Fundamentals of Pain Medicine

Jianguo Cheng
Richard W. Rosenquist
Editors

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Part I

Diagnosis of Pain States

Overview of Pain States

1

Jianguo Cheng

Key Concepts

- Pain medicine is a subspecialty of medicine dedicated to the relief and/or control of pain in patients with various painful conditions/states. It is rapidly expanding and has become a true multidisciplinary specialty to meet the enormous needs of patients. The complexity of pain conditions often requires multimodal, multidisciplinary approaches to prevention, management, and rehabilitation.
- Therapeutic strategies depend on proper clinical assessment and, to some extent, mechanistic understanding of each pain condition in each patient. Adequate and effective clinical assessment with appropriate methodology (history, physical exam, and diagnostic imaging and diagnostic procedures) holds the key to clinical understanding of pain conditions. Relevant anatomy, cellular and molecular pathophysiology, and pharmacology are fundamental elements in the mechanistic understanding of pain states.
- Effective treatment of pain may involve mechanistic therapy, evidence-based therapy, and personalized therapy. In many cases, mechanistic and evidence-based therapy may not be readily available. Each patient is unique in their pain presentation and response to therapy. Therefore, physicians need to weigh the risk and benefits of available treatment options and tailor therapeutic strategies to fit the individual needs of each patient.

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Defining Pain

"Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of damage." Pain sensation is essential to the survival, well-being, learning, and adaptation of human beings. The ability to detect noxious stimuli is a key function of the nervous system through which humans interact with the ever-changing environment to anticipate, plan, react, and adapt. However, pain may become pathological when it is no longer useful as an acute warning system and instead becomes chronic and debilitating. The mechanisms of transition from acute to chronic pain, from physiological to pathological pain, and from protective to harmful pain are poorly understood. However, peripheral and central sensitizations seem to be critical elements in the development of pathological pain. Alterations of the pain pathway lead to hypersensitivity, hyperalgesia (exaggerated pain to

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painful stimuli), and allodynia (pain response to non-painful stimuli). For instance, individuals who suffer from arthritis, postherpetic neuralgia, or bone cancer often experience intense and unremitting pain that is not only physiologically and psychologically debilitating but may also hamper recovery. Chronic pain may even persist long after an acute injury, such as trauma or surgery. The elucidation of molecules and cell types and the interactions that are involved in normal (acute) pain sensation are key to understanding the mechanisms underlying the transition from physiological to pathological pain states.

Classification of Pain States

Pain is the most common presenting symptom in medicine. It can occur in any part of the body, from the head to the toes, and affect any system. It can be acute or chronic, episodic or continuous, and occurring regularly or irregularly. It is necessary to classify pain states to provide an understanding of pain disorders, establish standards for diagnosis and description, and allow exchange of standardized information. Although it may be classified in many ways, pain is generally classified as nociceptive, neuropathic, idiopathic, psychogenic, and mixed. The use of specific classifications makes it possible to compare statistical data between professionals within countries and internationally. The International Classification of Diseases, tenth revision (ICD-10), copyrighted by the World Health Organization (WHO) is used worldwide for the purpose of documenting mortality and morbidity. A slightly modified version with clinical modification (ICD-10-CM) was adopted in the USA in 2015. This classification system facilitates statistical comparisons of the occurrence of disease and management outcomes but also serves as a means of defining work and providing standards for billing and payment.

Common Pain States

Acute Pain Acute pain begins suddenly and is usually sharp in quality. It serves as a warning of disease or a threat to the body. Acute pain may be mild and last just a moment, or it may be severe and last for weeks or months. In most cases, acute pain does not last longer than 3–6 months, and it disappears when the underlying cause of pain has been treated or has healed. Typical acute pain states include surgical pain, traumatic pain, labor pain, and ischemic pain.

Chronic Pain Unrelieved acute pain may lead to chronic pain. Chronic pain persists longer than 6 months, often despite the fact that an injury has healed. Physical effects include tense muscles, limited mobility, lack of energy, and changes in sleep and appetite. Emotional effects include depression, anger, anxiety, and fear of reinjury. These effects frequently hinder a person's ability to return to normal work or leisure activities. Typical chronic pain conditions include neuropathic pain, arthritic pain, and fibromyalgia.

Nociceptive Pain Nociceptive pain is caused by activation of nociceptive afferent fibers typically through thermal, mechanical, or chemical stimulation. Based on the location of the nociceptors in body structures, nociceptive pain may also be divided into visceral pain, deep somatic pain, and superficial somatic pain.

Neuropathic Pain Neuropathic pain is caused by damage or disease affecting any part of the somatosensory system. Peripheral neuropathic pain is caused by damage or dysfunction of peripheral nerves. Painful diabetic neuropathy, complex regional pain syndrome type II (causalgia), postherpetic neuralgia, and radicular pain are examples of this type of pain. Neuropathic pain is often described as "burning," "tingling," "electrical," "stabbing," or "pins and needles." Central pain is caused by a primary lesion or dysfunction in the central nervous system and is usu-

ally associated with abnormal sensibility to temperature and noxious stimulation. Common examples include poststroke pain, pain related to spinal cord injury, and pain due to multiple sclerosis. Phantom pain (pain felt in a part of the body that has been lost or from which the brain no longer receives signals) may also be considered in this category.

Idiopathic Pain Idiopathic pain is a pain that persists after the trauma or pathology has healed or that arises without any apparent cause. Some argue that such pain is psychogenic.

Psychogenic Pain Psychogenic pain is pain caused, increased, or prolonged by mental, emotional, or behavioral factors. This type of pain is also called *psychalgia* or *somatoform pain*. Sufferers are often stigmatized, because such pain may be considered as "not real." However, specialists believe that it is no less actual or hurtful than pain from any other source.

Mixed Type of Pain The mechanisms of pain are complex, and the classification of pain conditions is often complex as well. Many types of pain can coexist in the same individual, leading to a mixed type of pain. Examples of this type of pain include complex regional pain syndrome (CRPS) and fibromyalgia. In such circumstances, identifying the chief component of the pain may facilitate planning of therapeutic strategies.

- *Complex regional pain syndrome* (*CRPS*), formerly called reflex sympathetic dystrophy (RSD) or causalgia, is a chronic systemic disease characterized by severe pain, swelling, and changes in the skin. It often initially affects an arm or a leg and often spreads throughout the body. It is a multifactorial disorder with clinical features of neurogenic inflammation, nociceptive sensitization, vasomotor dysfunction, and maladaptive neuroplasticity, generated by an aberrant response to tissue injury. There are two types of CRPS:
  - Type I, formerly known as RSD, does not have demonstrable nerve lesions. The vast majority of patients diagnosed with CRPS are of this type.
  - Type II, formerly known as *causalgia*, has evidence of specific nerve damage and therefore is a neuropathic pain state. This type tends to be a more painful and difficult to control form of CRPS.
- *Fibromyalgia* is characterized by chronic widespread pain and allodynia (a heightened and painful response to pressure). Pain is considered widespread when it is present in all of the following: the left and right sides of the body and above and below the waist. In addition, axial skeletal pain (cervical spine or anterior chest or thoracic spine or low back) must be present. Its exact cause is unknown but is believed to involve psychological, genetic, neurobiological, and environmental factors that lead to central sensitization. Fibromyalgia symptoms are not restricted to pain. Other symptoms include debilitating fatigue, sleep disturbance, and joint stiffness.

In addition to these common pain states, pain in special patient populations deserves special attention. Distinct assessment and therapeutic skills are required to effectively manage pain in patients with cancer, pain in pediatric patients, pain in geriatric patients, pain in critically ill patients, and pain in those with substance abuse.

Global Strategies of Pain Assessment and Treatment

Therapeutic strategies depend on proper clinical assessment and mechanistic understanding of the pain condition affecting each patient. Adequate and effective clinical assessment with appropriate methodology (history, physical exam, and diagnostic imaging and diagnostic procedures) holds the key to developing a clinical understanding of the pain conditions in question. Relevant anatomy, cellular and molecular pathophysiology, pharmacology, and psychological effects are fundamental elements involved in the mechanistic understanding of a pain state and its treatment.

Effective treatment of pain involves mechanistic therapy, evidence-based therapy, and personalized therapy. Examples of mechanistic therapy include antivirals for herpes zoster, decompression of spinal stenosis for neurogenic claudication and pain, and control of glucose in cases of diabetic neuropathy. Examples of evidence-based therapy include spinal cord stimulation for failed back surgery syndrome, radiofrequency ablation of facet joint innervation for neck and back pain, and pharmacological interventions for neuropathic pain. Mechanistic or evidence-based therapy may not be readily available for many painful conditions and because each patient is unique in their presentation of pain and responses to pain therapy. Therefore, it is extremely important to weigh the risks and benefits of the available treatment options and tailor therapeutic strategies to fit the individual needs of each patient.

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Pathways of Pain Perception and Modulation

2

Kiran Rajneesh and Robert Bolash

Key Concepts

- Pain sensation occurs in the periphery via specialized nociceptors with free nerve endings.
- The first sensation of pain is transmitted by myelinated Aδ fibers which carry a well-localized pain signal.
- C fibers are unmyelinated fibers which transmit poorly localized pain to the dorsal horn of the spinal cord.
- First-order neurons synapse with second-order neurons within Rexed lamina I. Second-order neurons then cross midline and ascend to the brainstem via the spinothalamic tracts.
- Second-order neurons synapse with third-order neurons in the thalamus. Third-order neurons project to the cortex.
- These second- and third-order neurons relay to brain and brainstem centers responsible for arousal, emotional experience, and behavior.
- Afferent pain signals are modulated at the level of the dorsal horn, brainstem, and cortex via inhibitory interneurons and inhibitory and excitatory descending pathways.
- Therapeutic targets exist on the afferent neurons, ascending pathways, and descending pathways.
- Acute pain can be adaptive and life-sustaining, while chronic pain often results in comorbid maladaptive behavioral and arousal patho logies.

Introduction

Pain perception is essential to human well-being and survival. The sensation of pain originates through complex signaling pathways which begins in the periphery, ascends in the spinal cord or brainstem (cranial sensory input), and is ultimately interpreted in the cortex of the brain. These ascending pathways are susceptible to injury owing to mechanical, toxic, or pathological aberrations originating at any point along their course.

More complex than a simple one-way circuit, pain is also modulated by descending pathways which serve to mitigate painful inputs throughout the classic pain pathways. An understanding of the pain pathways provides a foundation for discussions of both pathological processes and therapeutic interventions.

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Peripheral Receptors for Pain

Nociceptors are capable of sensing thermal, mechanical, or chemical insults via specialized receptors or free nerve endings located throughout the body. Nociceptors are the peripherally located terminal ends of specialized pseudounipolar neurons called Aδ and C fibers.

Aδ fibers are medium-diameter fibers that carry well-localized pain signals. Because they are thinly myelinated, Aδ fibers permit relatively rapid transmission of impulses toward the spinal cord and are responsible for the initial sensation of pain. Aδ fibers are further divided into two main subtypes: type I, or high-threshold mechanical nociceptors, that respond to both mechanical and chemical stimuli, and type II nociceptors which have a heat threshold close to 42 °C and are responsible for the transmission of painful thermal insults.

C fibers are small-diameter, unmyelinated fibers that mediate poorly localized pain. Their impulses reach the spinal cord at a tenfold slower rate than Aδ fibers and are responsible for the second pain. The majority of unmyelinated C fibers are polymodal, carrying painful stimuli arising from both chemical and noxious insults.

Ascending Pathways

Aδ and C fibers enter the central nervous system through the dorsal horn of the spinal cord and many synapse at the same level in a histologically defined area of the dorsal horn. Some of the fibers either ascend or descend in a specialized pathway called Lissauer's tract before synapsing with their second-order neuron. Among these laminae, Rexed laminae I, II, and V are the most important in pain signaling with C fibers synapsing in laminae I and II, while Aδ fibers synapse in laminae I and V.

Lamina V receives convergent input from Aδ and Aβ fibers conducting proprioception and fibers arising from the viscera. Because of the diversity of inputs into lamina V, these neurons are termed wide dynamic range (WDR) neurons. Projection neurons within laminae I and V constitute the major output from the dorsal horn to the brain. These neurons are at the origin of multiple ascending pathways, including the spinothalamic and spinoreticulothalamic tracts, which carry pain messages to the thalamus and brainstem, respectively (Fig. 2.1). The former is particularly relevant to the sensory-discriminative aspects of the pain experience, whereas the latter may be more relevant to poorly localized pains. In addition, spinal cord projections to the parabrachial region of the dorsolateral pons of the brainstem provide for a very rapid connection with the amygdala, a region generally considered to process information relevant to the aversive properties of the pain experience.

There is somatotopic organization of the second-order neurons within the spinothalamic tract with medial fibers carrying information about the arms and lateral fibers carrying painful sensation from the legs. This becomes important in pathological conditions such as syringomyelia when the central canal becomes pathologically enlarged and pushes on the anterior commissure. Because of this, second-order neurons of the spinothalamic tract crossing the midline are preferentially affected. Patients complain of pain in "cape-like distribution" affecting both shoulders due to the somatotopic distribution of fibers.

The spinothalamic tracts ascend through the medulla and pons before reaching the ventral posterior nucleus of the thalamus. Along its course to the thalamus, the spinothalamic tracts interact with numerous collaterals. In the medulla, branches of the spinothalamic tract transmit to the reticular formation which modulates alertness when pain is perceived. In the pons, spinothalamic projections transmit to the hypothalamus and amygdala to modulate mood and motivation.

Within the thalamus, the spinothalamic tracts synapse with third-order neurons in the ventral posterior lateral nucleus. These third-order neurons project to the cortex and enable perception of discrete sensations of pain such as the quality and location from which the painful signal originates. Simultaneously, nuclei adjacent to the thalamus receive projections from the spinothalamic tract and mediate some pain behavior such as arousal and emotion.

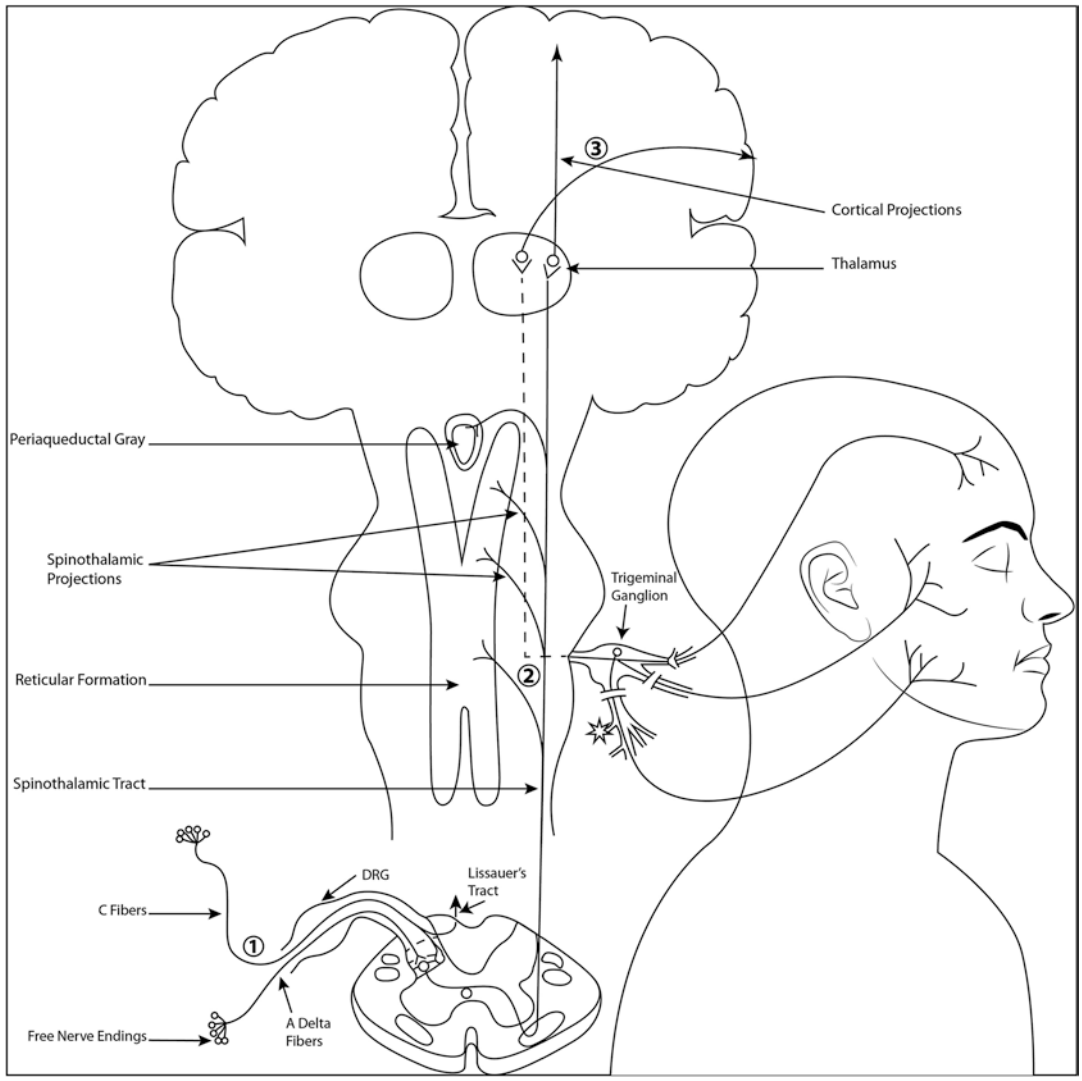

Fig. 2.1 Nociceptive input from the body is sensed at the free nerve endings before traveling (*1*) to the dorsal horn of the spinal cord via A delta and C fibers. Second-order neurons ascend in the spinothalamic and spinoreticulothalamic tracts (*2*) before synapsing in the thalamus and brainstem. Third-order neurons project (*3*) to the cortex. Neurons transmitting facial pain transit through the trigeminal ganglion and synapse in the spinal nucleus of the trigeminal nerve. Second-order neurons run parallel and medial to the spinothalamic tract before synapsing in the thalamus

Pain transmission from the face and sinuses follows a pathway which does not involve the spinal cord. Instead, nociceptive neurons from the face, transit the trigeminal ganglion, and terminate in the spinal nucleus of the trigeminal nerve. Fibers of the second-order neurons in the trigeminal spinal nucleus then ascend through the brainstem and synapse directly in the ventral posterior medial nucleus of the thalamus.

Pain Perception in the Cerebral Cortex

From the thalamus, third-order neurons carry projections to the primary somatosensory cortex in the postcentral gyrus, specifically to Brodmann areas 1–3. Projections from the primary somatosensory cortex then transit to the secondary somatosensory cortex which acts

to integrate pain with visual, auditory, and gustatory inputs.

The importance of these thalamic connections is seen in central pain syndromes such as Dejerine-Roussy syndrome. After suffering an ischemic insult to the posterior cerebral artery, thalamic pain may develop. Though arising from a central source within the thalamus, these patients perceive pain throughout the body at locations which are remote from the area affected by the ischemic thalamic insult.

Modulation of Pain

Pain perception is modulated at several discrete areas including the dorsal root ganglion, the spinal cord dorsal horn, the reticular system of the brainstem, and the cortical areas of the brain. These mechanisms serve to increase or decrease the painful impulses before reaching the cortex of the brain. In the dorsal horn, lamina V receives convergent input from both Aδ nociceptive fibers and Aβ sensory fibers which carry proprioception such as touch. It is hypothesized that within lamina V, the gate theory of pain operates.

In 1965, Melzack and Wall described a "gate control theory of pain" whereby sensation of non-painful stimuli, such as touch, diminishes the ability to sense painful input. They theorized that non-painful stimuli "close a gate" to the transmission of noxious stimuli. The theory was subsequently refined with the description of an inhibitory interneuron located within the dorsal horn of the spinal cord. In the presence of mechanical Aβ stimulation, the inhibitory interneuron is activated and thus diminishing transmission through the nociceptive C fibers. Though the gate theory has undergone further clarification since its initial description, this observation has been exploited therapeutically with the development of transcutaneous electrical nerve stimulation (TENS). TENS acts to selectively trigger Aβ sensory fibers, thereby inhibiting the transmission of noxious stimuli at the level of the dorsal horn via an interneuron.

Following the description of the gate theory, further descending pain-modulating pathways were elucidated. The raphe nuclei, rostral ventral medulla, and periaqueductal gray have high concentrations of enkephalins, endorphins, and dynorphins which act to diminish painful input via descending pathways. These pathways arise from the brainstem and impart their effect at the dorsal horn of the spinal cord. Originally thought to function only as inhibitors of pain transmission, descending pathways serve to either amplify or mitigate pain transmission. Most notably, the periaqueductal gray matter of the midbrain utilizes both excitatory and inhibitory neurotransmitters including norepinephrine, acetylcholine, serotonin, and dopamine to facilitate or inhibit nociceptive input. These neurotransmitters work throughout multiple sites along the pain pathway including the distal synaptic terminals, dorsal horn, and midbrain. It is postulated that the use of selective serotonin reuptake inhibitors in the treatment of chronic pain syndromes act through these descending pathways.

Summary

More than simple ascending circuits, pain pathways are redundant intricate systems which undergo modulation at peripheral, spinal cord, brainstem, and cortical sites. Because of connections with behavioral, arousal, and physiological centers, acute pain can enable an organism to survive, while chronic pain can lead to maladaptive behavior. A variety of pathological processes affect both pain signaling and processing at sites both peripherally and centrally. Both pharmacological and surgical treatments have been developed to target these pathological processes, and an understanding of the mechanism of pain transmission serves as the basis for understanding therapeutic strategies.

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Mechanisms of Physiologic Pain

3

Siu Fung Chan, Salim M. Hayek, and Elias Veizi

Key Concepts

- Physiological pain is an adaptive protective mechanism.
- Nociceptors are primary sensory neurons specialized to detect environmental threatening or damaging inputs to initiate a protective response.
- The pain perception is a cascade of events starting with transduction, followed by conduction, transmission, and eventually modulation and perception.
- Endogenous attenuation of the nociceptive pain signal involves segmental inhibition, the endogenous opioid system, and the descending inhibitory system.

Introduction

Nociception and pain perception comprise two different events. *Nociception* is the activation of sensory neuronal pathways upon stimulation by noxious stimuli, while *pain* refers to one's perception of this experience after the brain processes the transmitted signal. Nociception may lead to pain, yet a person may experience pain without activation of the nociceptive pathway. Noxious perception is a complex process that begins in periphery, extends along the neuraxis, and terminates in supraspinal regions responsible for perception, interpretation, and reaction. This process includes nociceptor activation, neural conduction, spinal transmission, and modulation of the stimuli and ultimately spinal and supraspinal responses (Fig. 3.1).

Transduction

Transduction is the process by which potential harmful mechanical, chemical, or thermal stimuli are converted by peripheral nociceptors into action potential within the distal fingerlike nociceptor endings.

Nociceptors

Sherrington first described nociceptors about a century ago. These are sensory neurons with free nerve endings consisting of receptor subtypes that can be excited by mechanical, temperature, and chemical stimuli applied to skin, muscles, joints, bone, viscera, and dura. Yet, they are not excited by innocuous stimuli (e.g., gentle warming or light touch). The intensity of the stimulus determines the initial response. Nociceptors have a high threshold and normally respond only to stimuli of sufficient energy to potentially or actually damage tissue.

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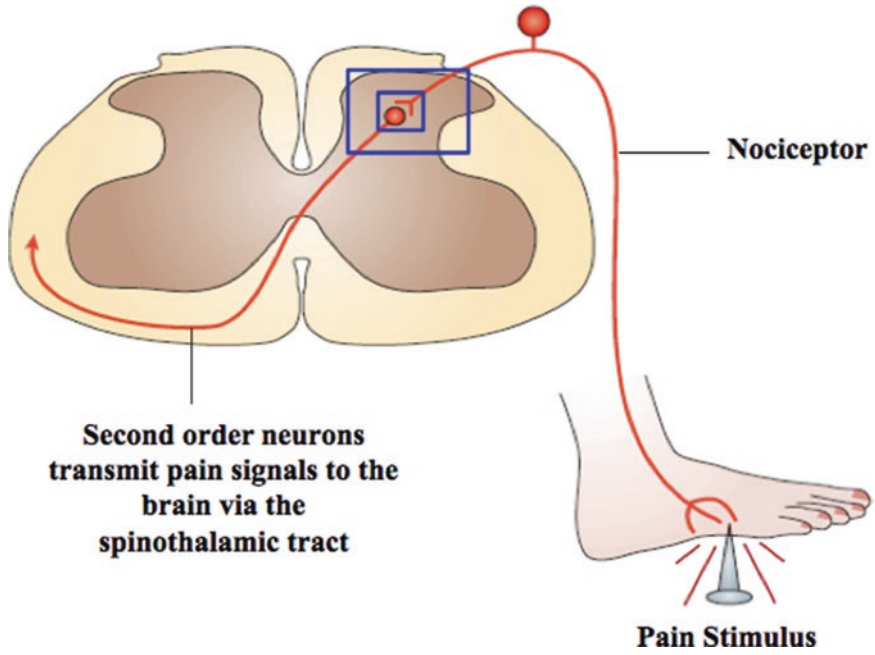

Fig. 3.1 General schematic diagram showing nociception from the site of injury to the spinal cord (CNS). Transmission occurs in the blue boxes, which are discussed in more detail in Fig. 3.3 (With permission from Nature Publishing Group, GLIA: Watkins LR, Maier SF. A novel drug discovery target for clinical pain. *Nat Rev Drug Discov*. 2003;2(12), fig 1)

There are two categories of nociceptors: (a) thinly myelinated (Aδ fibers) and (b) unmyelinated (C fibers). These primary sensory neurons have their cell bodies in dorsal root ganglia [DRG] and give rise to a single axon that bifurcates into a peripheral branch that innervates peripheral target tissue and a central axon that enters the CNS to synapse on nociceptive second-order neurons in the dorsal horn of the spinal cord. As such the unit components of the nociceptor include:

- Peripheral terminal that innervates target tissue and transduces noxious stimuli
- Axon that conducts action potentials from the periphery to the central nervous system
- Cell body in the dorsal root ganglion
- Central terminal where information is transferred to second-order neurons at central synapses.

Following their origin from the neural crest, nociceptors undergo a distinct differentiation pathway that leads to formation of two characteristic subgroups:

(a) "Peptidergic": Express CGRP and substance P. Calcitonin gene-related protein [CGRP] is a 37-amino acid peptide found in peripheral and central terminal of nearly 50% of the C fibers and 35% of Ad fibers. Substance P is an 11-amino acid peptide found in a subset of nociceptive neurons.
(b) "Non-peptidergic": Do not express peptides but express signaling components to respond to glial cell-derived growth factor [GDNF].

Nociceptor Activation

Noxious stimuli are converted into an ion flux. A heterogeneous group of receptors is present on the surface of nociceptors, and they are responsive to various stimuli [polymodal] primarily due to the presence of polycationic channels. Tissue injury mediators activate transducer molecules such as transient receptor potential [TRP] ion channel. TRP channels are a diverse family of ion channels that respond to thermal [TRPV1],

traumatic, and chemical [TRPA and TRPM] stimuli. TRPV1/capsaicin receptor is the best-described member of the family. It is a 4 subunit receptor which upon stimulation by H^+ ions, heat, or capsaicin permits an inward flux of Ca^{2+} and Na^+. This inward flux is responsible for generation of action potential by causing membrane depolarization and lowering the activation threshold (Fig. 3.2).

Tissue injury and cellular damage are associated with the release of noxious mediators such as arachidonic acid [AA] from lysed cell membranes as well as intracellular H^+ and K^+ ions. Furthermore, active metabolites of AA such as PGE2 PGG2 bradykinin play a significant role in the activation of peripheral nociceptor. They bind G-protein receptor proteins and activate intracellular signaling cascade such as extracellular-regulated kinase and adenylate cyclase which in turn a) activate ion channels by phosphorylation [e.g., TrpV1 phosphorylation] and b) increase the cell membrane ion channel turnover from internal stores. The net result is activation of Ca^{2+} and Na^+ influx and membrane depolarization. There are different sodium channels expressed in somatosensory neurons. These include tetrodotoxin (TTX)-sensitive channels (Nav 1.1, 1.6, and 1.7) and TTX-insensitive channels (Nav 1.8 and 1.9). Of particular note, Nav 1.7 is largely involved with pain perception, as patients with loss-of-function mutations of this gene cannot detect noxious stimuli. The C nociceptors express both Nav 1.7 and Nav 1.8 sodium channels. These voltage-gated sodium channels are targets of local anesthetic drugs.

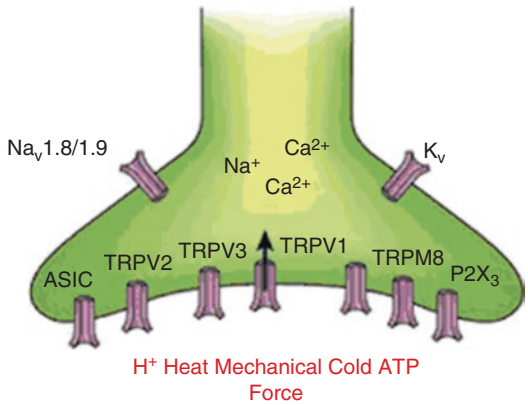

Fig. 3.2 This is an illustration of a close-up area of the circle in Fig. 3.1. A heterogeneous group of receptors on nociceptors respond to various stimuli, leading to an influx and calcium and sodium, generating an action potential. While TRP channels respond to trauma, heat, and chemical stimuli, there are other channels that may be expressed. Na 1.8/1.9, TRPM8, and ASIC channels respond to mechanical, cold/menthol, and protons, respectively. P2X3 channels respond to ATP released from inflamed cells (Adapted from Macmillan Publishers Ltd., Scholz J, Woolf CJ. Can we conquer pain? *Nat Neurosci*. 2002;5:1062–7, fig 2)

Conduction

The action potentials generated by activated nociceptors are conducted through different types of nociceptive fibers: thinly myelinated afferent nociceptors (Aδ nociceptors) and smaller diameter unmyelinated afferent nociceptors (C nociceptors) (Table 3.1). The Aδ fibers mediate the "first" wave of pain (acute, sharp pain), while the C fibers mediate the "second" wave of pain (delayed, diffuse, dull) perceived by the brain. These fibers conduct pain signals through the cell bodies, which are located in the dorsal root ganglia and the trigeminal ganglion for the body and face, respectively, and continue toward the dorsal horn of the spinal cord, where the nociceptive fibers synapse with second-order neurons.

While it is anticipated to think of the nociceptive pathway as a one-way process, in reality it is more complicated. Primary afferent fibers are described as "pseudounipolar," where the nociceptor can send and receive input from either the periphery or central terminals. Both ends serve as targets for endogenous regulatory factors and pharmacotherapy that alter the neuron's threshold to fire in order to regulate pain.

Nociceptive signals are transduced to synapses in the dorsal horn through action potentials mediated mostly through voltage-gated sodium and potassium channels. Voltage-gated calcium channels facilitate neurotransmitter release at the dorsal horn synapse of nociceptor terminals to transmit pain signals. The activation of the various nociceptors

Table 3.1 Classification of primary sensory neurons

Fiber type	Aβ	Aδ	C
Myelination	Myelinated	Thinly myelinated	Unmyelinated
Diameter size	Largest (20–45 μm)	Small (~15 μm)	Very small (~8 μm)
Conduction velocity, m/s	14–30	2.2–8	0.4–2
Activation stimulus	Light touch, movement, and vibration	Brief, intense	High intensity, long duration
Threshold	Low	High	High
Localization	Joints, skin	Skin, deep somatic, viscera	Skin, deep tissues, viscera

and ion channels leads to the propagation of action potentials from peripheral nociceptive endings via myelinated and unmyelinated nerve fibers, in a process termed conduction.

A heterogeneous group of voltage-gated calcium channels are also expressed on nociceptors. All calcium channels are heteromeric proteins, consisting of α1 pore-forming subunits and modulatory subunits α2δ, α2β, or α2γ. In C nociceptors, the α2δ subunit is upregulated in nerve injury and contributes to hypersensitivity and allodynia. This is the target of gabapentin and pregabalin, used to treat neuropathic pain.

Transmission

Transmission refers to the transfer of noxious impulses from primary nociceptors to cells in the spinal cord dorsal horn. Both Aδ and C fibers conduct nociceptive input via first-order neurons, which upon entering the spinal cord travel up or down for one to two vertebral levels in Lissauer's tract before synapsing with second-order neurons in the dorsal horn of the spinal cord. When the signal arrives at the central terminals of nociceptors, depolarization leads to activation of the N-type calcium channel. The influx of calcium leads to the release of the predominant excitatory neurotransmitters at the level of the dorsal horn, glutamate, and substance P (see Fig. 3.3).

Glutamate activates postsynaptic AMPA and kainate subtypes of ionotropic glutamate receptors. Substance P activates postsynaptic NK1 receptors (Table 3.2). The activation of these receptors generates excitatory postsynaptic currents (EPSCs) in the second-order neurons located in the dorsal horn. The summation of subthreshold EPSCs results in action potential firing and transmission of pain signals to higher-order neurons. Transduction of pain is also modulated by neurotransmitters and neuropeptides that influence nerve transmission threshold, thus affecting one's increased or decreased sensitivity of pain perception.

Of note, glutamate and substance P lead to activation of glial cells. Microglia function as macrophages and are homogeneously dispersed in the gray matter of the spinal cord. These are presumed to function as sentinels of injury or infection. Glia found outside of the spinal cord may be involved in pain enhancement. Their expression is upregulated in pain conditions while they produce proinflammatory and neuroexcitatory substances, including interleukin-1β, tumor necrosis factor-α, and IL-6, among others. Glial activation increases neuronal excitability while opposing opioid analgesia and enhancing opioid tolerance and dependence.

In the dorsal horn, primary nociceptor afferent nerve fibers synapse into specific laminae (Table 3.3). Predominantly, second-order cells are located in Rexed's laminae II (substantia gelatinosa) and V (nucleus proprius). Spinal cord neurons within lamina I and II are generally responsive to noxious stimulation, while neurons located in laminae III and IV are responsive to non-noxious stimuli (Aβ fibers). Neurons in lamina V receive both non-noxious and noxious inputs via direct Aδ/Aβ inputs and non-direct C fiber inputs through interneurons in lamina II.

The second-order neurons in lamina V are collectively referred to as wide dynamic range (WDR) neurons as they respond to a wide range of stimulus intensities. It is also the location of where some