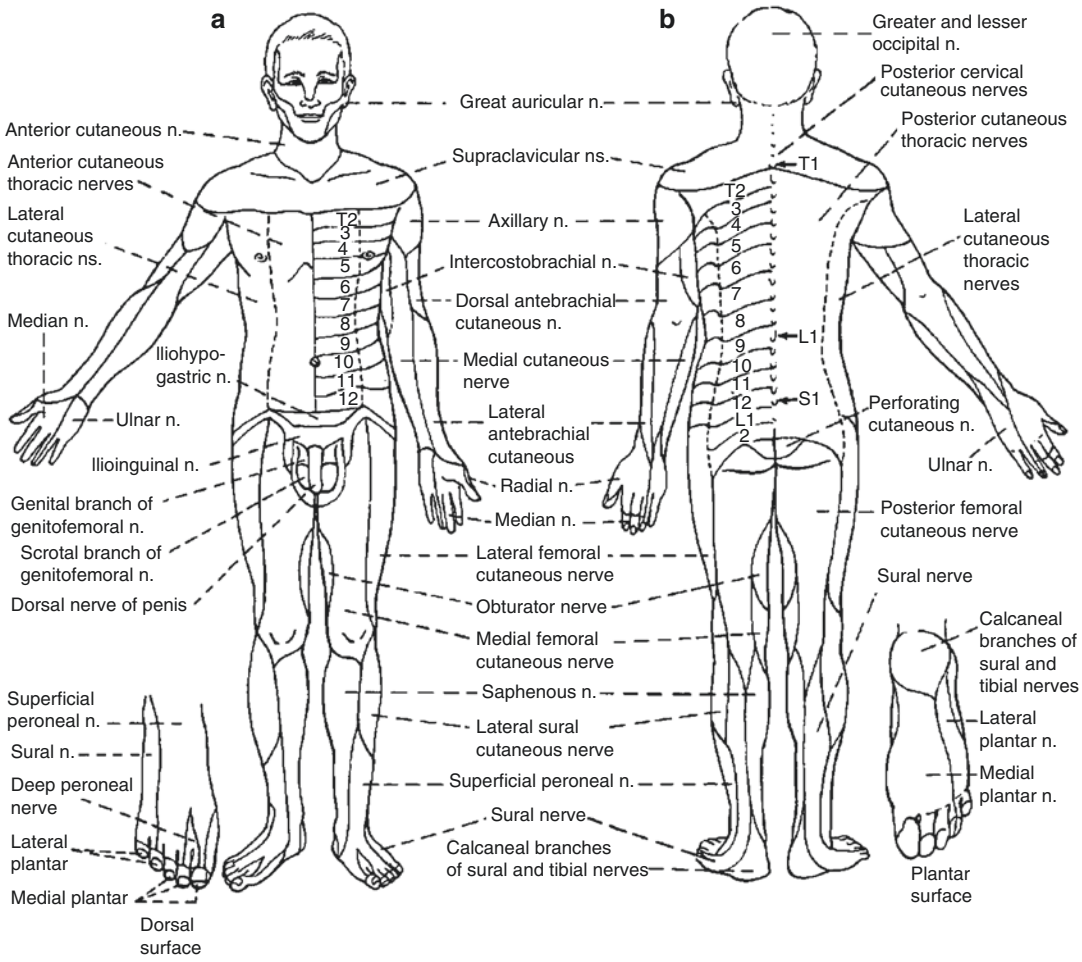


Fig. 4.7 The cutaneous fields of peripheral nerves (n.). (**a**) Anterior view. (**b**) Posterior view. In both figures, the numbers on the trunk refer to the intercostal nerves (modified from Haymaker W, Woodhall B. Peripheral nerve injuries: principles of diagnosis. Philadelphia: WB Saunders; 1945) (adapted from LeResche L, Bonica's Management of Pain, 3rd ed; 2001)

splanchnic components of the sympathetic nervous system (Fig. 4.9). These conduits ensure coverage of visceral tissues, smooth muscles, and glands located both in the body wall and in the core regions of the body. As long as the peripheral nerves are intact, damage to an individual nerve root will not result in complete loss of sensation in the area supplied by the damaged root. By contrast, damage to a peripheral nerve will result in a complete loss of sensation in the area served. An understanding of the differences between the patterns of dermatomal and peripheral nerve, thus, is important in assessing localization of site of injury and for determining the effect of diagnostic and therapeutic interventions.

Differential growth also results in an important disparity between boney vertebral levels, the location of the dorsal root ganglia, the location of the caudal end of the spinal cord, and the dorsal root entry zone of the spinal cord observed at different stages of development and in the adult. Figure 4.10 depicts the changes in the relative relationship between neural and boney elements from early stages in development (30, 67, and 111 mm) to shortly after birth (221 mm). In the

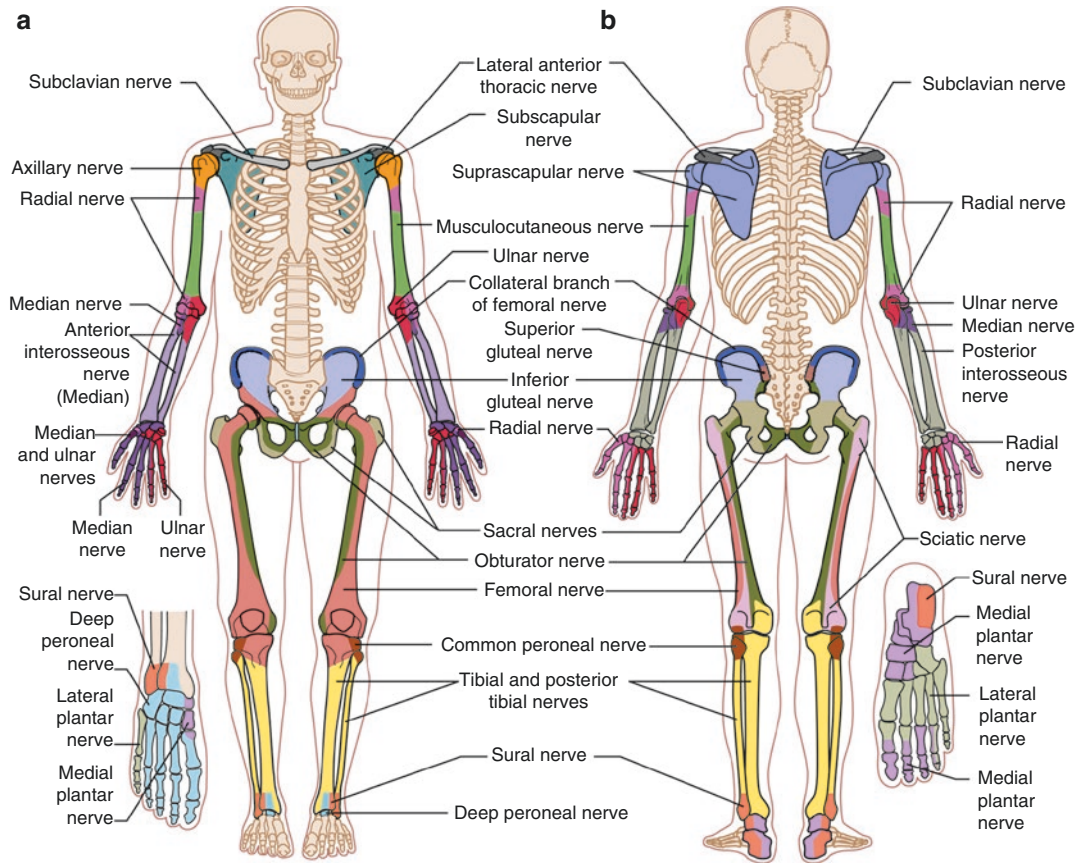


Fig. 4.8 The peripheral nerve supply of the skeleton. (**a**) Anterior view. (**b**) Posterior view. The various peripheral nerve fields are indicated by different patterns (modified from Dejérine J. Sémiologie du système nerveux. Paris: Masson; 1914) (adapted from LeResche L, Bonica's Management of Pain, 3rd ed; 2001)

adult, the relative disparity between level of the spinal nerve and its respective entry into the spinal cord generally follows the following formula: vertebral level (vertebral spinous process) + n = spinal cord level, where $n = 0$ for the upper cervical region, 1 between the lower cervical and upper thoracic region (vertebral prominence), 2 between T3 and T9, and 3 between T9 and T11 (Fig. 4.11). The conus medullaris is located between the spinous processes of the T12–L2 vertebrae. Figures 4.12, 4.13, and 4.14 depict boney landmarks and lines of reference to aid in identifying vertebral levels. An understanding of the disparity and knowledge of superficial landmarks is important for guiding and determining the best approaches for performing interventions on individual nerve roots and spinal cord levels. For example, the knowledge that the adult spinal cord extends inferiorly only to the L2–L3 vertebrae offers a degree of safety when inserting needles for obtaining spinal fluid from the lumbar cistern when the approach is made below the L3 vertebral level.

Stimulus Transduction and Transmission

Two fiber systems are responsible for the transmission of nociceptive signals from the body wall and viscera to the central nervous system, the Aδ and the C fiber systems (Fig. 4.15). A third system, the Aβ system, is primarily responsible for processing non-noxious mechanical

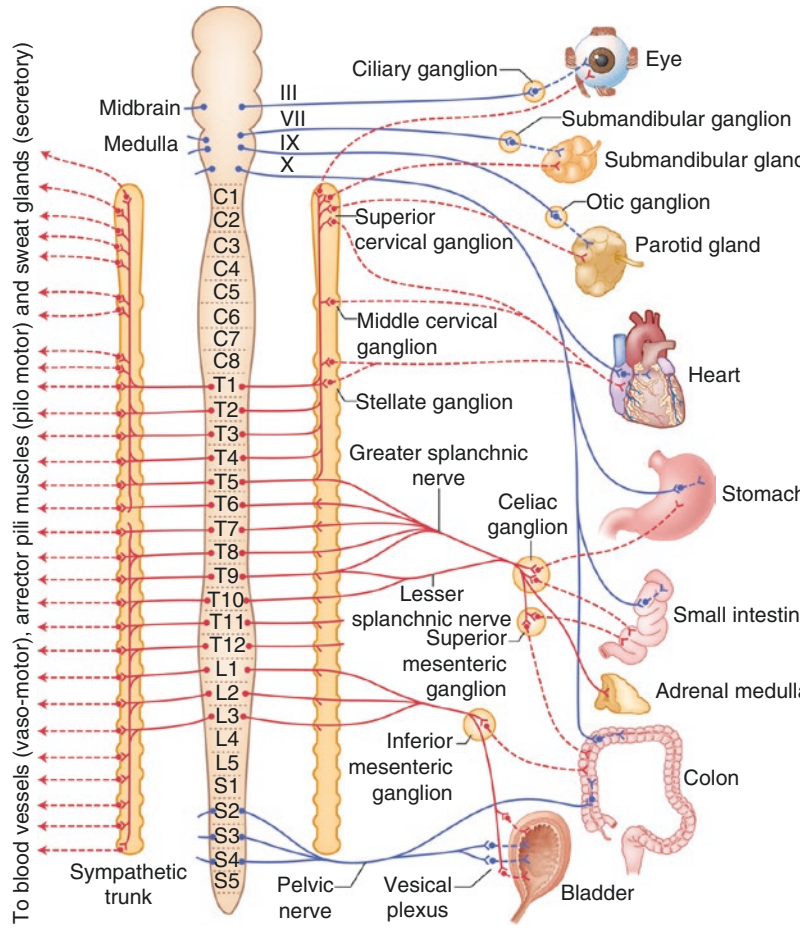


Fig. 4.9 Schematic diagram showing general arrangement of the autonomic system. The sympathetic components are shown in red, while the parasympathetic components are in blue. Solid lines represent preganglionic fibers; broken lines indicate postganglionic fibers. The sympathetic fibers to the blood vessels, hair, and sweat glands are not shown (adapted from Carpenter MB, Sutin J. Human Neuroanatomy. 8th ed. Baltimore: Williams & Wilkins; 1983)

stimuli and serves as a tactile discriminator, but it also plays a role in modulating nociceptive signals that enter the dorsal horn of the spinal cord (Fig. 4.15). These fiber systems are supported by pseudounipolar cell bodies that, along with supportive satellite cells, are located in the spinal dorsal root ganglia (DRG) and cranial nerves V, VII, IX, and X. The ganglia are located in or adjacent to intervertebral foramina of the spinal column or in or near boney canals and foramina of the skull, respectively. The intervertebral foramina and boney canals allow passage of elements of the peripheral nervous system into and out of the spinal cord and brain stem. The conducting elements of these fiber systems are composed of peripheral axons with free nerve endings or specialized receptor organs that are distributed in peripheral tissues and are contiguous with central elements that terminate either in the dorsal horn of the spinal cord or in nuclei of the brain stem. They are connected to their respective pseudounipolar perikarya by a T-segment of axonal membrane (Fig. 4.16). No synapses occur between primary afferents in the peripheral ganglia, but the proximity of the neuronal perikarya affords the possibility for electrochemical cross excitation between neurons to occur.

Free nerve endings comprise the distal terminals of nociceptive neurons. They are distributed within the epidermis of the skin, deep tissues, elements of the musculoskeletal system, and internal visceral organs. The nociceptors are optimally positioned to monitor changes in the thermal, mechanical, and chemical environment of every region of the body. Potentially injurious stimuli, when present in the peripheral tissues, trigger the release of a myriad of chemical mediators that set into motion a constellation of events

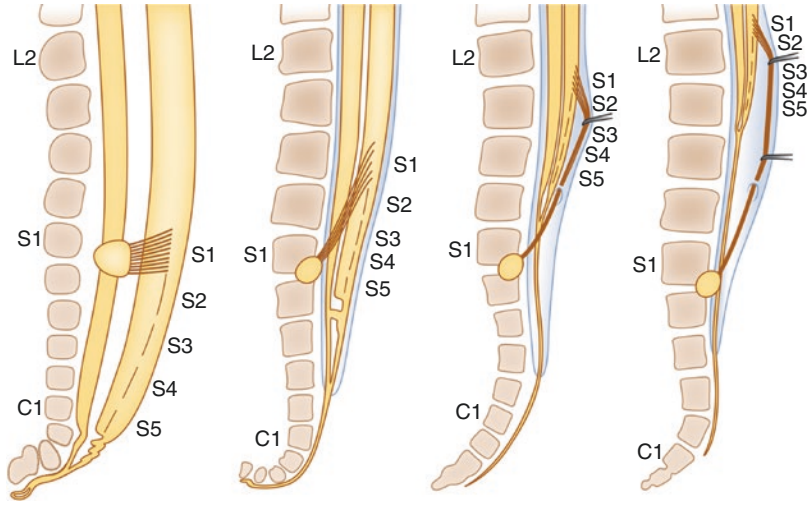


Fig. 4.10 Four successive stages in development of the caudal end of the human spinal cord (after Streeter). They show the formation of the filum terminale and the progressive obliquity of the first sacral nerve which is caused by the differential growth of the spinal cord and vertebral column. From left to right in the figure, the sizes of the embryos from which the reconstructions were made are as follows: 30, 67, and 221 mm (adapted from Hamilton WJ, Boyd JD, Mossman HW. Human embryology: Prenatal Development of Form and Function. 4th ed. London: Williams & Wilkins Company:Macmillian Press Ltd; 1978)

that alters the membrane permeability of afferent nerve terminals to charged ions. Among the inciting nociceptive events are the release of potassium ions, protons, and bradykinin and the initiation of the arachidonic acid cascade which leads to the production of prostaglandins and leukotrienes. Bradykinin, through activation of phospholipase C, stimulates the production of inositol 1, 4, 5-trisphosphate (IP3) and diacylglycerol (DAG) from membrane phospholipids. IP3 stimulates the release of calcium ions, while DAG, through protein kinase C (PKC)-mediated pathways, enhances the release of sodium ions and the production of arachidonic acid. The phospholipase A2-mediated metabolism of arachidonic acid increases tissue levels of adenylyl cyclase, cyclic AMP, and prostaglandins PGE_2 and PGI_2 [3–6]. These events, coupled with complimentary increases in the levels of mediators such as histamine, serotonin, adenosine, tumor necrosis factor-α (TNF-α), nerve growth factor (NGF), substance P (sP), glutamate, norepinephrine (NE), and cytokines (IL-1, IL-6), lead to a shift in the electrochemical gradient, the development of a generator current, the depolarization of the membrane, and the initiation of an action potential that is transmitted through the system of peripheral nerves to the central nervous system [5, 7] (Figs. 4.17 and 4.18).

Axons of the Aδ system range in diameter from 1 to 6 μm and are ensheathed by a thin layer of myelin [4]. The myelin provides a supportive and trophic effect for axons, and in addition to insulating axons within a nerve bundle from each other for the maintenance of temporal and spatial integrity of the signal, it serves to enhance conduction velocity. The Aδ axons are supported by cell bodies that measure 25–30 μm in diameter and serve small receptive fields. They respond to relatively low levels of noxious stimulation and conduct impulses at velocities between 5 and 30 m/s. Although they respond preferentially to mechanical stimulation, they also respond to noxious heat. As the axons approach the spinal cord, they diverge from the main nerve trunk and enter the dorsal root where they course by their cell bodies in the DRG and enter the spinal cord to terminate on neurons in Rexed laminae I, II, III, V, and X [8] (Fig. 4.19). The axons of the C fiber system are unmyelinated [5]. They are supported by DRG neurons measuring 10–15 μm in diameter, serve larger receptive fields than those served by Aδ

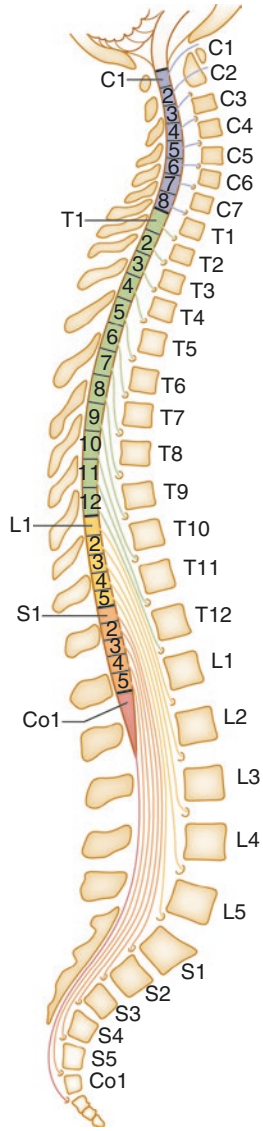


Fig. 4.11 Diagram of the position of the spinal cord levels in relation to the vertebral bodies and spinous processes of the vertebral column

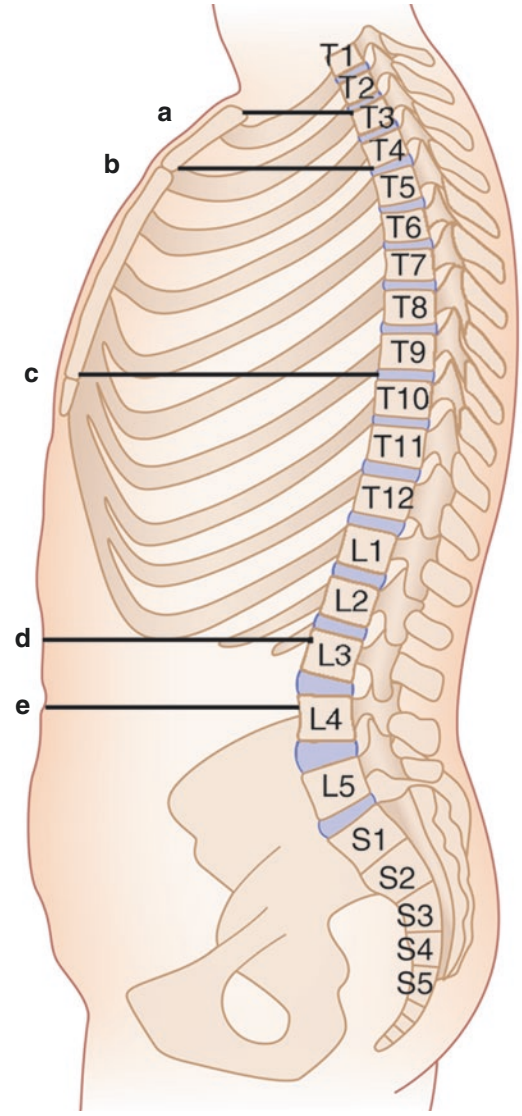


Fig. 4.12 A lateral view of the body, showing the vertebral levels of certain landmarks on the anterior thoracic and abdominal walls: (**a**) suprasternal notch, (**b**) sternal angle, (**c**) xiphisternal joint, (**d**) subcostal line, and (**e**) umbilicus (adapted from Crafts RC. A Textbook of Human Anatomy. 2nd ed. New York: Wiley Medical Publication; 1979)

fibers, require a higher stimulus intensity to initiate an action potential, and convey information at velocities between 0.5 and 2 m/s. C fibers respond to polymodal stimuli and can be classified into distinct populations [9]. Peptidergic C fibers respond to heat, but not to mechanical or cold stimuli. They also respond to sP, calcitonin gene-related peptide (CGRP), and capsaicin and express transient receptor potential cation channel subfamily V member 1 (TRP V1), tropomyosin receptor kinase (Trk) A, and μ-opioid receptors. Their activity is modulated by nerve growth factor (NGF). Peptidergic C fibers course medially in the dorsal root and terminate preferentially in Rexed lamina I, the outer portion of lamina II, and lamina V [8] (Fig. 4.20). A second population of C fibers

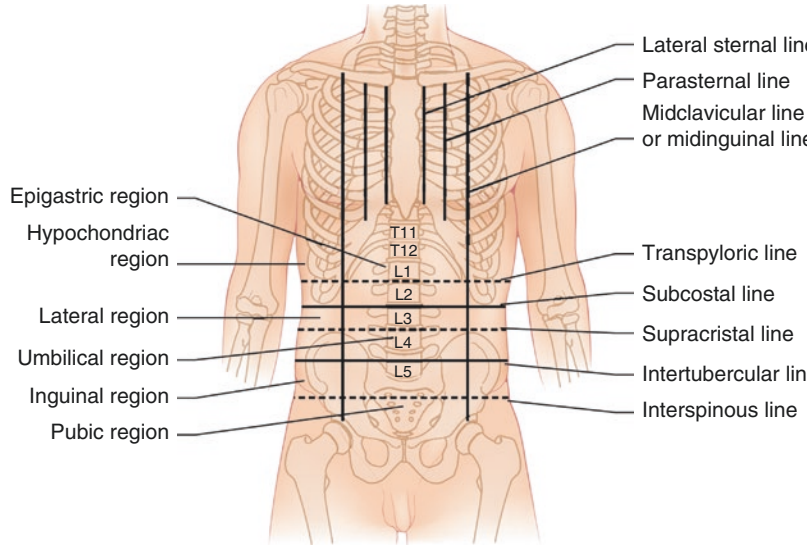


Fig. 4.13 Lines of reference on anterior thoracic and abdominal walls (adapted from Crafts RC. A Textbook of Human Anatomy. 2nd ed. New York: Wiley; 1979)

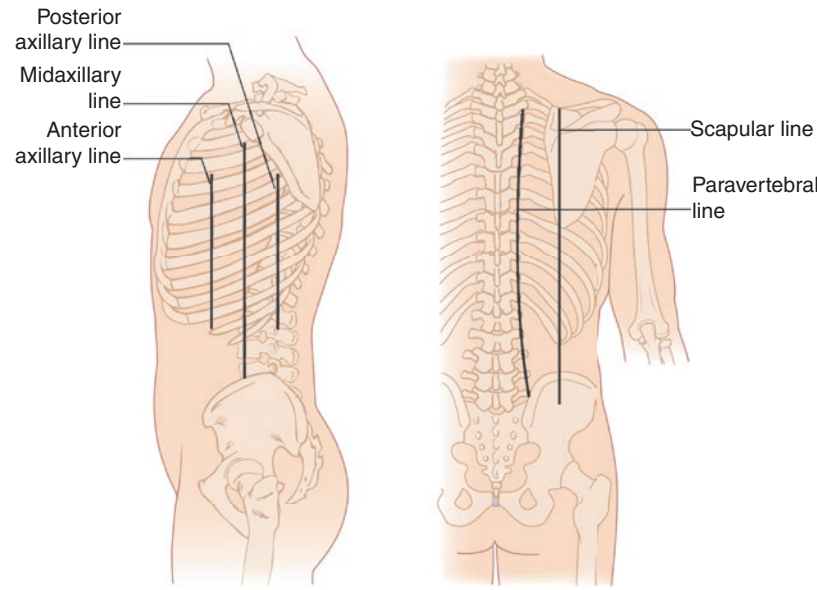


Fig. 4.14 Lines of reference on lateral and posterior chest wall (adapted from Crafts RC. A Textbook of Human Anatomy. 2nd ed. New York: Wiley; 1979)

responds to cold rather than to heat or mechanical stimulation and is not peptidergic. The cells respond to ATP and express P2X purinoceptor-3-isolectin B4, c-Ret neurotropin, and δ-opioid receptors. Unlike the peptidergic afferents, these cells terminate in the inner portion of lamina II and are modulated by glial-derived neurotrophic factor (GDNF). Some C fibers, "silent nociceptors," are typically unresponsive to normal noxious stimulation but become active during periods of inflammation or tissue injury, and others respond to peripherally released pruritogens. These specialized neurons release B-type natriuretic peptide (BNP) that activates natriuretic peptide receptor-A (Npra)-expressing neurons that subsequently release gastrin-releasing peptide (GRP) onto relay neurons in Rexed lamina I and II and are responsible for itch [10]. Upon entering the spinal cord, the axons of the primary nociceptors ascend and descend in the zone of Lissauer. The majority of these fibers ascend approximately two spinal levels before terminating in the dorsal horn.

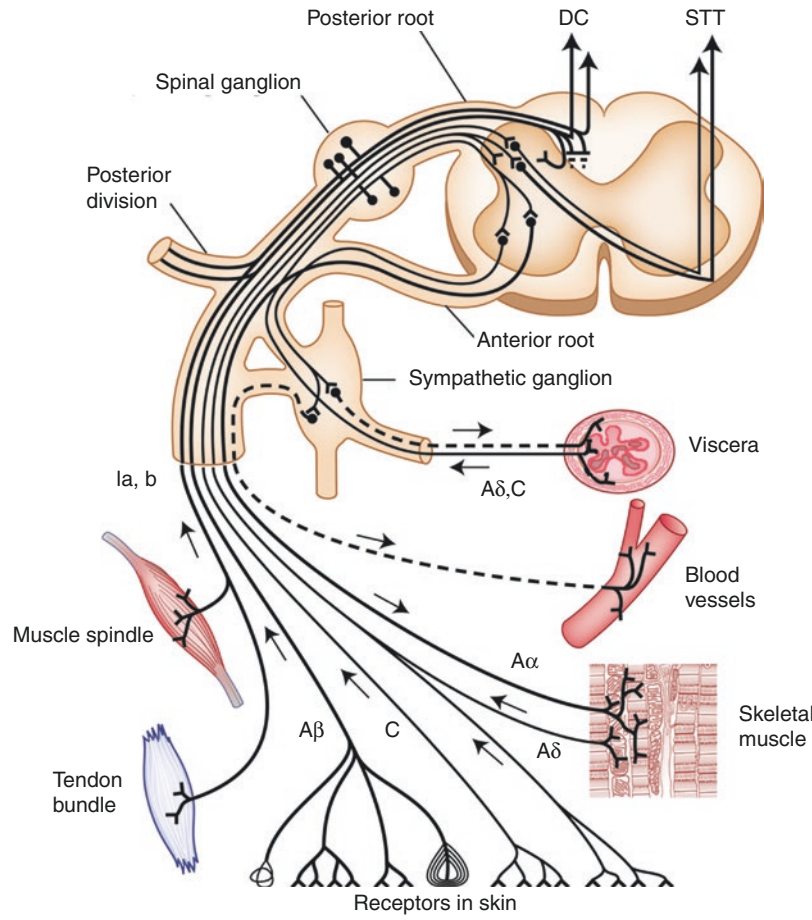


Fig. 4.15 A simplified schema of a spinal nerve and the different types of fibers contained therein (*DC* dorsal columns; *STT* spinothalamic tract) (adapted from Byers MR, Bonica JJ. Peripheral pain mechanisms and nociceptor plasticity. In: Loeser JD, Butler SH, Chapman CR, Turk DC, editors. Bonica's Management of Pain. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2001. p. 26–72)

In the resting state, the free nerve endings of nociceptive afferents maintain a polarized membrane with a higher concentration of sodium ions outside the cell. Noxious heat (>45–55 °C), cold (8–25 °C), mechanical (pressure or distention; 60 g/mm^2), or chemically mediated stimuli increase the permeability of the membrane to charged ions, thereby setting up a generator current (Fig. 4.18) that leads to a subsequent shift in the electrochemical gradient and voltage across the membrane [7, 11]. The change in voltage alters the configuration of voltage-gated channels, allowing entry of predominantly sodium ions into the cell in exchange for potassium ions, and the initiation of an action potential, which is propagated along the axon to the central nervous system. In myelinated axons like those of the Aβ and Aδ system, the excitable membrane that supports the propagation of action potentials is found only in the intervals between adjacent segments of myelin, called nodes of Ranvier, where there is a high density of sodium channels. Since membrane depolarization occurs at the nodes of Ranvier, impulses "jump" from one node to the next in a saltatory fashion, resulting in rapid conduction of the action potential (Fig. 4.21). The fiber diameter and the internodal distance are primary determinants of the conduction velocity of the axon. In unmyelinated axons like those of the C fiber system, sodium channels are distributed along the entire length of the axon (Fig. 4.21). Depolarization is propagated contiguously between adjacent membrane segments, resulting in the slowest impulse conduction of any system. After the passage of the action potential, the electrochemical gradient is reestablished through energy-dependent sodium/potassium pumps (Na^+/K^+, ATPase) that transport sodium ions out of the cell in exchange for potassium ions.

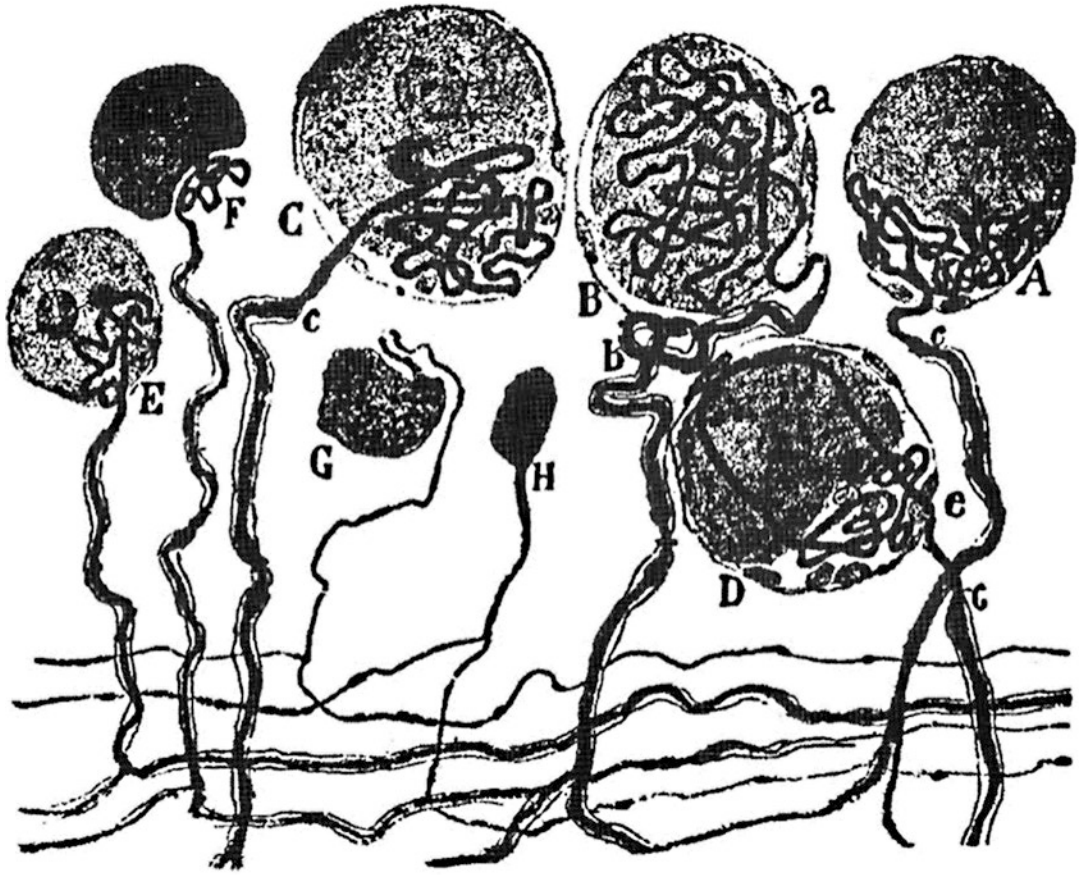


Fig. 4.16 Large and small DRG cell somata, the T-stem axon with its glomerulus, and the T-junction (adapted from Cajal, 1911, p. 428)

The differences in the receptive field sizes, the conduction velocity, and the thresholds for initiating action potentials between the Aδ and C fiber systems form the basis for the first and second pain responses. The first response occurs immediately upon stimulation, is often sharp in character, and is precisely localized. It results in a rapid, aversive withdrawal from the offending stimulus and a complimentary, supportive crossed extensor response. This basic mechanism is essential for survival and reduces the amount of tissue injury. Shortly after stimulation, a less well-localized feeling of discomfort is perceived, that is, often aching or throbbing in quality, and persists well after the stimulus has been removed. This second pain response raises the level of awareness of the injured body part during the healing process. The lowered threshold to activation of a nociceptive signal reduces the likelihood of additional injury due to subsequent activity and enhances vigilance until sufficient healing has occurred.

By contrast, when non-noxious mechanical stimuli are presented to specialized afferent end organs, e.g., Pacinian and Meissner corpuscles, Ruffini endings, and Merkel cells (Fig. 4.22), the membrane permeability of large (>25 μm in diameter), low-threshold neurons of the Aβ system is similarly altered, thus initiating action potentials conveying information of a non-noxious tactile nature [5]. These action potentials are conducted along large, 6–12-μm diameter myelinated axons at velocities between 30 and 70 m/s. Upon arriving at the spinal cord, the axons enter the cuneate

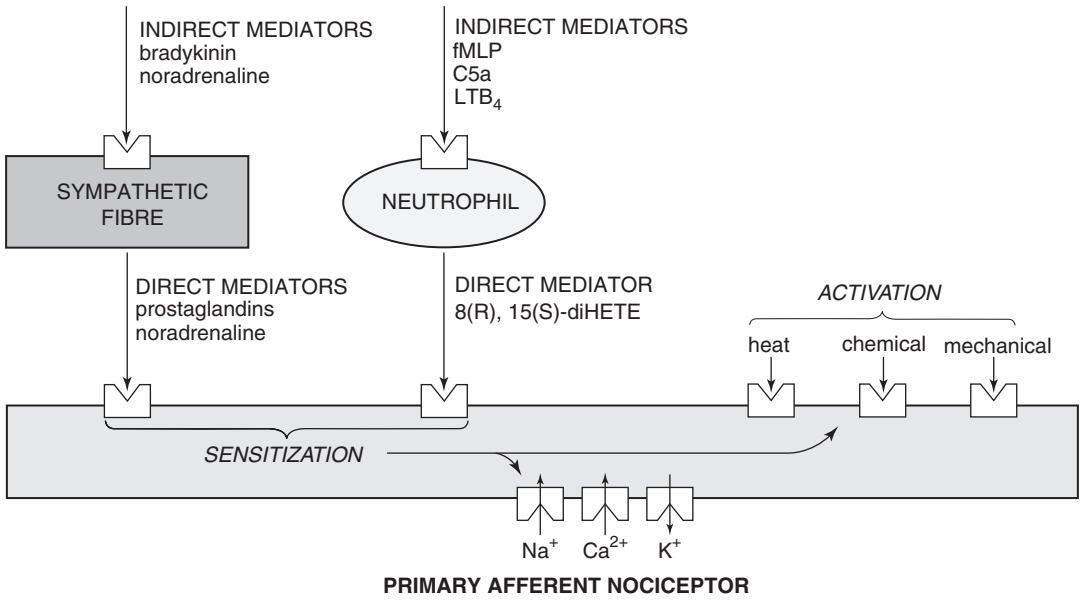


Fig. 4.17 Direct and indirect mechanisms by which inflammatory mediators sensitize primary afferent nociceptors (adapted from Levine JD, Reichling DB. Peripheral mechanisms of inflammatory pain. In: Wall PD, Melzack R, editors. Textbook of Pain. 4th ed. Edinburgh: Churchill Livingstone; 1999. p. 59–84)

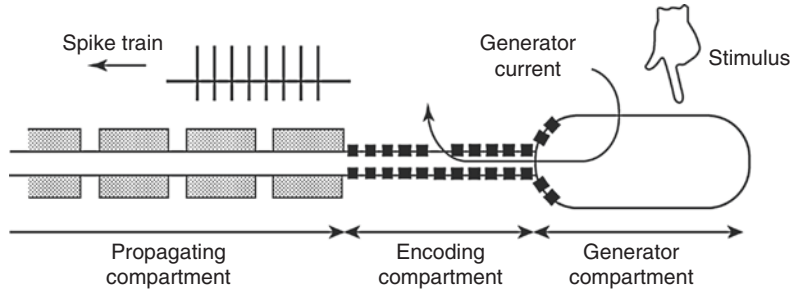


Fig. 4.18 Sketch of sensory ending showing generator, encoding, and propagating compartments (adapted from Devor M, Seltzer Z. The pathophysiology of damaged peripheral nerves. In: Wall PD, Melzack R, editors. Textbook of Pain. 4th ed. Edinburgh: Churchill Livingstone; 1999. p. 129–64)

and gracile fasciculi and ascend ipsilaterally in the spinal cord to terminate in the cuneate and gracile nuclei of the caudal medulla. Axons arising from neurons located in the cuneate and gracile nuclei then cross the midline of the neuraxis and ascend in the medial lemniscus to terminate in the lateral portion of the ventral posterior nucleus (VPN) of the thalamus. Collaterals from the Aβ afferents also project into the dorsal horn where they terminate in Rexed laminae III, IV, and V and, through stimulation of inhibitory interneurons, can reduce the intensity of nociceptive signals allowed through the dorsal horn (Fig. 4.23). Similar low-threshold tactile afferents arise from the head course in branches of the trigeminal nerve and enter the central nervous system at the level of the pons. These afferents terminate in the principal sensory nucleus. Axons arising from the principal sensory nucleus cross the midline, join the medial lemniscus, and ascend through the rostral brain stem to terminate in the medial portion of the VPN.

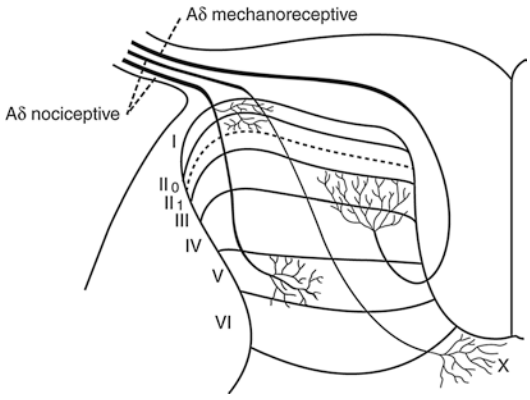


Fig. 4.19 Schematic diagrams of the course and termination of collaterals of the Aδ cutaneous fibers in the dorsal horn of the spinal cord (adapted from Byers MR, Bonica JJ. Peripheral pain mechanisms and nociceptor plasticity. In: Loeser JD, Butler SH, Chapman CR, Turk DC, editors. Bonica's Management of Pain. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2001. p. 26–72)

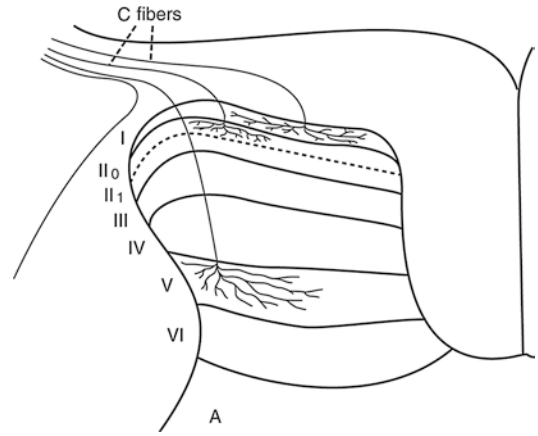


Fig. 4.20 Schematic diagrams of the course and termination of collaterals of unmyelinated C fibers in the dorsal horn of the spinal cord (adapted from Byers MR, Bonica JJ. Peripheral pain mechanisms and nociceptor plasticity. In: Loeser JD, Butler SH, Chapman CR, Turk DC, editors. Bonica's Management of Pain. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2001. p. 26–72)

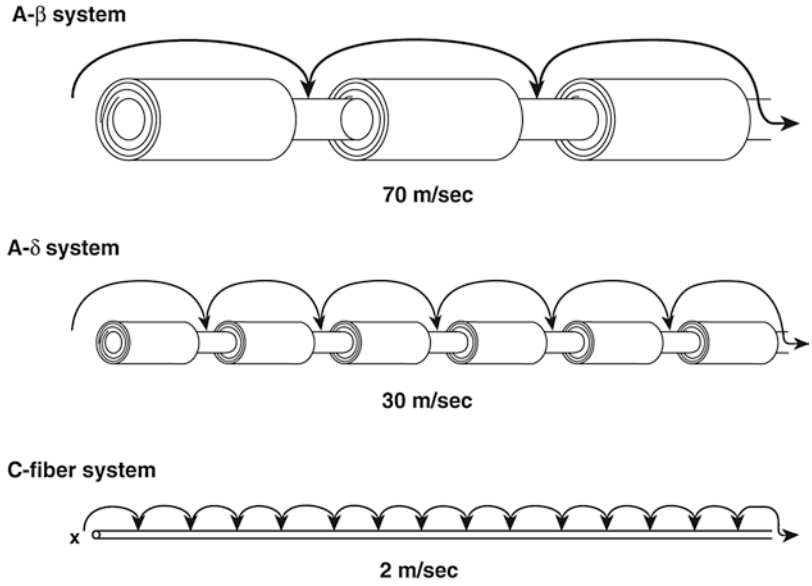


Fig. 4.21 Diagram depicts the relationship between fiber diameter, myelination, and conduction velocity in the peripheral nervous system (adapted from Gould HJ III. Understanding pain: what it is, why it happens, and how it's managed. New York: American Academy of Neurology Press, Demos; 2007)

Stimulus Modulation

Upon entry of the central gray matter, primary afferents release stored excitatory neurotransmitters, thereby relaying the initial nociceptive signal to either wide dynamic range or nociceptive-specific neurons of the dorsal horn (Fig. 4.24). Through this connection, the modality and the temporal and spatial aspects of the nociceptive signal are integrated. The sum of that integration is then transmitted to higher levels of the nervous system for further processing. The wide dynamic range neurons are found primarily in lamina V and are responsible for much of the information that is transmitted to the brain stem and thalamus. These neurons receive not only

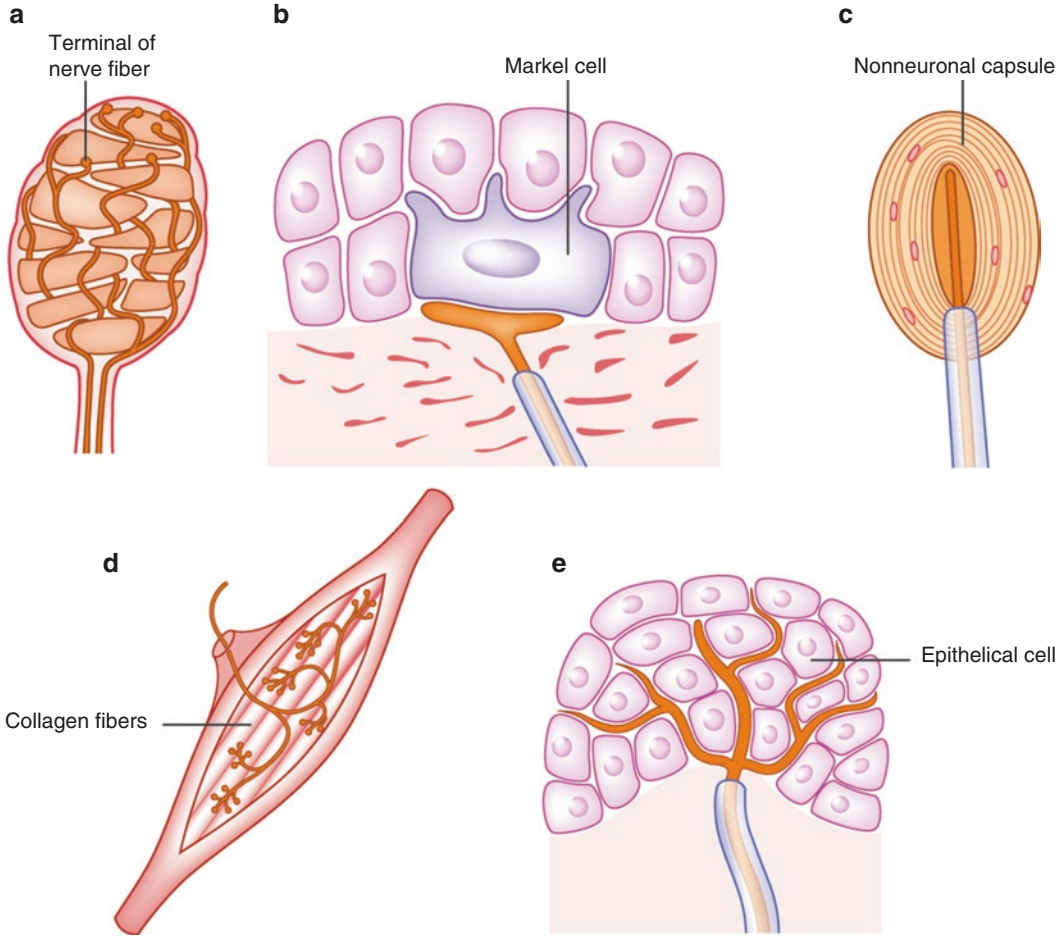


Fig. 4.22 Morphological features of somatosensory receptors, including the variation in non-neural components. (**a**) Meissner corpuscles are composed of axonal loops, separated by non-neuronal, supporting cells; (**b**) Merkel disks are characterized by the close association between afferent axons and Merkel cells; (**c**) Pacinian corpuscles include a central sensory axon, surrounded by a fluid-filled capsule that filters out all sustained stimuli; (**d**) Ruffini endings are driven by skin stretch because of the termination of primary afferents among collagen fibrils of the skin; and (**e**) free nerve endings, characteristic of nociceptors, are left unprotected from chemicals that are secreted or applied to the skin (adapted from Hendry SHC, Hsiao SS, Bushnell MC. Somatic sensation. In: Zigmond MJ, Bloom FE, Landis SC, Roberts JL, Squire LR, editors. Fundamental Neuroscience. San Diego: Academic Press; 1999)

polymodal inputs from high-threshold mechanical and heat-sensitive Aδ and C fiber nociceptors but also inputs from collaterals of non-nociceptive, low-threshold mechanical Aβ afferents and local internuncial neurons of the dorsal horn. They have a moderate threshold for initiating an impulse and are responsible for signals related to itch and flutter. Inputs to the wide dynamic range neurons provide the essential segmental framework for the "gate control theory" proposed by Melzack and Wall [12] whereby impulses transmitted by low-threshold mechanoreceptors can reduce the nociceptive signal that is relayed to higher integrative levels for conscious perception (Fig. 4.25). By comparison, nociceptive-specific neurons are located in laminae I and V and receive inputs only from high-threshold mechanical and heat-sensitive Aδ and C fiber nociceptors. Nociceptive-specific neurons receive inputs that may be either polymodal or

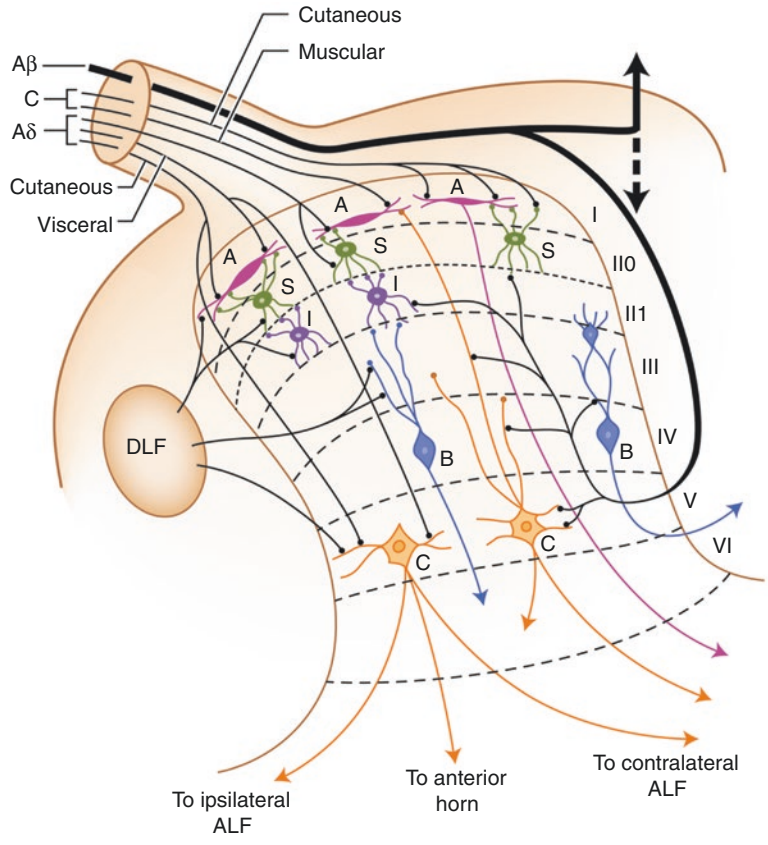


Fig. 4.23 Simplified schematic cross-sectional diagram of input and output of the dorsal horn of the spinal cord as well as interneurons and axonal terminals of descending control systems (adapted from Terman GW, Bonica JJ. Spinal mechanisms and their modulation. In: Loeser JD, Butler SH, Chapman CR, Turk DC, editors. Bonica's Management of Pain. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2001. p. 73–152)

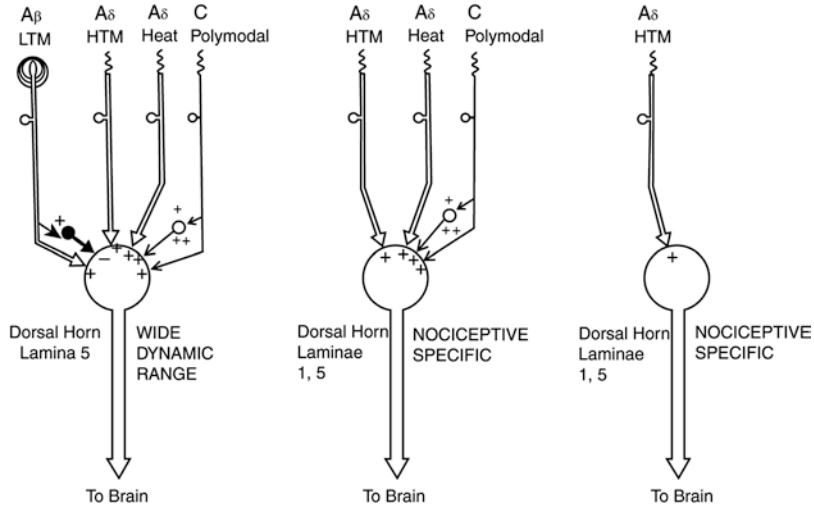


Fig. 4.24 Three types of nociceptive cells in the dorsal horn, their inputs from primary afferents, their location in the spinal cord, and their output to ascending systems. Wide dynamic range neurons receive inputs from low-threshold mechanoreceptive (LTM) primary afferents, high-threshold mechanoreceptive (HTM) primary afferents, and C-polymodal afferents. Nociceptive-specific neurons receive inputs exclusively from nociceptive afferents (adapted from Terman GW, Bonica JJ. Spinal mechanisms and their modulation. In: Loeser JD, Butler SH, Chapman CR, Turk DC, editors. Bonica's Management of Pain. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2001; p. 73–152)

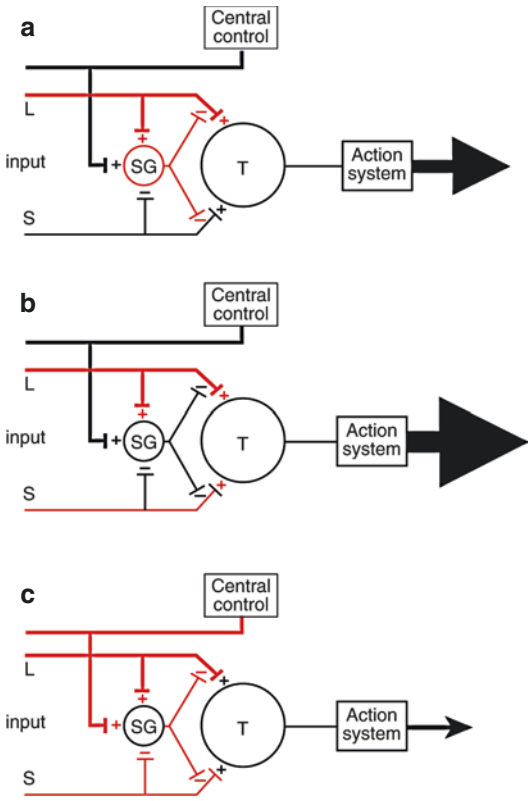


Fig. 4.25 Modified schematic diagram of the "gate control theory" of Melzack and Wall, 1965. SG represents an interneuron in the substantia gelatinosa of the dorsal horn. T represents a cell that transmits the nociceptive signal for higher central processing

modality specific and possess the capability of supporting after discharges, whereas the silent nociceptors are a special group of nociceptive-specific neurons that become active only during periods of inflammation and tissue injury and provide a means for amplifying the nociceptive signal.

When an action potential that is initiated by a nociceptive stimulus reaches the central afferent terminal, calcium enters the synaptic bouton through voltage-gated calcium channels (Fig. 4.26). In the presence of calcium, vesicles containing excitatory neurotransmitters, such as glutamate, aspartate, CGRP, sP, neurokinin, vasoactive intestinal peptide (VIP), neuropeptide Y (NP-Y), galanin, or somatostatin, fuse with the terminal cell membrane and release their contents into the synaptic cleft [4, 5]. The neurotransmitters cross the synaptic cleft, recognize receptors on the postsynaptic relay cell, and, through specific stoichiometric interaction, alter the membrane properties of ligand-gated receptors on the receiving neuron. The ligand-receptor interaction initiates a cascade of intracellular events that enables the triggering of the next impulse in the chain. The stability of the synapse is reestablished either by removal of the neurotransmitter from the synaptic cleft through

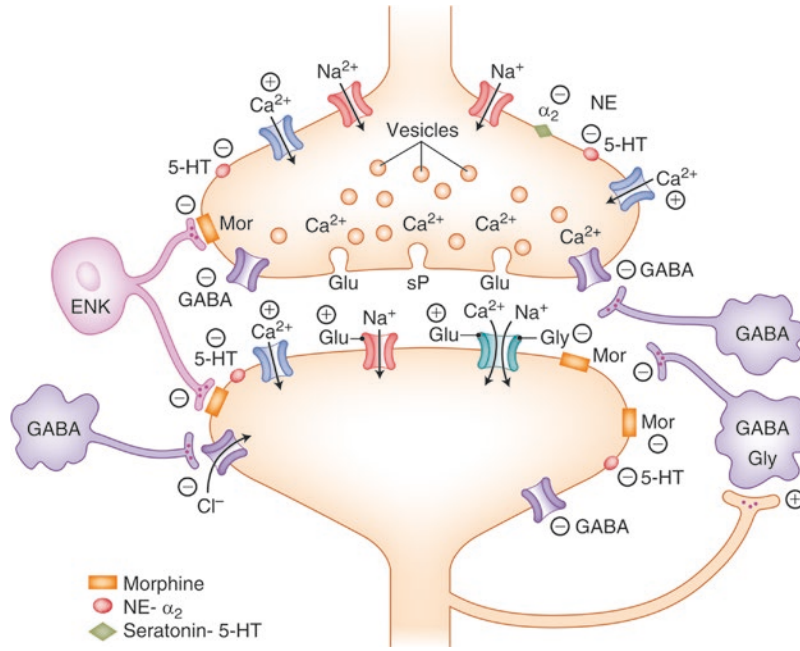


Fig. 4.26 Schematic depiction of a primary afferent synapse on a relay neuron in the dorsal horn of the spinal cord. *ENK* enkephalinergic neuron, *NE* norepinephrine, *5-HT* serotonin, *Glu* glutamate, *Gly* glycine, *MOR* μ-opioid receptor, and *GABA* gamma (γ)-aminobutyric acid (adapted from Gould HJ III. Understanding pain: what it is, why it happens, and how it's managed. American New York: Academy of Neurology Press, Demos; 2007)

enzymatic degradation; through reuptake into the presynaptic terminal or transport via glutamate transporter 1 (GLT1) and glutamate-aspartate transporter (GLAST), into astrocytes that support the synapse [13]; or through the activation of processes that inhibit synaptic transmission. One such process is the collateral activation of inhibitory interneurons within the dorsal horn that release inhibitory neurotransmitters such as glycine and gamma (γ)-aminobutyric acid (GABA). These transmitters inhibit further release of excitatory neurotransmitters from the presynaptic terminal and stabilize the postsynaptic cell. It is the critical balance between the excitatory components of the afferent pathway whose role is to ensure transmission of the signal warning of impending injury. It is the inhibitory components that through amplification can reduce or through suppression can enhance the amount of nociceptive signal that is allowed to pass to higher levels of the nervous system and be perceived at any given time (Fig. 4.27).

Stimulus Perception and Interpretation

Axons en route to the thalamus from the spinal cord course through the ventral white commissure of the spinal cord, cross the midline, and enter the contralateral lateral spinothalamic tract where they project rostrally through the central nervous system to terminate in the VPN. Similar projections that subserve the territory of the trigeminal nerve receive inputs from axons that, upon entering the pons, descend in the spinal trigeminal tract and terminate on neurons in the spinal trigeminal nucleus. The projections that arise from the relay neurons in the spinal trigeminal nucleus cross the midline and join the spinothalamic tract en route to the VPN (Fig. 4.28). There are two components of the lateral spinothalamic pathway. The first component, the neospinothalamic tract, provides for discriminative functions and is related to the Aδ system. It projects directly to the VPN and is rapidly conducting, precisely

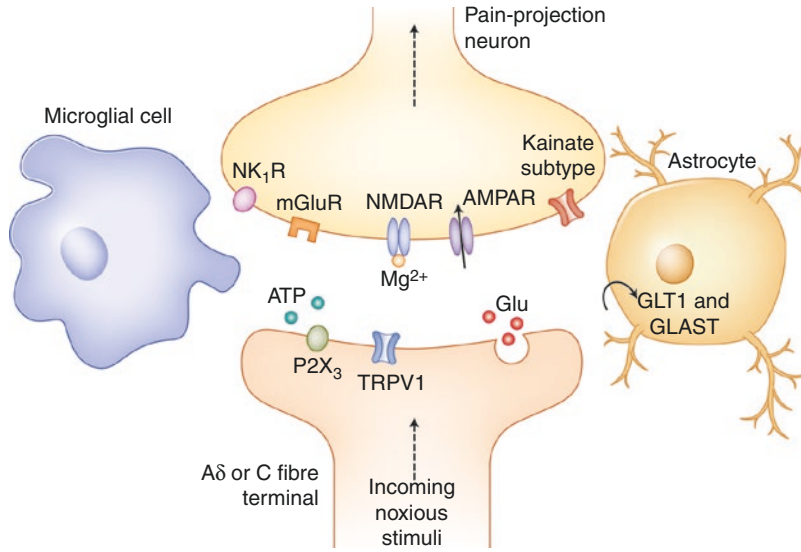


Fig. 4.27 Schematic depiction of the glial contribution to the processing of the primary afferent signal. Under healthy circumstances, low-frequency activation of Aδ and C fiber nociceptors by mild noxious stimuli leads to glutamate (Glu) release from the central presynaptic afferent nerve terminals in the spinal cord dorsal horn. Short-term activation of AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) and kainite subtypes of ionotropic glutamate receptors ensues. Although also present, the NMDA (*N*-methyl-D-aspartate) ionotropic glutamate receptor subtype (NMDAR) remains silent because it is plugged by Mg^{2+}. This signaling to dorsal horn pain-projection neurons provides information about the time of onset, duration, and intensity of noxious stimuli from the periphery. Both astrocytes and microglia remain unchanged by these synaptic events (adapted from Milligan ED, Watkins LR. Pathological and protective roles of glia in chronic pain. Nat Rev. 2009;10:23–36)

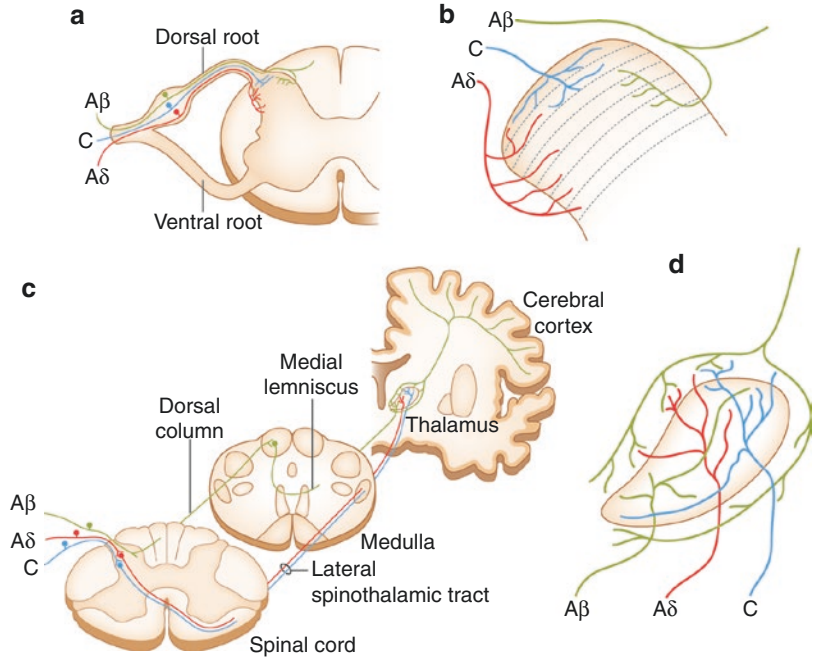


Fig. 4.28 Distribution of pathways involved in transmitting nociceptive information from peripheral nerves to higher levels of the brain for processing. (**a**) Depicts sensory nerves passing through dorsal roots en route to points of termination in the dorsal horn of the spinal cord and medulla. Specific fiber types terminate in different portions of the dorsal horn, as illustrated in (**b**). Signals effectively relayed in the spinal cord and brain stem course through the medical lemniscus and lateral spinothalamic tracts and terminate in a topographic fashion in the thalamus [(**c**) and enlarged in (**d**)] where the stimulus is consciously perceived. Projections from the thalamus connect with areas of the cerebral cortex (**c**) where further analysis and association with past experience are made (adapted from Gould HJ III. Understanding pain: what it is, why it happens, and how it's managed. New York: American Academy of Neurology Press, Demos; 2007)

somatotopically organized, and modality specific. The second component, the paleospinothalamic tract, provides the basis for the affective and modulatory components of pain and is associated with the C fiber system. Its projections are more diffusely organized. In addition to projecting to the VPN, the paleospinothalamic tract provides collateral connections to the nuclei of the rostral ventromedial medulla (RVM), the lateral tegmental nucleus (LTN), the periaqueductal gray (PAG), the posterior and intralaminar nuclei of the thalamus, the basal telencephalic regions, limbic and paralimbic forebrain, amygdala, fornix, habenula, septal nuclei, and the hypothalamus. Upon termination in the thalamus, the nociceptive signal is consciously perceived [14].

Neurons in the VPN relay the nociceptive signal to the primary and secondary somatosensory cortices for the processing of location, intensity, and stimulus characterization and to the inferotemporal and frontal cortices for cognitive and contextual content and for cognitive, affective, and executive responses, respectively (Fig. 4.28). In the cortex, nociceptive signals are integrated and compared with past experience, emotions, mood, and current status for interpretation and implementation of a behavioral response. It is in this integrative process that the initial nociceptive signal is transformed into the complex, uncomfortable sensory and emotional experience that we call pain. It is the dynamic relationship between the thalamic neurons and the cortical modulating cells that determines the intensity of the unique painful experience perceived by each individual at any moment in time. Following the integration of the discriminative and affective components of the pain pathway, corticofugal projections return to VPN and surrounding

thalamic association nuclei, to the hypothalamus, and to brain stem nuclei. These projections can either augment or diminish the level of pain that is perceived for facilitation of a fight-or-flight response, depending on the state of the individual.

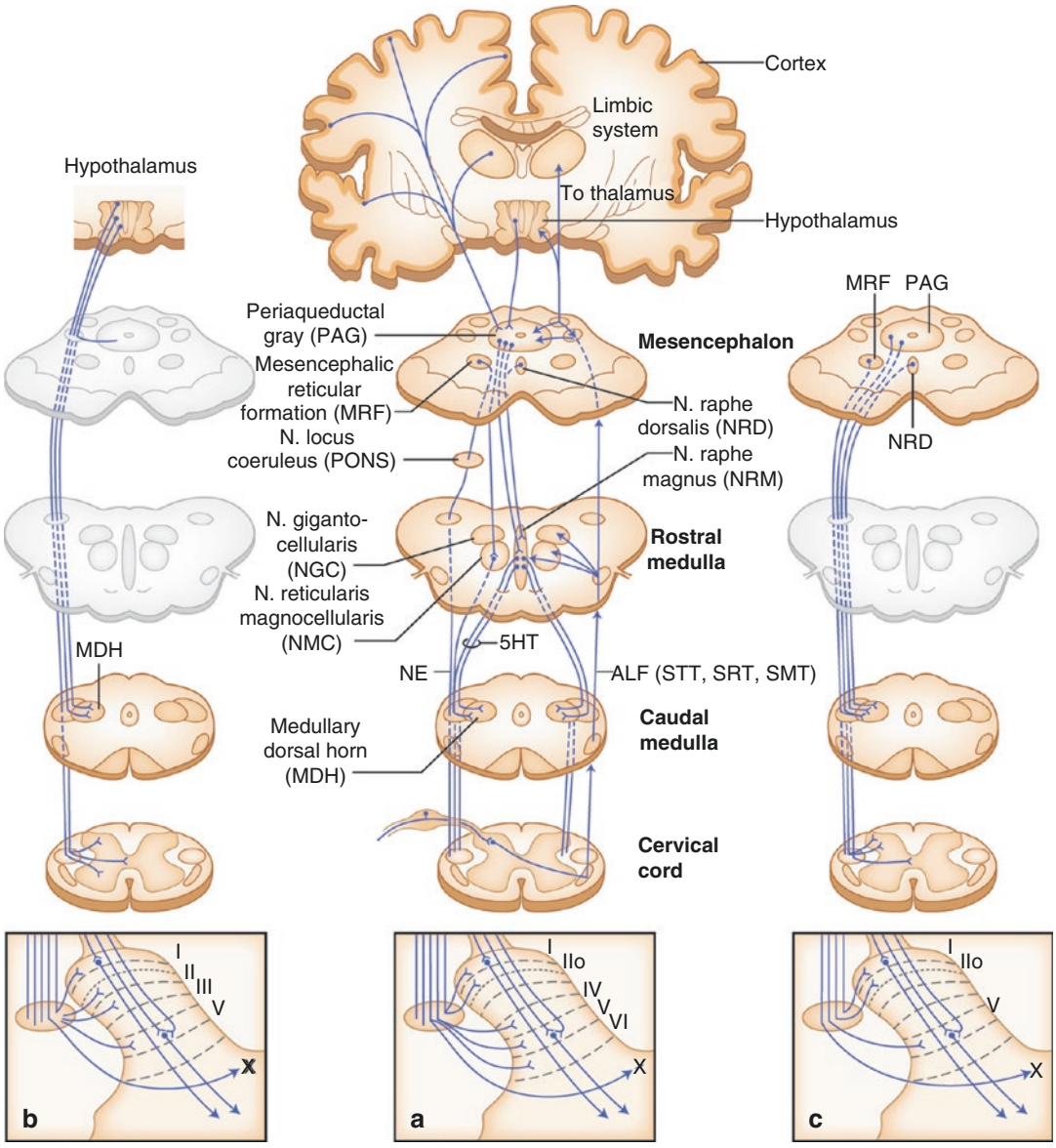
Stimulus Modulation and Behavioral Response

The hypothalamus monitors basal body functions, such as thirst, hunger, satiety, sexual function, blood pressure, temperature, and emotion, and influences behavior based on conscious and subconscious information sent from the cortex and from various body organs to maintain normal body function. Hypothalamic modulation of the behavioral response can be affected through the release of several hormones, including vasopressin, corticotropin-releasing factor (CRF), and pituitary adrenocorticotropic hormone (ACTH), that act centrally or peripherally to produce direct or indirect activity on pain-transmitting neurons. The process of modulation occurs through direct projections that affect the activity of enkephalinergic neurons of the PAG, the norepinephrine-containing neurons of the LTN, the serotonergic neurons of the RVM, and the neurons in the entry zones that receive primary afferent input [8, 15]. Projections from the RVM and the LTN descend through the brain stem and the dorsolateral funiculus of the spinal cord and synapse on the terminals of the primary afferent neurons and on inhibitory enkephalinergic and GABAergic interneurons of the dorsal horn, thereby indirectly affecting the transmission of nociceptive signals through the dorsal horn (Fig. 4.29). These projections can block the release of neurotransmitter from the primary afferent terminals, stimulate local inhibitory interneurons, or stabilize the membrane of the relay neurons and thus suppress the amount of nociceptive signal that is allowed to pass through the dorsal horn en route to higher integrative centers. Depending on the state of the individual, modulation of these descending systems can produce the opposite effect through reduction of the level of direct inhibitory input or through the disinhibition of local inhibitory circuits, thus amplifying noci-

Fig. 4.29 Descending endogenous pain inhibitory systems. (**a**) The most extensively studied and probably the most important descending system, composed of four-tiered parts. The ascending anterolateral fasciculus (ALF), composed of the spinothalamic, spinoreticular, and spinomesencephalic tracts, has important inputs into the nucleus raphe magnus (NRM), nucleus magnocellularis (NMC), nucleus reticularis gigantocellularis (NGC), and the periaqueductal gray (PAG) via the nucleus cuneiformis. The ALF also has input to the medullary/pontine reticular formation, the nucleus raphe dorsalis (NRD), and the mesencephalic reticular formation (MRF). The PAG receives input from such rostral structures as the frontal and insular cortices and other parts of the cerebrum involved in cognition and from the limbic system, thalamus, and hypothalamus, which sends β-endorphin axons to the PAG. The locus coeruleus in the pons is a major source of noradrenergic input to the PAG and dorsal horn (tract-labeled NE). These mesencephalic structures (PAG, NRD, MRF) contain enkephalin (ENK), dynorphin (DYN), serotonin (5-HT), and neurotensin (NT) neurons, but only the latter two send axons that project to NRM and NGC. Here, they synapse with neurons that are primarily serotonergic, whose axons project to the medullary dorsal horn and descend in the dorsolateral funiculus to send terminals to all laminae of the spinal gray (the densest populations are found in laminae I, II, and V of the dorsal horn and the motor neuron pools of lamina IX). The projection from NRM is bilateral, whereas the projection from NGC is ipsilateral. Noradrenergic fibers descend and project to the medullary dorsal horn and then descend in the dorsolateral funiculus of the spinal cord to send terminals to laminae I, II, IV, through VI, and X. (**b**) A simplistic schema to show the direct hypothalamospinal descending control system, which originates in the medial and paraventricular hypothalamic nuclei. This descending system consists of vasopressin and oxytocin neurons (and perhaps some enkephalinergic neurons), which not only send terminals predominantly to laminae I and X but also provide sparse input into laminae II and III and the lateral part of lamina V, as well as the homologous area in the medullary dorsal horn. (**c**) Direct PAG-spinal projection system, which bypasses the medullary nuclei and projects directly to the medullary dorsal horn and then descends in the dorsolateral funiculus to send terminals to laminae I, II_o, V, and X. Most of the axons are serotonergic and noradrenergic (adapted from Terman GW, Bonica JJ. Spinal mechanisms and their modulation. In: Loeser JD, Butler SH, Chapman CR, Turk DC, editors. Bonica's Management of Pain. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2001. p. 73–152)

ceptive signals and augmenting the likelihood that additional signals of a painful nature will be transmitted to the thalamus for perception [8].

For optimum survival, it is important to prepare the organism for an appropriate behavioral response and return the monitoring system to optimum levels of functioning in anticipation of additional warnings. This function is built into the nervous system. Since pain may well signal a threat to the survival of at least a part of an individual, painful stimuli automatically prepare the individual for rapid assessment of the afferent stimulus and the initiation of defensive "fight-or-flight" behavior through activation of the sympathetic nervous system (Fig. 4.30). The sympathetic nervous system controls blood pressure, heart and breathing rate, and the volume of blood that flows to specific tissues—more to voluntary muscles, heart, and lungs and less to the intestinal system and skin. The neurotransmitter that is released to produce these responses is norepinephrine. When released in the vicinity of peripheral afferent nerve



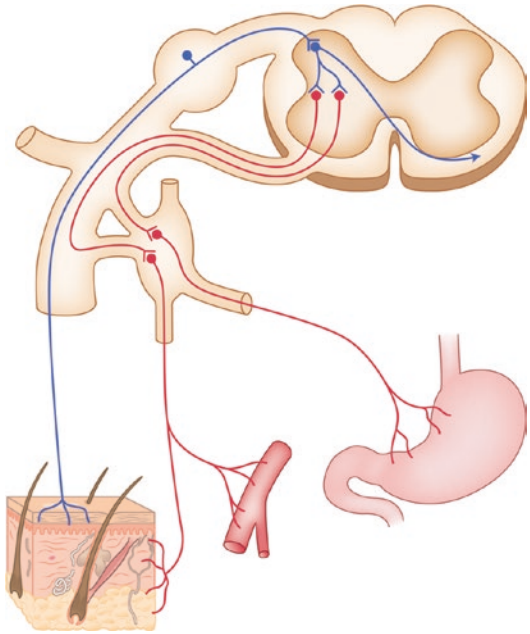


Fig. 4.30 Schematic depiction of sympathetic efferent projections in red that contribute to the "fight-or-flight" response to a nociceptive stimulus (from Gould 2007, modified from Byers MR, Bonica JJ. Peripheral pain mechanisms and nociceptor plasticity. In: Loeser JD, Butler SH, Chapman CR, Turk DC, editors. Bonica's Management of Pain. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2001. p. 26–72)

terminals, impulse generation is made easier. The sympathetic tone is modulated through descending cortical and hypothalamic projections that determine the firing frequency of preganglionic sympathetic neurons located in the intermediolateral cell column of the spinal gray matter from C8 (T1) to L1–L2 levels of the spinal cord.

After a nociceptive signal has been effectively relayed to the thalamus for further processing, the mechanisms responsible for receiving the nociceptive signals must be reset in the event that additional noxious stimuli requiring assessment arrive at the dorsal horn. To accomplish this, active relay neurons send axon collaterals to local inhibitory neurons in the dorsal horn that project back to the primary afferent terminal and to the initiating relay neuron to inhibit further activity and thus reduce the likelihood that multiple impulses will be sent to higher levels of analysis. The primary transmitters utilized by these inhibitory neurons are GABA and glycine.

Pathway Alterations Following Injury

After an injury, it is important to be aware of the area that has been injured so as not to subject it to further trauma that could exacerbate the injury. Mechanisms to enhance sensitivity in an injured region are also present in the normal nervous system, thereby aiding in recovery by increasing vigilance of the wound during the healing process. A significant portion of stimulus enhancement occurs during the process of peripheral sensitization. Peripheral sensitization is a by-product of the inflammation that is part of the mechanism of repair. It is present following injury and continues through the time that the wound has healed [16]. The process is initiated when tissue is injured by a thermal, mechanical, or chemical stimulus. Chemical mediators of inflammation are released from tissues in and around the site of injury. These chemicals increase blood flow to the injured area, carrying cells that engulf and destroy nonviable tissues and infectious agents, and increase levels of oxygen and nutrients necessary for repair. The inflammatory cells sequester particulate by-products of the cleanup and remove the by-products of metabolism. This process directly sensitizes the local nociceptors at the site of injury and, through the release of neurochemicals from collateral free nerve endings, indirectly sensitizes free nerve endings in adjacent tissues (Fig. 4.31). Consequently, the threshold for peripheral nociceptors is lowered, which increases the likelihood that a warning signal will be generated in a primary afferent nerve cell.

Abnormal sites for generation of a nociceptive signal that lead to repetitive firing and spontaneously generated pain can also develop when nerves are injured [7]. The mechanisms of injury vary, resulting in unique alterations in the normal function and integrity of the nerve. The alterations can include the destruction or damage to the neuronal cell bodies, the axons with their central and/or peripheral processes, the specialized endings in the peripheral tissues, and the supportive glial and Schwann cell elements as a result of toxic, metabolic, infectious, traumatic, and con-

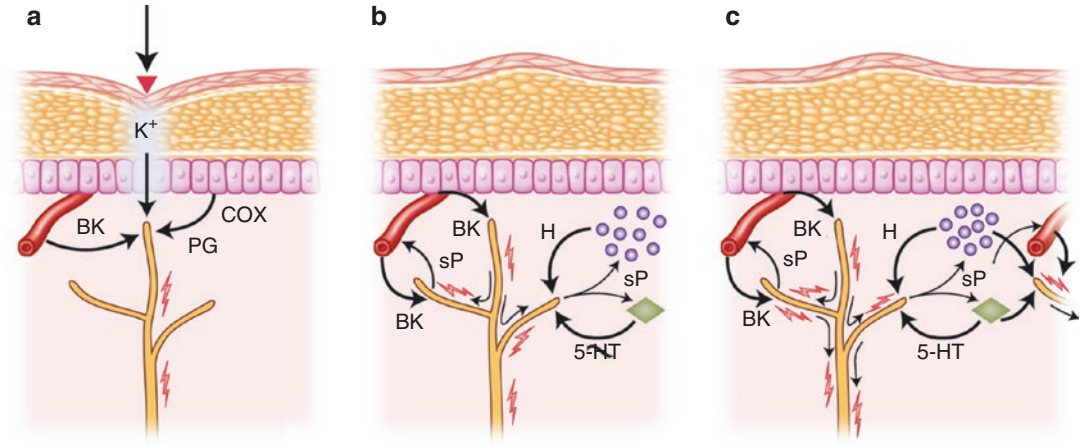


Fig. 4.31 Inflammatory enhancement of the pain signal. (**a**) Shows that noxious stimulation (arrow) results in the local release of protons (K^+) and inflammatory chemicals, bradykinin (BK) and prostaglandins (PG). A nociceptive signal is initiated and transmitted to the spinal cord. (**b**) Illustrates the nerve impulse as it extends into the peripheral terminal branches of free nerve endings causing the release of neurochemicals, e.g., substance P (sP), which stimulate the release of additional BK and other chemicals, histamine (H), and serotonin (5-HT). BK, H, and 5-HT make local and adjacent terminals (**c**) more sensitive to stimulation and thus more likely to generate a nociceptive signal. Modified from Byers and Bonica, 2001 (from Gould HJ III. Understanding pain: what it is, why it happens, and how it's managed. New York: American Academy of Neurology Press, Demos; 2007)

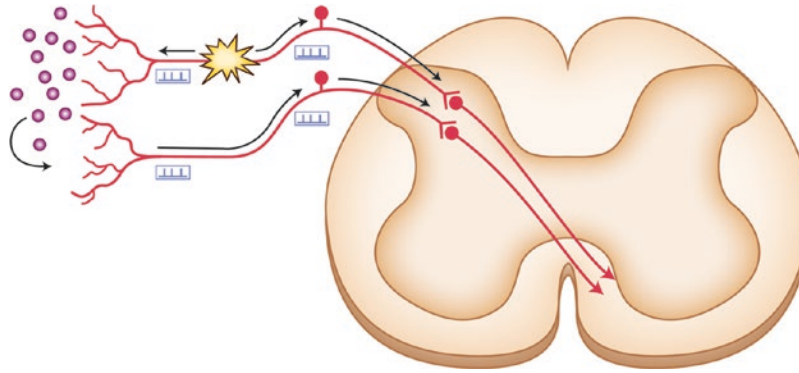


Fig. 4.32 Ectopic firing of injured nerve cells and peripheral sensitization. When peripheral nerves are injured, nerve impulses can be generated spontaneously at abnormal sites along the axon. An impulse is transmitted to the spinal cord and brain in the normal fashion but, in addition, is transmitted peripherally to the afferent terminals. Chemical mediators such as substance P are released and sensitize adjacent free nerve endings, enabling the initiation of a nociceptive signal in response to a non-noxious stimulus. Modified from Woolf and Mannion 1999 (from Gould HJ III. Understanding pain: what it is, why it happens, and how it's managed. New York: American Academy of Neurology Press, Demos; 2007)

genital processes involving either the central or the peripheral nervous system. Such changes potentially lead to alterations in the numbers and relative densities of ion channels responsible for cellular excitability. In a significant portion of the population, neuronal injury results in such changes that make it possible for impulses to be generated at abnormal sites along the course of an axon rather than just at the generator zone of nerve terminals and at synapses (Fig. 4.32) [17]. Because of altered numbers, types, and distribution of ion channels, spontaneous channel openings allow the entry of sufficient sodium ions into the axon to depolarize the membrane [7, 18]. In

the periphery, the wave of depolarization proceeds away from the active site both toward the spinal cord and toward the body surface [19]. When a nerve impulse reaches the free endings of the afferent nerve terminal, neurochemical mediators are released from the terminals as described earlier, resulting in peripheral sensitization of the adjacent nerve terminals and the generation of nerve signals as a result of either noxious or nonnoxious stimuli. The signals then project centrally; reach the spinal cord, thalamus, and cortex; and are perceived as pain in the region of the body served by the aberrantly firing nerve. The resulting perception of pain can thus occur in the absence of a noxious stimulus being delivered to the body at the time of perception.

Enhanced peripheral activity associated with tissue injury, especially in individuals susceptible to developing neuropathic pain related to nerve injury, potentially lays the foundation for the development of persistent or permanent pain states. The regular and frequent signals are passed to the central nervous system, and through a process of central sensitization called "windup," the repetitive firing of peripheral C fibers produces a gradual increase in the perception of a stimulus irrespective of an increase in stimulus intensity [20]. This phenomenon effectively increases the likelihood that a stimulus will be relayed to levels of cognitive perception through a sensitization of relay neurons in the dorsal horn of the spinal cord. If the process of central sensitization is allowed to persist, high levels of sP and glutamate remain in the synaptic cleft (Fig. 4.33). When concentrations of sP and glutamate remain high in the synaptic cleft due to repetitive firing of primary afferent neurons, NK-1, kainite, ionotropic (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and metabotropic (mGluR) receptors, and through continued depolarization of the postsynaptic membrane in the presence of increased levels of glycine, released from local inhibitory interneurons, *N*-methyl-D-aspartate (NMDA) glutamate receptors are activated allowing entry of calcium as well as sodium into the postsynaptic cell. Other voltage-gated calcium channels present in the relay cell membrane also are activated and allow the entry of additional calcium into the relay neurons. Excess levels of intracellular calcium lead to activation of calcium-calmodulin protein kinase II α (CaMKIIα), cyclic adenosine

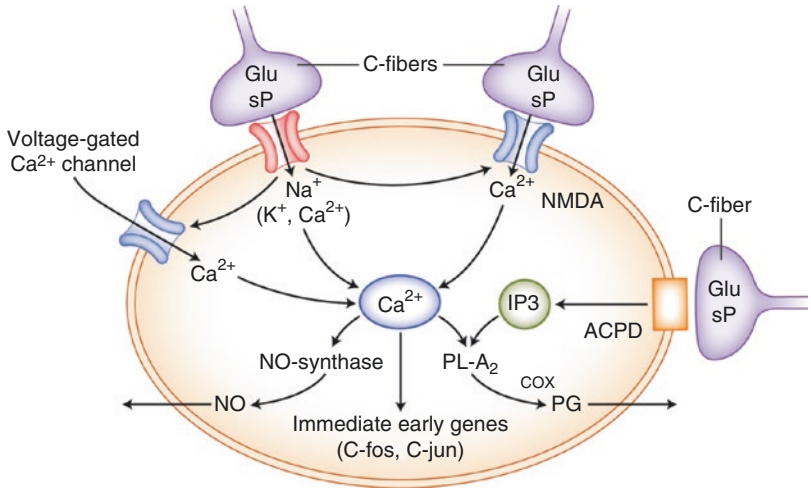


Fig. 4.33 Repetitive stimulation results in the activation of NMDA glutaminergic receptors and voltage-gated calcium channels. The entry of excess calcium stimulates the synthesis of nitric oxide and prostaglandins that are released from the neuron, resulting in sensitization of neighboring relay neurons and the possible initiation of the genetic process for the synthesis of cellular proteins. Modified from Ollat H, Cesaro P. Pharmacology of neuropathic pain. Clin Neuropharmacol. 1995;18:391–404 (from Gould HJ III. Understanding pain: what it is, why it happens, and how it's managed. New York: American Academy of Neurology Press, Demos; 2007)

monophosphate (cAMP), brain-derived neurotrophic factor (BDNF), protein kinase A and C (PKA and PKC), and a further increase in AMPA receptor activation [21]. Through activation of the IP3 and DAG pathways, there is enhanced production of nitric oxide and prostaglandins that are released into the local neuropil. These mediators decrease the firing threshold of adjacent relay neurons, thus strengthening signal transmission and making it possible for adjacent neurons to reach firing threshold upon receiving an input generated by any level of stimulation (Fig. 4.34). In addition, the activation of a prostaglandin-dependent PKC pathway is thought to be a crucial component in "hyperalgesic priming," a process by which an injurious event produces changes in peripheral afferents that results in an exaggerated and prolonged hyperalgesic response to a subsequent minimally noxious or non-noxious stimulus that sets the stage for the development of chronic pain [22]. The neuromodulating chemicals that are also released from hyperactive relay neurons can affect additional transmitter release from the primary afferent neuron and affect the release of cytokines, neurotransmitters, and trophic agents from local microglia and astrocytes (Fig. 4.35) [12]. The resulting cascade of events enhances the likelihood that both noxious and non-noxious stimuli will be sufficient to initiate transmission of a nociceptive signal to higher levels of the nervous system. Finally, continued high levels of intracellular calcium may initiate the synthesis of proteins such as extracellular signal-regulated kinase (ERK), p38, and c-Jun N-terminal kinase (JNK) for further sensitization of pathways that enhance nociceptive transmission and the synthesis of immediate early genes that provide a basis for generating new and permanent neuronal connections and establish the basic framework for permanent hypersensitivity or centrally generated pain [23, 24].

Clearly, the processing of painful signals within the nervous system is complex and involves many components that function sequentially and simultaneously to enhance survival of the individual. The system provides many fail-safe assurances to ensure the integrity of the

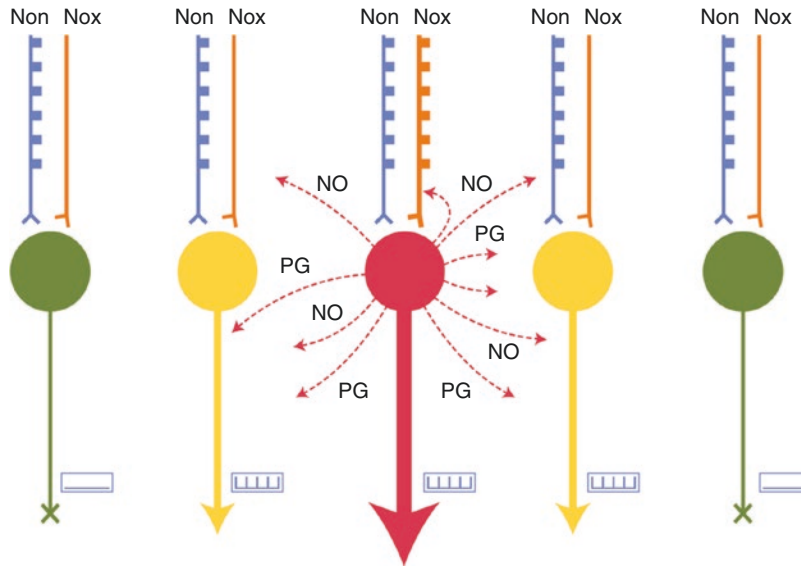
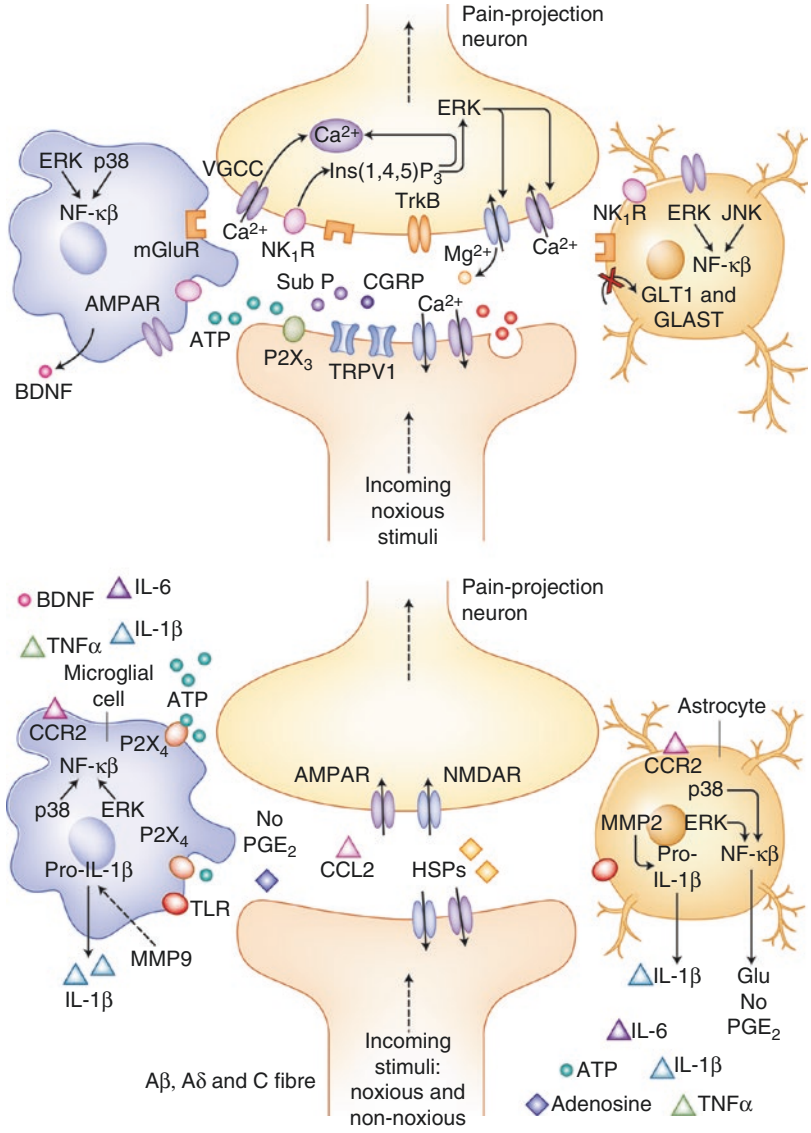


Fig. 4.34 Central sensitization enhances the transmission of a nociceptive signal. When nociceptive signals (Nox) repeatedly cause relay neurons to fire (arrowhead), prostaglandins (PG) and nitric oxide (NO) are released from the relay neuron (red), as illustrated in Fig. 4.32. PG and NO sensitize nearby nociceptive relay neurons (yellow) and enable them to respond to non-noxious stimuli (Non). Non-sensitized neurons (green) do not respond to non-noxious stimuli (from Gould HJ III. Understanding pain: what it is, why it happens, and how it's managed. New York: American Academy of Neurology Press, Demos; 2007)

warning system to protect against serious injury, yet these assurances provide problems and frustration in achieving complete or even adequate pain relief. To achieve the best possible treatment of pain, all components must be considered as possible sources for pain generation and possible avenues for pain control. Knowledge of the anatomical and physiological basis for nociceptive processing and an understanding of the most likely sites where damage and intervention can occur are essential for providing optimum care for your patients.

Acknowledgments The authors wish to thank Dr. Dennis Paul for his helpful comments and suggestions in the preparation of this manuscript.

Fig. 4.35 Schematic depiction of the role of glia in processing repetitive nociceptive input and pain processing during inflammation. After repetitive synaptic communication, which can occur after a short barrage of nociceptive afferent input, there is an increase in the responsiveness of dorsal horn pain-projection neurons to subsequent stimuli (known as central sensitization). A co-release of glutamate and neurotransmitters such as substance P (sP) and calcitonin gene-related peptide (CGRP) mediates NMDAR activation, leading to voltage-gated Ca^{2+} currents (VGCCs). In addition, inositol-1,4,5-triphosphate ($Ins(1,4,5,)P_3$) signaling and mitogen-activated protein kinases, such as extracellular signal-regulated kinase (ERK), p38, and c-Jun N-terminal kinase (JNK), are activated. In neurons, ERK can further sensitize excited AMPA receptors (AMPARs) and NMDARs. Activation of purinoreceptors ($P2X_3$) by ATP, activation of sP receptors (the neurokinin 1 receptor (NK_1R)), activation of metabotropic glutamate receptors (mGluR), and release of brain-derived neurotrophic factor (BDNF) all contribute to enhanced nociceptive transmission. Astrocytes and microglia express various neurotransmitter receptors and are activated by glutamate, ATP, and sP. At synapses, the glutamate transporters, glutamate transporter 1 (GLT1), and glutamate-aspartate transporter (GLAST), which are crucial for clearing synaptic glutamate, become dysregulated after prolonged exposure to high levels of p38 and JNK activation in microglia and astrocytes. Each of these kinases can activate the transcription factor nuclear factor κB (NF-κB), which induces the synthesis of inflammatory factors. Upregulation of the V1 transient receptor potential channel (TRPV1) after inflammation further contributes to the sensitization to noxious signals. During this time, normally non-nociceptive Aβ fibers can also activate pain-projection neurons. If noxious input persists, such as during chronic inflammation or nerve damage, sustained central sensitization leads to transcriptional changes in dorsal horn neurons that alter these neurons' function for prolonged periods. Astrocytes respond to this ongoing synaptic activity by mobilizing internal Ca^{2+}, leading to the release of glutamate (Glu), ATP that binds to $P2X_4$, tumor necrosis factor-α (TNF-α), interleukin 1β (IL-1β), IL-6, nitric oxide (NO), and prostaglandin E_2 (PGE_2). Activated microglia are also a source of all of these proinflammatory factors. Matrix metalloproteinase 9 (MMP9) induces pro-IL-1β cleavage and microglial activation, whereas MMP2 induces pro-IL-1β cleavage and maintains astrocyte activation. The activation of p38 mitogen-activated protein kinase (p38 MAPK) is induced in both microglia and astrocytes on IL-1β signaling. Astrocytes and microglia express the chemokine receptors CX3CR1 (not shown) and CCR2 and become activated when the respective chemokines bind. After nerve damage, heat shock proteins (HSPs) are released and can bind to Toll-like receptors (TLRs) expressed on both astrocytes and microglia, leading to the further activation of these cell types (adapted from Milligan ED, Watkins LR. Pathological and protective roles of glia in chronic pain. Nat Rev. 2009;10:23–36)


Pain-projection neuron
ERK
Ca2+
VGCC
Ins(1,4,5)P3
TrkB
ERK p38
NF-κβ
mGluR
Ca2+
NK1R
Mg2+
Ca2+
NK1R ERK JNK
NF-κβ
GLT1 and GLAST
Sub P
CGRP
Ca2+
AMPAR
ATP
P2X3
TRPV1
BDNF
Incoming noxious stimuli
BDNF
IL-6
TNFα
IL-1β
Microglial cell
ATP
CCR2
P2X4
NF-κβ
p38
ERK
P2X4
Pro-IL-1β
TLR
MMP9
IL-1β
Pain-projection neuron
AMPAR
NMDAR
No PGE2
CCL2
HSPs
Astrocyte
CCR2
p38
MMP2
ERK
Pro-IL-1β
NF-κβ
IL-1β
Glu
No PGE2
IL-6
ATP
IL-1β
Adenosine
TNFα
Aβ, Aδ and C fibre
Incoming stimuli: noxious and non-noxious

Review Questions

1. Inhibitory interneurons within the dorsal horn release inhibitory neurotransmitters such as:
   (a) Glycine and gamma (γ)-aminobutyric acid (GABA)
   (b) Glutamate and aspartate
   (c) Calcitonin gene-related peptide (CGRP), galanin, and substance P (sP)
   (d) Neurokinin, vasoactive intestinal peptide (VIP), and neuropeptide Y (NP-Y)
2. There are two components of the lateral spinothalamic pathway:
   (a) Neospinothalamic tract and paleospinothalamic tract
   (b) Subthalamic tract and cerebellar vermis tract
   (c) Anterior and posterior longitudinal tract
   (d) Neocerebellar and tuberculum tract
3. When glutamate concentration remains high due to repetitive firing of primary afferent neurons, the depolarized postsynaptic membrane in the presence of increased levels of glycine, released from local inhibitory interneurons, stimulates the opening of:
   (a) Serotonin receptors
   (b) Bradykinin receptors
   (c) Muscarinic receptors
   (d) *N*-methyl-D-aspartate (NMDA) glutamate receptors
4. Inputs to the wide dynamic range neurons provide the essential segmental framework for the "gate control theory" proposed by:
   (a) Melzack and Wall (1965)
   (b) Racz and Raj (1971)
   (c) Bonica (1958)
   (d) Lema (1986)
5. The gate control theory:
   (a) Is completely false
   (b) States that impulses transmitted by low-threshold mechanoreceptors can reduce the nociceptive signal that is relayed to higher integrative levels for conscious perception
   (c) Explains the mechanism of the gamma reflex loop
   (d) Is the basis of our understanding of saltatory conduction
6. The regular and frequent signals which can be passed to the central nervous system and through a process of central sensitization are called:
   (a) "Windup"
   (b) Diffusion
   (c) Archicerebellum redundancy
   (d) Schmidt-Lanterman syndrome
7. The consequences of "windup" include:
   (a) Quicker reflexes
   (b) Increased micturition and defecation
   (c) The repetitive firing of peripheral C fibers which produces a gradual increase in the perception of a stimulus irrespective of an increase in stimulus intensity
   (d) The sequential discharge of β fibers which produces γ-mediated pain
8. Unique structures, which are depolarized by stimuli in response to tissue damage:
   (a) Touch receptors
   (b) Nociceptors
   (c) Temperature receptors
   (d) Chloride channels
9. As the axons approach the spinal cord, they diverge from the main nerve trunk and enter the dorsal root where they course by their cell bodies in the DRG and enter the spinal cord to terminate on neurons in:
   (a) Rexed laminae I and II
   (b) Rexed laminae III and V
   (c) Rexed lamina X
   (d) All of the above
10. The axons of the C fiber system:
    (a) Are unmyelinated
    (b) Are myelinated
    (c) Are never found in the peripheral nerves of the somatic sensory system
    (d) Have fast conduction velocity of over 20 m/s
11. Neurons in the ventral posterior nucleus (VPN) of the thalamus relay the nociceptive signal to:
    (a) The primary somatosensory cortex
    (b) The secondary somatosensory cortex
    (c) The inferotemporal and frontal cortices
    (d) All of the above
12. After an injury, a significant portion of stimulus enhancement can occur during the pro-

cess of peripheral sensitization and is limited to injury by:
(a) Thermal stimulus
(b) Mechanical stimulus
(c) Chemical stimulus
(d) All of the above

13. Which is false regarding wide dynamic range neurons?
(a) They are found primarily in lamina V.
(b) They are responsible for much of the information that is transmitted to the brain stem and thalamus.
(c) These neurons receive polymodal inputs.
(d) One limitation is that they do not receive inputs from collaterals of non-nociceptive, low-threshold mechanical Aβ afferents and local internuncial neurons of the dorsal horn.

14. C fibers:
(a) Respond to polymodal stimuli but preferentially respond to noxious heat.
(b) Their central elements course medially in the dorsal root and terminate on neurons in Rexed lamina I, the outer portion of lamina II, and lamina V.
(c) Upon entering the spinal cord, the axons of the primary nociceptors ascend and descend in the zone of Lissauer.
(d) The majority of these fibers ascend approximately two spinal levels before terminating in the dorsal horn.

15. In myelinated axons, the excitable membrane that supports the propagation of action potentials found only in the intervals between adjacent segments of myelin is called:
(a) Nodes of Ranvier
(b) Basilar sulci
(c) Nervus intermedius
(d) Riopelle lipofuscin

Answers:

1. a
2. a
3. d
4. a
5. b
6. a
7. c
8. b
9. d
10. a
11. d
12. d
13. d
14. d
15. a

References

1. Woolf CJ, Decosterd I. Implications of recent advances in the understanding of pain pathophysiology for the assessment of pain in patients. Pain. 1999;6(Suppl):S141–7.
2. Woolf CJ, Max MB. Mechanism-based pain diagnosis. Issues for analgesic drug development. Anesthesiology. 2001;95:241–9.
3. Bevan S. Nociceptive peripheral neurons: cellular properties. In: Wall PD, Melzack R, editors. Textbook of pain. 4th ed. Edinburgh: Churchill Livingstone; 1999. p. 85–104.
4. Raja SN, Meyer RA, Ringkamp M, Campbell JN. Peripheral neural mechanisms of nociception. In: Wall PD, Melzack R, editors. Textbook of pain. 4th ed. Edinburgh: Churchill Livingstone; 1999. p. 11–57.
5. Byers MR, Bonica JJ. Peripheral pain mechanisms and nociceptor plasticity. In: Loeser JD, Butler SH, Chapman CR, Turk DC, editors. Bonica's management of pain. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2001. p. 26–72.
6. Rang HP, Bevan S, Dray A. Nociceptive peripheral neurons: cellular properties. In: Wall PD, Melzack R, editors. Textbook of pain. 3rd ed. Edinburgh: Churchill Livingstone; 1994. p. 57–78.
7. Devor M, Seltzer Z. The pathophysiology of damaged peripheral nerves. In: Wall PD, Melzack R, editors. Textbook of pain. 4th ed. Edinburgh: Churchill Livingstone; 1999. p. 129–64.
8. Terman GW, Bonica JJ. Spinal mechanisms and their modulation. In: Loeser JD, Butler SH, Chapman CR, Turk DC, editors. Bonica's management of pain. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2001. p. 73–152.
9. Basbaum AI, Bautista DM, Scherrer G, Julius D. Cellular and molecular mechanisms of pain. Cell. 2009;139:267–84.
10. Snyder LM, Ross SE. Itch and its inhibition by counter stimuli. Handb Exp Pharmacol. 2015;226:191–206.
11. Meyer RA, Campbell JN, Raja SN. Peripheral neural mechanisms of nociception. In: Wall PD, Melzack R, editors. Textbook of pain. 3rd ed. Edinburgh: Churchill Livingstone; 1994. p. 13–44.

12. Melzack R, Wall PD. Pain mechanisms: a new theory. Science. 1965;150:971–9.
13. Milligan ED, Watkins LR. Pathological and protective roles of glia in chronic pain. Nat Rev. 2009;10:23–36.
14. Adams RD, Victor M. Principles of neurology. 4th ed. New York: McGraw Hill; 1989.
15. Basbaum AI, Fields HL. Endogenous pain control systems: brain stem spinal pathways and endorphin circuitry. Annu Rev Neurosci. 1984;7:309–38.
16. Levine JD, Reichling DB. Peripheral mechanisms of inflammatory pain. In: Wall PD, Melzack R, editors. Textbook of pain. 4th ed. Edinburgh: Churchill Livingstone; 1999. p. 59–84.
17. Paul D, Gould HJ III. Sodium channel modulation in the perception and management of pain. Spec Top Pain Manag Sci Am Pain Manag. 2018. In press.
18. Amir R, Devor M. Spike-evoked suppression and burst patterning in dorsal root ganglion neurons. J Physiol (Lond). 1997;501:183–96.
19. Woolf CJ, Mannion RJ. Neuropathic pain: aetiology, symptoms, mechanisms, and management. Lancet. 1999;353:1959–64.
20. Wall PD, Woolf CJ. The brief and the prolonged facilitatory effects of unmyelinated afferent input on the rat spinal cord are independently influenced by peripheral nerve section. Neuroscience. 1986;17:1199–205.
21. Voigt AW, Gould HJ III. Chronic daily headache—mechanisms and principles of management. Curr Pain Headache Rep. 2016;20:1–7.
22. Reichling DB, Levine JD. Critical role of nociceptor plasticity in chronic pain. Trends Neurosci. 2009;32:611–8.
23. Woolf CJ, Shortland P, Coggeshall RE. Peripheral nerve injury triggers central sprouting of myelinated afferents. Nature. 1992;355:75–8.
24. Kaye AD, Novitch MB, Gould HJ III. Pain, a comprehensive review and update. Neurosci Biobehav Psychology: Elsevier; 2017. ISBN 9780128093245.