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Brief History

Before 1800

In the oriental medicine or traditional Chinese medicine (TCM), the term “pain” appeared for the first time in an ancient medical book of more than 3,000 years ago *Huang Di Nei Jing*, which was translated into English as *The Yellow Emperor’s Classic of Internal Medicine* (Veith 1966) or *The Medical Classic of the Yellow Emperor* (Zhu 2001). In this TCM canon, pain was believed to be a result of imbalance of “yin” and “yang.” Predominance of the “yin” results in “han” (cold) that causes damage to the “xing” (form of a substance) that is now known as tissue injury or damage and leads to swelling, while predominance of the “yang” results in “re” (hyperthermia or heat) that causes damage to the “qi”, namely pneuma (previously referred to as “chī” that is the conception of energy circulating in the hypothetical 12 channels), and leads to pain. That was probably the first description of the symptoms and signs of nociceptive and inflammatory pain in medical literatures. Based upon this principle, any TCM treatment of pain regardless of either pharmacological or non-pharmacological approaches has been focusing on restoration of the balance between “yin” and “yang,” including the use of acupuncture analgesia.

In the Western countries, the description of pain appeared for the first time in Homer’s epic such as *the Iliad* and *the Odyssey* from around the eighth century B.C. in ancient Greece. The term “pain” appearing in literatures of the occidental medicine can be traced back to the fifth century B.C. of the Hippocratic period when he and his followers published *the Hippocratic Collection*. However, the brain had not been believed to be the seat of pain sensation until the fifteenth century of the Renaissance (during fourteenth to seventeenth century) when systematic studies of autopsies were carried out by Andreas Vesalius (1514–1564), the founder of modern human anatomy, who published a classical book of human anatomy *On the Fabric of the Human*
Before the Renaissance, according to Aristotle’s postulate, the heart is the seat of sensations (hearing, vision, smell, taste, and pain), emotions, and mental functions. Actually, the idea that the brain was the seat of perception had been postulated by a few philosophers and physicians, such as Pythagoras (570–495 B.C.), Anaxagoras (500–428 B.C.), Galen (130–201) in the ancient times, and Avicenna (980–1037) in the Middle Ages. Galen recognized the brain as the site of feeling. According to his careful observation of patients suffering from various pain problems, he proposed pain to be a specific characteristic of the tactile sensation that is corresponding to the phenomenon of allodynia (now referred to as a painful sensation caused by previously non-painful stimulus under pathological state). Galen also described inflammation characterized by pain (dolor), heat (calor), redness (rubor), and swelling (tumor). In China, Hua Tuo (145–208), an ancient Chinese physician, used to administer “mafeisan,” ingredients of cannabis in wine to patients receiving surgeries. Hua Tuo was probably the first Chinese physician introducing the concept of anesthesia and analgesia in the TCM history. Avicenna was a renowned Muslim philosopher and physician. In his work *Canon of Medicine* and *Poem of Medicine*, he proposed for the first time that pain is an independent sensation that can dissociate from touch or temperature recognition. Avicenna has been regarded as the first man formulating the specificity theory.

In the seventeenth century, the functions of the brain were significantly promoted by René Descartes (1596–1650), Thomas Willis (1621–1675), and Thomas Sydenham (1624–1689). Descartes, a French writer and Father of Modern Philosophy, provided a famous hypothetical drawing that showed the transmission of pain information via the peripheral nerves and the spinal cord to the brain ventricles and the pineal organ where the conscious perception of a painful stimulus was proposed to be produced. Thomas Willis, recognized as the discoverer of the “circle of Willis,” was a pioneer of the brain anatomy. In his work *Cerebri Anatomae* (1664), he provided with strong evidence supporting the roles of the brain (including the cerebral cortex), but not the ventricles, in perception of pain. Thomas Sydenham was the first user of laudanum, a composite of opium, saffron, cinnamon, and cloves in wine and promoted the consistent and systematic treatment of pain. He was also the first physician describing gout, a disease he had himself.

After 1800

The concept of pain has been gradually shaped with the development of experimental sciences since 1800. However, the ideas about pain have long been debated due to the complexity of pain itself and the brain, the generator of pain (Perl 2007). The main dispute is to see whether pain is mediated by a specific, hard-wired pathway or a nonspecific, unwired pathway in the nervous system. So far, four theories of pain have been proposed by different people, but none of them has been generally accepted to be the only right one (Fig. 28.1). These are specificity theory, intensity theory, pattern theory, and gate-control theory.
Fig. 28.1 Theories of pain. Diagrams depicting typical assumptions about relationships between stimuli and primary afferent signaling in theories about pain. (a) According to the specificity theory, specialized sense organs (nociceptors) have thresholds at or near noxious levels, increasing activity with stronger noxious stimuli. These special peripheral afferent neurons have selective connections to particular spinal and brain stem projection neurons. (b) The intensity theory suggests that peripheral sense organs are not differentiated into low- and high-threshold types. It proposes that afferent fibers transduce innocuous stimuli (e.g., skin pressure) by generating a certain level of activity, whereas noxious stimuli are signaled by a greater level of discharge. The intensity-coded primary afferent fibers, in turn, activate projection neurons with a wide dynamic range (WDR). Weak activation of WDR projections indicates innocuous stimuli; strong activation indicates painful (noxious) events. (c) The pattern theory proposes that somatic sense organs have an extensive range of responsiveness. Individual afferent neurons respond to stimuli with differing relationships to intensity. The mode and locus of stimulation are indicated by the composite pattern of activity in the population of fibers from a particular body region. Central projection neurons code the nature and place of stimulation by the pattern and distribution of their discharges. (d) According to gate-control theory, the spectrum of primary afferent neurons has
The specificity theory (Fig. 28.1a) is one of the most influential theories of pain in the history. In 1811, Charles Bell (1774–1842), a Scottish physician and anatomist, described in his privately circulated book, *An Idea of a New Anatomy of the Brain*, that the dorsal and ventral roots of the spinal nerves serve different functions. However, he emphasized involvement of the ventral roots in control of muscle contraction without clear description of the functions of the dorsal roots. Eleven years later, in 1822, François Magendie (1783–1855), a French physiologist, verified sensory characteristic of the dorsal root nerves. There was a continuous dispute and rivalry between them because both insisted that he was the first discoverer. It was finally referred to as Bell-Magendie law stating that the anterior branch of spinal nerve roots contains only motor fibers and the posterior roots contain only sensory fibers. These discoveries provided a fundamental basis for scientific study of the pain issues. Based largely on this law, Johannes P. Müller (1801–1858), a German physiologist, developed a concept of sensory nerve specificity, the law of specific energies of the sense that resulted in a long-time influence on the theories of pain until now. The specificity theory was further coined by Moritz Schiff (1823–1896), Magendie’s student, who demonstrated, by his experiments in dogs in 1849, that the pathway conveying information of temperature and pain differed from that of other sensations, such as touch, and crossed in the spinal cord and did not ascend in the dorsal column. Schiff’s proposal was confirmed by his contemporary Charles-Edouard Brown-Séquard (1817–1894) who published a series of animal results and human cases with loss of pain and temperature sensibilities contralateral and distal to a transverse hemisection of the spinal cord (Brown-Séquard syndrome or hemiplegia) in the 1860s. The dissociation of ascending pathways mediating pain and touch in the spinal cord was also more intensively confirmed by both basic anatomical research in animals (Edinger 1890, 1892) and clinical cases reported by Sir William Gower (1845–1915) in 1878 and William Gibson Spiller (1863–1940) in 1905. As an example of “proof of concept,” Spiller and Edward Martin (1859–1938) published their first clinical result in 1912 in which a good relief of pain was achieved in one of their patients by cutting the anterolateral quadrants of the spinal cord. In 1884, Magnus Blix (1849–1904) and Adolf Goldscheider (1858–1935) demonstrated mosaic of skin sensation and pain spots. During 1894–1897, Max von Frey (1852–1932) further provided evidence linking the specific sensory nerve endings in the skin to the sensation of pain. Sir Charles Scott Sherrington (1857–1952), the Nobel laureate in physiology or
medicine in 1932, introduced the concept of nociception (1906) that put emphasis on tissue injury as a common nature of pain. The emergence of the concept of nociception is of particular importance because, on one hand, it set up a common stage for debate regardless of which pain theory is correct. On the other hand, Sherrington also provided an experimental model of the spinal nociceptive flexion reflex as surrogate of pain sensation which has been widely used in the field of pain since then. In his book *The Integrative Action of the Nervous System*, he also proposed the concept of synapse that leads to discoveries of pre- and postsynaptic components anatomically and discoveries of synaptic transmission and modulation in the CNS, a principle of the brain structures and functions.

Before the emergence of nociception concept, the specificity theory was mostly supported by physiologists and physicians but not accepted by psychologists and some physicians. In 1874, W. Erb, a German neurologist, proposed the intensity theory of pain in which he did not believe existence of some specific organs in the body, and instead, he proposed pain to be produced by stronger activation of the nerves by intensive stimulus, while weak stimulus produced non-painful sensation (Fig. 28.1b). The discovery of wide-dynamic-range (WDR) neurons in the dorsal horn of the spinal cord and that of stimulus–response characteristics in the visceral sensory system in the twentieth century support the existence of the intensity theory of pain.

The emergence of the pattern theory was mostly dependent upon the development of the cathode-ray oscilloscope (CRO) and the use of electrophysiological recordings in identification and classification of single sensory afferent fibers according to the size and conduction velocities by Joseph Erlanger (1874–1965) and Herbert Spencer Gasser (1888–1963), co-recipients of Nobel Prize for physiology or medicine in 1944, and other electrophysiologists. Anatomically, the primary afferent fibers have been classified into myelinated and unmyelinated fibers. According to the conduction velocities, A-α and A-β are rapidly conducting fibers that belong to thickly myelinated fibers, while A-δ fibers are slowly conducting, thinly myelinated fibers. C fibers are the ones of the most slowly conducting, unmyelinated fibers. In the very beginning of the twentieth century, some researchers proposed that there are two different classes of somatic sensory pathways subserving epicritic or discriminating sensations (e.g., touch and pressure) and crude or protopathic sensations (e.g., pain) (Head et al. 1905). Later, S. W. Ranson (1915) proposed that fine, unmyelinated nerve fibers were conductors of protopathic sensation. Clearly, these proposals favored the specificity theory. However, galvanometer recordings of the action potentials in the mid-1920s by Sir Edgar Douglas Adrian (1889–1977), co-recipient of Nobel Prize for physiology or medicine in 1932 with Sir Charles Sherrington, and CRO-aided electrophysiological recordings by Erlanger, Gasser, and their collaborators identified different patterns of neural activities from primary afferent nerve fibers in response to different stimulus modalities (mechanical, thermal, and chemical). These discoveries led to formulation of the pattern theory proposed by J. P. A. Nafe, an American psychologist, in 1929 (Fig. 28.1c). The pattern theory was developed into the gate-control theory by Ronald Melzack and Patrick D. Wall.
(1965) (Fig. 28.1d), which has been prevailing and directing the development of pain research all over the world in the following 45 years, although it has been recently argued to be too simple to underlie the pain mechanisms (Cervero 2005; Perl 2007).

The gate-control theory proposes that there is a “gating” at the first synaptic relay between primary afferents and transmission (T) cell (pain-signaling neurons) in the lamina II (substantia gelatinosa, SG) of the spinal dorsal horn (Fig. 28.1d). The core of the theory consists of the following: (1) when the neural activities mediated by large (L) non-nociceptive afferent fibers prevail, it inhibits activities mediated by small (S) nociceptive afferent fibers via activation of inhibitory SG interneurons, resulting in hypoalgesia or analgesia; (2) when activities mediated by nociceptive afferent fibers prevail, it exacerbates pain via deactivation of inhibitory SG interneurons; and (3) the “gating” is dynamically modulated by central control of descending or segmental origins. The flaws of the gate theory are obviously known today as suggested by Cervero (2005) who reviewed “The Gate Theory, Then and Now” in the book The Paths of Pain: 1975–2005 (Merskey et al. 2005). Cervero stated:

The main point of the theory was a restatement of pattern interpretations of pain mechanisms, which has been found, in the intervening years, to be a great simplification for the CNS or even plainly wrong for the organization of the peripheral input to the spinal cord. Other details of the theory regarding the dorsal horn organization of presynaptic links between A and C fibers have also been proven incorrect. However, the gate theory has had an overall positive effect in the field of pain research and has helped to draw attention to previously forgotten aspects of pain modulation.

Although development of the specificity theory has been of wax and wane before and after the emergence of the gate-control theory, it keeps fighting for survival without stop. Actually, between 1930 and 1965, some electrophysiologists identified a class of thinly myelinated and unmyelinated fibers that could be selectively activated by stronger stimulus (Zotterman 1936, 1939; Iggo 1959, 1960, for details see Perl 2007). The major reason why it failed to result in wide influence was probably that single C fiber recordings were too difficult to be widely carried out due to technical limitations, and the results from a small number of labs were not consistent. However, this situation had been greatly changed by a series of publications from Edward R. Perl’s lab since 1967. Perl and his collaborators, using modified single-fiber recording technique, steadily and reliably identified a class of nociceptors innervated with either thinly myelinated or unmyelinated fibers in the cutaneous nerves of cats and monkeys (Burgess and Perl 1967; Perl 1968; Bessou and Perl 1969; Bessou et al. 1971). These discoveries of nociceptors in animals were soon confirmed by Torebjörk and his collaborators in conscious human subjects using psychophysical microneurography (Hagbarth et al. 1970; Torebjörk 1974; Torebjörk and Ochoa 1980; Ochoa and Torebjörk 1983; for details, see Perl 2007). They verified that pain sensation could only be evoked by activation of nociceptors, but not by low-threshold mechanoreceptors. Three years after they discovered nociceptor fibers in the periphery, Perl and his collaborator Christensen (1970) further identified a class of central neurons within lamina I of the spinal
dorsal horn that were referred to as nociceptive specific (NS) neurons, a novel class that can only be activated by noxious stimuli, differing significantly from the characteristics of WDR neurons. NS neurons have been identified in the ventrobasal complex of the thalamus and the primary somatosensory cortex since the mid-1980s. Moreover, neurochemical studies provided with another line of evidence showing localization of neuropeptides (e.g., SP and CGRP) in a small population of DRG (or trigeminal ganglia) cells innervating thinly myelinated and unmyelinated fibers that project their central terminals mainly to the superficial layers of the dorsal horn (Höökfelt et al. 1975; Light and Perl 1979). According to the neurochemical properties and central projections of the primary afferent fibers, nociceptors are generally accepted to be divided into two classes: peptidergic and nonpeptidergic (Snider and McMahon 1998; see Figs. 28.2, 28.3). Identification of TRPV1, a type of thermal nociceptor molecules, was achieved by Julius and his colleagues (1997) which has been regarded as a landmark in the history of pain for

**Fig. 28.2** Primary afferent fibers and the dorsal horn of the spinal cord. The spinal dorsal horn is the gate of primary nociceptive afferent fibers and constitutes a lamination structure proposed by Rexed in the early 1950s, including superficial layers (laminae I and II) and deep layers (laminae V–VI) and the proper part just in between (laminae III–IV). Superficial layers are the major region receiving the central terminals of the unmyelinated C nociceptors. The central terminals of the peptidergic dorsal root ganglion (DRG) neurons that contain substance P (SP), calcitonin-gene-related peptide (CGRP), and nerve growth factor receptor TrkA (red color) terminate within lamina I and outer part of lamina II (IIo) and make synaptic connections with lamina I nociceptive-specific (NS) neurons (red color cells) and interneurons (yellow color circles), while those of the nonpeptidergic DRG cells that contain isolectin IB4 and glial cell line-derived neurotrophic receptor Ret (green color) terminate within inner part of lamina II (IIi) and make synaptic connections with interneurons (green color circles). Large myelinated A-β and thinly myelinated A-δ fibers project to the deep layers (IV–VI) and make synaptic connections with wide-dynamic-range (WDR) neurons (purple color cells). Both NS and WDR neurons send their axonal fibers across the anterior white commissure to form spinothalamic or spinoreticulothalamic tracts ascending along the anterolateral funiculus of the contralateral cord (upward arrow) (With permission from Jun Chen)
understanding of molecular and cellular mechanisms of pain. Although discoveries of nociceptors, central NS neurons, and even nociceptor molecules add more weight to the specificity theory; however, none of the existing theories is almighty. Pain has two faces and is state-dependent in terms of physiological and pathological natures. Pain is also a complex experience associated with multiple dimensions of brain functions, including sensory discrimination, affective motivation, and cognitive evaluation that so far we know very little.

In the history of pain, other profound events are the discoveries of endogenous descending pain modulation system and opioid peptides and their receptors in the CNS. These have been regarded to be cardinal for the effect of the gate theory because they, for the first time, clearly proposed central origins of pain modulation at the level of the spinal cord. Actually, however, 1 year before the publication of the gate theory, Tsou and Jang (1964), two neuropharmacologists in China, discovered that microinjection of morphine into the midbrain periaqueductal gray (PAG) resulted in powerful analgesia in rabbits that led to presumption of existence of endogenous “receptors” of morphine. Five years later, Reynolds (1969) discovered that electrical stimulation of the PAG also resulted in strong antinociception in rats receiving surgery. These two discoveries produced profound and fruitful influences upon the field of pain research, leading to series of discoveries of µ-, δ-, and κ-opioid receptors and opioid peptides (enkephalin, endorphin, dynorphin,
endomorphin, etc.) during the 1970s to the 1990s. Identification and characterization of the cellular and molecular identities of opioid receptors and their endogenous ligands in the CNS underlie the mechanisms of morphine-induced analgesia and brain stimulation-induced analgesia (Merskey et al. 2005). The discoveries associated with the endogenous opioid peptides and their receptors also promoted interpretation of acupuncture analgesia that has been proven to involve frequency-dependent release of endorphins and dynorphins at both brain and spinal cord levels (Han 2003, 2011; Han and Ho 2011). Now it has been generally accepted that the neural circuits of the endogenous descending pain modulation system comprise PAG-rostroventral medulla (RVM)-dorsal horn pathway (Fields and Basbaum 1978). Within the RVM, two types of cells have been identified: (1) ON-cell that can be activated by painful stimulation and (2) OFF-cell that can be inhibited by painful stimulation but activated by morphine (Fields 2004). It is discovered that the balance between the states of these two types of RVM cells determines the pain control effect of opioids. However, under inflammatory and neuropathic pain states, endogenous descending pain modulation system is changed due to the RVM facilitation that exacerbates pathological pain state (Ossipov and Porreca 2005; Ossipov et al. 2010). Moreover, activation of endogenous opioid system in the CNS has been demonstrated to be associated with the placebo effects (Zubieta and Stohler 2009).

Pain is essential to human evolution by the force of natural selection because it can serve as a sensory detection and alarm system for escape and survival when the body is hurt by harmful insults. It can also facilitate healing of injury on the body. However, pain is harmful to the health when it becomes persistent or chronic under pathological state. Although the history of pain problems is as long as that of the birth of human beings, the understanding of pain mechanisms is far from sufficient. The existing theories of pain may be appropriate for the interpretation of some aspects of pain, but never be almighty. Thus, calls for intensive research on pain are necessary. This historical review of the ideas about pain is mainly focusing on the development of pain theories and the fundamental discoveries in the field. The historical events concerning the development of pain therapies and remedies are beyond the scope of this brief introduction. For details, please refer to the following literatures: (1) Rey (1993). (2) Finger (1994). (3) Merskey et al. (2005). (4) Perl (2007). (5) Chen (2011).

Peripheral Nociceptors and Nociception

Nociception is the process that neural information about actual or potential tissue damage can be detected, transduced, encoded, and transmitted from the site of origin to the higher brain centers perceived as pain sensation. The term “nociception” is derived from the Latin word “nocere,” which means “to injure.” Nociceptor is originally based on the concept of nociception proposed by Charles Sherrington (1906), a Nobel laureate of 1932 in medicine. He suggested that events producing disruption of tissue or representing a physical threat to its integrity could
be labeled noxious regardless of their natures. Nociceptor is heterogenous in nature and suggested to be classified into at least five categories (Perl 1996, 2007; Schmidt and Willis 2007): (1) high-threshold mechanoreceptor that responds vigorously to noxious mechanical stimulation applied to the skin; (2) polymodal nociceptor that responds to noxious heat, mechanical, and irritant chemicals; (3) mechano-heat nociceptor that responds to both noxious mechanical and heat applied to the glabrous skin; (4) mechano-cold nociceptor that responds to both noxious low skin temperature and noxious mechanical stimuli; and (5) “silent” nociceptor which is revealed originally in the inflamed joint capsule that it can only be excited by mechanical stimuli when sensitized by local inflammation (or histamine). Figure 28.4 illustrates (2)–(4), respectively. Neurochemically, nociceptors are suggested to be divided into two subpopulations (Figs. 28.2, 28.3). One is referred to as peptidergic population of C nociceptors that contain neuropeptides calcitonin-gene related peptide (CGRP) and substance P (SP) and TrkA, a subtype of neurotrophin tyrosine kinase (Trk) receptors that selectively binds nerve growth factor (NGF). The other is referred to as nonpeptidergic population of C nociceptors that binds the isolectin B4 (IB4) and express c-Ret, a subtype of neurotrophin receptors that selectively binds glial cell line-derived neurotrophic factor (GDNF). The nonpeptidergic nociceptors also co-express purinergic receptor subtype P2X3, neurturin, artemin, and G-protein-coupled receptors (GPCRs) of the Mrg family, and GFRα1 and GFRα2 of GDNF receptor family. The peptidergic nociceptors project their central terminals to lamina I, while nonpeptidergic nociceptors project their central terminals to inner part of lamina II of the spinal dorsal horn, implicating anatomically distinct central target of their projections.

Since the first cloning of transient receptor potential vanilloid receptor 1 (TRPV1) (Caterina et al. 1997), cellular and molecular mechanisms of thermal nociception have been gradually unraveled (Fig. 28.4). TRPV1, a nonselective cation channel with high Ca$^{2+}$ permeability, also known as capsaicin receptor, is the first molecule that is proposed to be a sensor of thermal nociception. TRPV1 can be activated by capsaicin (the main pungent ingredient in “hot” chili peppers), noxious heat (>42°C), and proton. The gene encoding TRPV1 is highly expressed in the primary sensory neurons innervating A-δ and C fibers of dorsal root ganglia (DRG) and trigeminal ganglia (TG). TRPV2, another defined thermal nociceptor, is characterized by a property of activation by temperature higher than 52°C and insensitivity to capsaicin. The cellular and molecular mechanisms underlying cold nociception and mechanical nociception are not as clear as what we know for the thermal nociception. TRPA1 and TRPM8 are believed to be candidates of cold nociceptors, while TRPV1, purinergic receptors for adenosine 5’-triphosphate (ATP) (P2X3 and P2Y1), and acid-sensing ion channels (ASICs), etc., are likely to be the candidates of chemical nociceptors. Some subtypes of voltage-gated sodium channels (VGSCs, e.g., Na$v_{1.7}$, Na$v_{1.8}$, Na$v_{1.9}$), voltage-gated calcium channels (VGCCs, e.g., N-type, P-/Q-type), voltage-gated potassium channels (VGPCs), and two-pore domain potassium channels (e.g., TRAAK, TREK1/2) are proposed to be a sensor or transducer and encoder of nociception (Fig. 28.4) (for details, see Basbaum et al. 2009; Gold and Gebhart 2010).
Peripheral Nociceptors and Transducers

*TRPV1*, a member of the family of TRP channels, has been detected in many tissues including DRG, TG, and visceral sensory neurons. TRPV1-expressing or

**Fig. 28.4 Nociceptor diversity and heterogeneity.** There are a variety of nociceptor subtypes that express unique repertoires of transduction molecules and detect one or more stimulus modalities. For example, heat-sensitive afferents express TRPV1 and possibly other, as-yet-unidentified heat sensors; the majority of cold-sensitive afferents express TRPM8, whereas a small subset likely expresses an unidentified cold sensor. Polymodal nociceptors also express chemoreceptors (e.g., TRPA1) and one or more as-yet-unidentified mechanotransduction channels. These fibers also express a host of sodium channels (such as NaV1.8 and 1.9) and potassium channels (such as TRAAK and TREK-1) that modulate nociceptor excitability and/or contribute to action potential propagation. Three major C fiber nociceptor subsets are shown here, but the extent of functional and molecular diversity is undoubtedly more complex. Furthermore, the contribution of each subtype to behavior is a matter of ongoing study (From Fig. 3 of Basbaum et al. Cellular and molecular mechanisms of pain. Cell, 2009, 139:267–284, with permission from Elsevier)

**Peripheral Nociceptors and Transducers**

*TRPV1*, a member of the family of TRP channels, has been detected in many tissues including DRG, TG, and visceral sensory neurons. TRPV1-expressing or
capsaicin-sensitive neurons are the major subpopulation of sensory cells with peripheral branches of unmyelinated (C fibers) and thinly myelinated (A-\(\delta\) fibers) axons. TRPV1 can be activated by capsaicin, low pH, and high temperature and modulated by a variety of endogenous and exogenous substances such as ATP, NGF, prostaglandins, and bradykinin. Moreover, the genes encoding TRPV1 can be upregulated under some pathological and chronic conditions, and blocking of TRPV1 has been a potential target for pain relief.

TRPV2, also known as vanilloid receptor-like protein 1 (VRL1), is thought to be a structural homologue of TRPV1 with 50% amino acid identity. TRPV2 is insensitive to capsaicin or protons but can be activated by higher temperature (>52°C), osmolarity, membrane stretch, and 2-aminoethoxydiphenylborate (2-APB). TRPV2 is widely expressed in neuronal and nonneuronal cells indicative of broad physiological functions. However, in the somatosensory system, the genes encoding TRPV2 is highly expressed in medium-sized DRG neurons that are believed to be a subpopulation of thinly myelinated A-\(\delta\) fibers, a sensor of high-threshold mechanical and heat nociception.

TRPA1 is also a nonselective cation channel and its encoding genes are expressed in a subset of small-sized primary afferent neurons in mammals. It is revealed that almost all TRPA1-expressing DRG neurons contain TRPV1. TRPA1 is activated by some chemical compounds (such as allyl isothiocyanate, cinnamaldehyde, formaldehyde, etc.) and environmental irritants (such as acrolein) and also targeted by 4-hydroxynonenal, an endogenous aldehyde, and cold temperature. TRPA1 is sensitized by some inflammatory mediators through their GPCRs and the downstream intracellular PLC or PKA signaling. TRPA1 gene knockout mice exhibit pronounced deficits in bradykinin-evoked nociceptor excitation and pain hypersensitivity, and near complete attenuation of formalin-induced pain behaviors. Inhibiting TRPA1 activity decreases cigarette smoke-induced neurogenic inflammation in airway, alleviates gastric distention-induced visceral pain, and reduces arthritic hyperalgesia. Thus, TRPA1 is thought to be an important component of the transduction machinery of noxious stimuli.

TRPM8 is thought to be a principal sensor of cold temperatures. It is expressed in a small population of sensory neurons located in the DRG and TG. TRPM8 detects a broad range of cooling temperatures below 25°C. In addition to cooling temperatures, TRPM8 channel can also be activated by a number of cooling compounds such as menthol, an active ingredient in peppermint. TRPM8 channel is involved in cold pain under physiological conditions. It may also be involved in pathological pain sensations such as cold allodynia under disease conditions.

P2X3 receptor is a ligand-gated ion channel that belongs to the family of purinoceptors for ATP. It is expressed in a subpopulation of primary sensory neurons that are positive to IB4 labeling. P2X3-expressing neurons usually express TRPV1 receptors but not neuropeptides, such as substance P and/or CGRP. P2X3 transduces ATP-evoked nociceptor activation and plays a role in peripheral pain responses. The receptor is also involved in the modulation of sensory synaptic transmission from the central terminals of primary afferent neurons to dorsal horn.
neurons in the spinal cord. The receptor may also be involved in pathological pain following tissue inflammation and nerve injury.

$P2Y$ receptors are a family of G-protein-coupled purinergic receptors that can be activated by nucleotides such ATP-, ADP-, UTP-, and UDP-glucose. To date, 12 subtypes of $P2Y$ receptors have been identified and cloned in mammalian tissues. $P2Y1$, $P2Y2$, $P2Y4$, and $P2Y6$ receptors have been found in sensory neurons. $P2Y1$ and $P2Y2$ are the most highly expressed $P2Y$ receptors in sensory neurons. They are expressed in separate populations of nociceptors, with $P2Y1$ highly colocalized with $P2X3$, and $P2Y2$ colocalized with the noxious heat sensor TRPV1 in non-peptidergic neurons. These $P2Y$ receptors may play a role in transducing nociceptive signals at peripheral nerve terminals. $P2Y$ receptors are expressed in spinal cord glial cells and dorsal horn neurons, where they are involved in modulation of nociceptive transmission.

$ASIC$s are members of sodium-selective cation channels belonging to the epithelial sodium channel/degenerin (ENaC/DEG) family. At least six ASIC subunits (ASIC1a, 1b, 2a, 2b, 3, and 4) which form both homo- and heterotrimeric channels have been identified in mammalian tissues. Each ASIC subunit is composed of cytosolic N- and C-termini, two transmembrane helices, and a disulfide-rich, multidomain extracellular region. ASICs are acid-sensitive ion channels that have an ability to detect changes in extracellular protons (tissue acidosis) produced in ischemia. ASIC1, 2, and 3 are thought to be mechanotransducers of tactile sensation due to their distribution in primary sensory neurons. However, whether any of ASIC1/2/3 serves as a sensor of mechanosensation remains unresolved.

$VGSC$s, also termed as $Na_v$, are a family of voltage-gated sodium channels responsible for the depolarizing phase of action potentials and contributes to neuronal excitability. $VGSC$s comprise of nine pore-forming $\alpha$-subunits ($Na_v1.1$–$Na_v1.9$) and accessory $\beta$-subunits. $Na_v1.7$, $Na_v1.8$, and $Na_v1.9$ are preferentially expressed in small-sized DRG neurons, while $Na_v1.3$ is only expressed in small DRG neurons after nerve injury. Due to lack of specific activators and inhibitors, pharmacological properties of each VGSC have not been clearly identified. Genes encoding $Na_v1.1$, $Na_v1.6$, $Na_v1.7$, $Na_v1.8$, and $Na_v1.9$ can be detected in the normal DRG where TTX-resistant sodium channels $Na_v1.8$ and $Na_v1.9$ are selectively expressed in nociceptive cells. In human, $Na_v1.7$ gain-of-function mutation causes inherited erythromelalgia and paroxysmal extreme pain disorder, while $Na_v1.7$ loss-of-function mutation leads to congenital insensitivity to pain. VGSCs are targets of local anesthetics (e.g., lidocaine) and promising for development of novel subtype-specific analgesics.

$VGCC$s, also termed as $Ca_v$, are a family of voltage-gated calcium channels that play crucial physiological roles in mammalian nervous system. There are at least six subtypes of $VGCC$s identified pharmacologically (L-, N-, R-, P-, Q-, and T-type). Among them, roles of N-, P-/Q-, and T-type in nociception have been mostly studied. P-/Q-type calcium channels are densely localized in the central terminals of the primary sensory cells projecting to the superficial layer of the spinal dorsal horn, highlighting its roles in mediation of neurotransmitter release from presynaptic components. N- and T-type calcium channels are expressed in the
primary nociceptor cells that can be upregulated by peripheral nerve injury. Blocking N-type calcium channels by ziconotide, a synthesized peptide of \( \omega \)-conotoxin GVIA, has been shown to be effective in relief of intractable cancer pain clinically, implicating an important role of N-type channels in mediation of nociception in humans. Besides the pore-forming \( \alpha 1 \) subunit, there are also modulatory subunits (\( \alpha 2\delta, \alpha 2\beta, \alpha 2\gamma \)) supporting for the functions of heteromeric VGCCs. Modulatory subunit \( \alpha 2\delta \) has been demonstrated to be upregulated after nerve injury and is the target of gabapentinoid class of anticonvulsants that are used widely to relieve neuropathic pain.

VGPCs, also termed as \( K_v \), are a family of membrane proteins and water-filled pores permeable to potassium ions that open and close in response to change of membrane potentials. \( K_v \) channels are normally closed at the resting potential of the cells, but open on membrane depolarization. \( K_v \) channels function to shape action potentials and regulate membrane excitability of nerve, cardiac myocytes, and muscle fibers. A native complex of \( K_v \) is composed of a pore-forming \( \alpha \)-subunits and additional auxiliary (or \( \beta \)) subunits. The crystal structure of \( K_v1.2/\beta 2 \) complex was solved in 2005 following the structure of bacterial \( K^+ \) channel KcsA published by scientists of MacKinnon laboratory in 1998. The first \( K_v \) \( \alpha \)-subunit was identified from the \textit{Shaker} gene of the fruit fly \textit{Drosophila melanogaster} that causes flies to shake when exposed to anesthetic ether in 1987. Following the identification of \textit{Shaker}, subfamilies of \textit{Shaker}-related genes from \textit{Drosophila} that bear about 40% sequence homology with \textit{Shaker} was subsequently cloned in 1990, known as \textit{Shab}, \textit{Shaw}, and \textit{Shal}. For \textit{Shaker}-related mammalian counterparts, they are defined as \( K_v1 (\textit{Shaker}), K_v2 (\textit{Shab}), K_v3 (\textit{Shaw}), \) and \( K_v4 (\textit{Shal}) \). \( K_v \) \( \alpha \)-subunits form a tetrameric assembly with a central pore of ion conductance pathway. Among 40 cloned human \( \alpha \)-subunit genes, \( K_v \) channels have been grouped into 12 classes known as \( K_v1–12 \). Auxiliary subunits are proteins which associate with \( \alpha \)-subunits normally at \( \alpha 4\beta 4 \) stoichiometry. These subunits (such as \( K_v\beta, \text{minK}, \) and KChIPs) do not conduct current on their own but rather modulate the activity of \( K_v \) channels. Binding of auxiliary subunits can change the functional properties of \( K_v \) \( \alpha \)-subunits at the membrane surface, their intracellular trafficking, gating kinetics, and pharmacology. The roles of VGPCs in mediation of nociception remain unknown.

\( K2P \) is a family of two-pore domain potassium channels (also known as “leak channels”) including 15 members (KCNK1–7/\( K2p1.1–7.1 \), KCNK9–10/\( K2p9.1–10.1 \), KCNK12–13/\( K2p12.1–13.1 \), KCNK15–18/\( K2p15.1–18.1 \)). \( K2P \) possesses a nature of Goldman-Hodgkin-Katz (open) rectification. These channels can be regulated by oxygen tension, pH, mechanical stretch, and G-proteins. \( K2P \) contains \( \alpha \)-subunits comprising four transmembrane segments where each contains two-pore loops (two inward-rectifier \( \alpha \)-subunits). Three members of \( K2P \) have been suggested to modulate nociceptor excitability and propagation of action potentials, including TREK1 (KCNK2 or \( K2p2.1 \)), TREK2 (KCNK10 or \( K2p10.1 \)), and TRAAK (KCNK4 or \( K2p4.1 \)). TREK is shortened for TWIK-related potassium channel where TWIK stands for tandem of P domains in a weak inward-rectifier \( K^+ \) channel. TRAAK is shortened for TWIK-related arachidonic acid-activated \( K^+ \) channel.
Fig. 28.5 Peripheral sensitization. An experimental model of peripheral sensitization induced by subcutaneous injection of bee venom solution (100 μg, 50 ml) into a hind paw pad of a rat experiencing persistent spontaneous nociception and pain hypersensitivity. On the left column, venom sac and sting apparatus is shown at the tip of a honeybee abdomen. The major polypeptides and enzymes of the bee venom are listed below. Subcutaneous injection of bee venom by a syringe is shown on the left top, while a nerve terminal of primary nociceptive afferent is shown on the bottom right. The direct and indirect actions of each ingredients of the bee venom are proposed. Color symbols representing each ingredient of the bee venom (left) can be clearly seen on the right where melittin (dark red double strand), mast cell degranulating (MCD) peptide (red-colored circle), apamin (green-colored circle), and tertiapin (light blue rectangle) bind directly to the membrane of a nociceptor cell leading to activation of it. Meanwhile, melittin, MCD peptide, bv phospholipase A2 (PLA2) (light green “H”), and hyaluronidase (dark green double balls) cause tissue damage (gray) and release ATP (small blue circles) and H⁺ (small green circles) that activate P2X3 and P2Y, TRPV1, and ASICs. Indirect actions of melittin, MCD peptide, and bv PLA2 cause degranulation of mast cells (purple) and release histamine (large pink circles), BK (large dark green circles), and 5-HT (large dark blue circles) that activate H1 receptor, 5-HT3 receptor, and BK1/2 receptors. The firing of nociceptor terminals will be mediated by VGSC (TTXr Nav1.8/1.9), VGCC, VGPC, Kir, and Ca2+-K+. Dorsal root reflex and axon reflex may cause release of glutamate and neuropeptides (SP and CGRP) that further activate their autoreceptors on the nociceptor terminals or blood vessels causing inflammatory extravasation (neurogenic) with infiltration of macrophage, immune cells and platelets, and many cytokines/chemokines (TNF-α, IL1-1β/IL6, PAF, etc.). The syringe indicates transcutaneous injection of bee venom. Abbreviations: 5-HT3 5-hydroxytryptamine receptor 3, 12-HETE 12-hydroxyeicosatetraenoic acids, AA arachidonic acid, ASIC acid-sensing ionic channel, ATP adenosine triphosphate, BK1/2 bradykinin receptors 1/2, bv PLA2 bee venom phospholipase A2, Ca²⁺-K⁺ calcium-dependent potassium channel, CGRP calcitonin-gene-related peptide, COX-1/2 cyclooxygenases1/2, Glu glutamate, H1 histamine receptor type 1, iGluRs ionotropic glutamate...
Peripheral Mechanisms of Pain and Hyperalgesia

Activation of Nociceptors Nociceptors are receptors that respond selectively to stimuli that can damage tissue. They respond directly to some noxious stimuli and indirectly to others by means of one or more chemical intermediaries released from cells in the traumatized tissue (Fig. 28.5). Nociceptors are peripheral terminals of two types of primary afferent fibers that stem from neuronal cell bodies in DRG or TG (Basbaum and Jessell 2000; McMahon and Koltzenburg 2006; Basbaum et al. 2009): thinly myelinated A-α or A-β fibers and unmyelinated C or A-δ fibers. As described above, nociceptor can be activated by various modalities of stimuli, in terms of physical (mechanical and thermal) and chemical characteristics. Activation of mechanical nociceptors results in sensations of sharp, pricking pain. Activation of thermal nociceptors (e.g., TRPV1) results in sensations of slow, burning pain, while activation of cold nociceptors (e.g., TRPA1, TRPM8) will produce miscellaneous, unpleasant sensations. Some naturally occurring agents, such as the chemical mediators released from the cells in the damaged tissues, ATP, potassium, serotonin, bradykinin, histamine, prostaglandins, leukotrienes, and SP, can activate or sensitize nociceptors. Both A-α and C fibers are widely distributed in skin as well as in deep tissues. The viscera are innervated by DRG neurons with free nerve endings and have mechanosensory and chemosensory receptors. The mechanosensory visceral afferents are similar to that in the skin and can be activated by distension and stretching of visceral muscle, which may evoke sensations of pain. Chemosensory nerve endings are very important for monitoring visceral function and provide the afferent limb for many autonomic reflexes. In contrast, non-nociceptors are those responding to non-noxious stimuli, such as touch, warmth, cooling, and proprioception. These receptors can be divided into cutaneous and subcutaneous mechanoreceptors, muscle and skeletal mechanoreceptors, and thermal and cool receptors. Virtually, all these sensations mediated by the fast, myelinated A-α or A-β fibers.

The primary sensory (e.g., DRG) neurons are pseudo-unipolar in morphology, which convey somatosensory information from the body to the CNS. The morphology of the DRG neurons is well suited to its principal functions: transduction and transmission of encoded stimulus information to the CNS. The DRG neurons differ in a variety of ways that reflect their distinct roles in sensation. Each cell can be

distinguished by (1) the morphology of its peripheral terminal, (2) its sensitivity to a stimulus energy, (3) the presence (or absence) of a myelin sheath, and (4) the diameter of its axon and cell body. The cells can be divided into three groups based on the sizes of the cell body (diameter, μm): the large cell ≥50, the medium 30–50, and the small 10–30. The A-α or A-β fibers are the axons of the large-sized cells, the A-δ fibers are that of the medium-sized cells, and the C fibers are that of the small-sized cells. The muscle afferent fibers include four types of axons: large myelinated (I), medium myelinated (II), small myelinated (III), and unmyelinated (IV) fiber. A-α, A-β, A-δ, and C are also used. The peripheral branch and the central branch (dorsal roots) of the axon of DRG cells are called the primary afferent fiber and transmit the encoded somatic information to the CNS. Under physiological conditions, the terminal of the peripheral branch is the only portion of the DRG cell that is sensitive to stimulus energy. However, after peripheral and/or central parts of the axon or the cell body are injured, these DRG somata can become sensitive to various chemical stimuli and pressures. The peripheral terminal is either a bare nerve ending or an end organ consisting of a non-neural capsule surrounding the axon terminal. The dorsal roots enter and terminate in the spinal cord or the brain stem. The axons of the DRG cells conduct action potentials to the CNS. The speed at which an afferent fiber conducts action potentials is related to the diameter of the fiber. The bigger the diameter, the faster the speed, the sooner the CNS can act on the information. The conduction velocity (m/s) is approximately five to six times the axon diameter (μm) for the large and thinly myelinated fibers, respectively. The factor for converting axon diameter to conduction velocity is smaller (1.5–2.5) for unmyelinated fibers.

Under physiological condition, nociceptor molecules can be activated specifically by its optimal stimulus modality, for example, TRPV1 is activated phasically by a temperature beyond 42°C. However, under pathological conditions induced by tissue or nerve injury or inflammation, TRPV1 will become sensitized due to modulation by various endogenous substances released from immune cells (T cells, neutrophils, and monocytes) and immune-related cells (keratinocytes, resident mast cells, macrophages, and vascular endothelial cells) through interactions with nociceptors (Fig. 28.5; for details, see below).

Modulation of Nociceptors by Pro-inflammatory Cytokines/Chemokines

Cytokines are small secreted multifunctional proteins released by various cells and have specific effects on the interactions and communications between immune cells and nociceptors (Ren and Dubner 2010). Many cytokines (interleukin (IL)-1β, IL-6, tumor necrosis factor (TNF-α)) with previously established roles in the immune system have also been found to have direct and indirect effects on nociceptors and to play key roles in pathologic pain conditions. Within the nervous system, cytokines and their receptors are widely expressed in both neuronal and nonneuronal cells such as satellite glial cells in the DRG. Peripheral nerve injury and local inflammatory irritation result in upregulation of a number of pro-inflammatory cytokines/chemokines and downregulation of certain anti-inflammatory cytokines. Pro-inflammatory cytokines (e.g., IL-1β, IL-6, and TNF-α) can produce hyperalgesia (increased pain evoked by previously painful stimulus) and allodynia (pain evoked by
previously non-painful stimulus) and can increase the production of SP and prostaglandin E2 (PGE2) in a number of neuronal and glial cell types. Blocking endogenous cytokines or administrating anti-inflammatory cytokines effectively reduces pathological pain caused by peripheral nerve injury or inflammation. One particular sub-group of structurally related cytokines is known as chemokines, originally identified based on their ability to induce chemotaxis of immune cells. Various chemokines including MIP-1α, MCP-1, and GRO/KC are upregulated in nerve tissue, not only in models of neuroinflammatory and demyelinating diseases, but also in various forms of CNS trauma and in injured peripheral nerve. Receptors for chemokines (MCP-1, MIP-1α, and GRO/KC) are all expressed in DRG neurons. Some of the chemokines and its receptors (e.g., MCP-1 and CCR2) can be upregulated in the somata of DRG neurons in a condition of chronic compression of DRG. Interestingly, mice lacking the CCR2 receptor completely fail to develop mechanical allodynia in the partial sciatic nerve injury model, although pain sensitivity in uninjured animals is normal. This suggests that the chemokines, including MCP-1 in particular, play very key roles in neuropathic pain as well as in neuroinflammatory conditions through interactions between immune cells and nociceptors.

Peripheral nociceptors or nociceptive neurons are activated or sensitized when exposed to certain pro-inflammatory cytokines/chemokines (e.g., TNF-α, IL-1β, IL-6, MCP-1, and GRO/KC). The excitatory effects of cytokines/chemokines on sensory neurons are at least in part mediated by modulating ion channel activity. It has been revealed that VGCC currents can be modulated through activation of chemokine receptors. Fractalkine, SDF-1α, RANTES, and MDC are shown to inhibit the I(Ba) current in CX3CR1-, CXCR4-, CCR5-, and CCR4-expressing G1A1 cells, as well as in a subpopulation of DRG neurons. In addition, MCP-1/CCR2 signaling may enhance the excitability of DRG neurons via (1) activation of a non-voltage-dependent depolarizing current with characteristics similar to a nonselective cation conductance and (2) inhibition of a voltage-dependent outward current, presumably a delayed rectifier type K+ conductance. These data provide evidence that chemokines can potentially modulate neuronal signaling through the inhibition of neuronal Ca2+ currents. With a longer exposure (24 h), pro-inflammatory cytokine TNF-α affects calcium currents in cultured sympathetic neurons, and IL-1β increased TTX-sensitive Na+ currents in trigeminal nociceptors. TTX-resistant and TTX-sensitive VGSC currents in both IB4-positive and IB4-negative DRG cells have also been demonstrated to be modulated by the chemokine GRO/KC, leading to increased excitability of nociceptors without altered voltage dependence or kinetic changes. VGPC currents are also shown to be increased by overnight incubation of IB4-negative neurons with GRO/KC, without marked changes in voltage dependence or kinetics. Cytokines/chemokines may also affect other types of channels. A pretreatment with TNF-α for 24 h significantly increases the peak inward current evoked by capsaicin in sensory neurons. The same TNF-α pretreatment also induces similar but less-pronounced and less-uniform increases in the responses to acid (pH 6.5–5.5), 2-aminoethoxydiphenyl borate, a common activator of TRPV1, V2, and V3 channels, and allyl isothiocyanate, a selective activator of TRPA1 channel.
In summary, cytokines/chemokines play important roles in pathogenesis of a variety of pain states (Fig. 28.5). Just as specific cytokines and their neutralizing antibodies have been introduced into clinical trials for the treatment of stroke, Alzheimer’s disease, autoimmune diseases, wound healing, and amyotrophic lateral sclerosis, one could utilize local or systemic delivery of anti-inflammatory cytokines or inflammatory cytokine antagonists for the treatment of chronic pain. These specific cytokines or antagonists would act to disrupt the hyperexcitability cycle taking place in the sensory neurons, providing a new, non-opioid therapeutic approach for the treatment of pathological pain due to inflammation or peripheral nerve injury.

**Modulation of Nociceptors by Neurogenic Inflammation**

Inflammatory pain results from the effects of a variety of endogenous chemical agents that are released from damaged cells, immune cells, or nerve terminals. This process irritates the sensory terminals (nociceptors) of primary afferents to cause and/or enhance pain. Inflammation that is initiated by release of pro-inflammatory agents from sensory nerve terminals is referred to as neurogenic inflammation (Willis 1999; Cervero et al. 2003; Schmidt and Willis 2007). Clinically, neurogenic inflammation has been implicated in the pathophysiology of many inflammatory pain syndromes, including arthritis, inflammatory bowel disease, interstitial cystitis, and migraine.

Antidromic activation of primary nociceptive afferents is well known as a key mechanism for driving the release of pro-inflammatory agents, such as inflammatory neuropeptides, in the periphery leading to neurogenic inflammation (Fig. 28.5). Many primary afferent nociceptive axons are peptidergic with the capability to release inflammatory neuropeptides, such as CGRP and SP, which are synthesized and stored in medium- and small-sized primary afferent nociceptive neurons with thinly myelinated A-δ and unmyelinated C axonal fibers. It has long been known that these retrogradely conducted action potentials invade the arborizations of the primary afferent neurons and drive the release of neuropeptides from their terminals by propagation of an “axonal reflex.” There is now increasing evidence that retrogradely conducted action potentials propagated along primary afferents are driven spinally by dorsal root reflexes (DRRs) (Willis 1999; Cervero et al. 2003) (Fig. 28.5). DRRs are triggered pathophysiologically by excessive primary afferent depolarization (PAD) of the central terminals in the spinal dorsal horn (Willis 1999, 2006). PAD is produced by the efflux of Cl⁻ ions from the synaptic terminals of primary afferents when GABA_A receptors are activated by GABA released from spinal GABAergic interneurons. Under normal conditions, PAD is evoked to produce presynaptic inhibition, reducing pain sensation. Following tissue injury, persistent nociceptive stimulation, or inflammation that sensitizes nociceptors, strong nociceptive barrages in turn sensitize GABAergic interneurons by activating NMDA and/or non-NMDA receptors on these interneurons, which produces excessive PAD to generate DRRs that are then conducted antidromically in the primary afferents toward the periphery, causing neurogenic inflammation and orthodromically causing excitation of nociceptive neurons and enhance pain. Under these circumstances, PAD is no longer inhibitory but rather becomes an excitatory event.
Activation (or sensitization) of primary afferent nociceptors is the process of perceiving and processing pain. Nociceptors are not only excited by intense stimuli, but can also be sensitized during the process of inflammation by the actions of pro-inflammatory agents on many receptors and ion channels contained in the surface membranes of the nociceptors (see above). They are responsible for the transduction of nociceptive stimuli and are present not only on the peripheral terminals, but they may also be found along the length of the axons and in the cell bodies of the nociceptors in the DRG. Of these receptors, TRPV1 is a major target by pro-inflammatory agents critical for initiation and maintenance of neurogenic inflammation-induced pain. Modulation of TRPV1 is one of the key mechanisms by which pain is exacerbated via neurogenic inflammation. There is increasing evidence that the sensitivity of nociceptors is modulated by a variety of pro-inflammatory substances including neuropeptides, cytokines, inflammatory soups, NGF, and neurotransmitters (see above). CGRP and/or SP released from primary afferent nociceptive terminals and driven by DRRs can enhance the capsaicin-evoked sensitization of primary afferent nociceptors. The mechanisms include (1) the release of neuropeptides helps to facilitate immune activation (mast cells) by releasing more cytokines that have direct interaction with TRPV1 by the evidence that cytokine receptors on DRG neurons are coupled to TRP and sodium channels; (2) inflammatory soup and/or extracellular acidification that are caused by tissue injury can activate TRPV1, leading to Ca\(^{2+}\) influx that can trigger several second messenger cascades; and (3) neurotransmitters, such as norepinephrine and ATP released after tissue injury or inflammation, participate in neurogenic inflammation by modulating TRPV1 via activation of signal transduction pathways, such as PKC. New evidence has recently been provided that glia-neuron signaling (especially cross talk between satellite glial cells and DRG neurons) becomes enhanced after persistent peripheral noxious stimulation or injury, which increases neuronal excitability and enhances primary afferent input. The underlying mechanism is that secretion of pro-inflammatory cytokines from satellite glial cells is increased, which in turn sensitizes TRPV1.

Plasticity of Primary Sensory Neurons Caused by Nerve Injury and Neuropathies

Peripheral nerve injury often causes neuropathic pain, which is difficult to be treated. Therefore, one of the major interests in pain research is to reveal the mechanisms of neuropathic pain. It has been shown that peripheral nerve injury results in changes in expression of a large number of molecules in the sensory neurons in DRGs (Zhang and Xiao 2005; Costigan et al. 2009). These molecules include neuropeptides, GPCRs, ion channels, and enzymes. It is thought that the regulation of certain molecules may be associated with the changes in the excitatory afferent transmission in the dorsal horn of the spinal cord that may accompany the induction of trophic effects and the promotion of survival and regeneration. Plastic changes have been found in neurons and glial cells in the spinal dorsal horn after peripheral nerve injury. Peripheral nerve injury may cause ectopic ongoing activities, afterdischarges, and in some cases, hypersensitivity. The structural and neurochemical alterations in the spinal sensory pathways perhaps contribute to the abnormal pain sensation, such as hypersensitivity. It is hoped that a better
understanding of the significance of the changes in the somatosensory pathway will lead to development of new strategies for the treatment of neuropathic pain.

The nerve injury-induced neural plasticity in the spinal sensory circuits includes alterations in the gene expression, the synthesis and modification of proteins, the structures of cellular connections, and the synaptic transmission. Changes in the gene expression have been found in both the DRG and the dorsal spinal cord. Microarray techniques were ever used to monitor genes expressed in the DRG after peripheral nerve injury. Primary sensory neurons containing neuropeptides, for example, are subpopulations that are subjected to the most dramatic changes following the peripheral nerve injury. However, some types of neuropeptides, such as vasoactive intestinal polypeptide, galanin, and neuropeptide Y (NPY), are upregulated, while others such as SP and CGRP are downregulated. Meanwhile, several neuropeptide receptors, such as cholecystokinin B receptor (CCKB), the NPY Y2 and Y5 receptors, a nicotinic acetylcholine receptor subtype (α7), a purinoceptor (P2Y1), the α2A adrenergic receptor, and the benzodiazepine receptor of the peripheral type are also upregulated. Peripheral nerve injury also alters the expression of TTX-sensitive sodium channels in DRG neurons, with NaV1.3 being upregulated and NaV1.1, NaV1.2, NaV1.6, NaV1.7, NaV1.8, and NaV1.9 being downregulated. Importantly, the expression of the α2 δ1 subunit of VGCC, a target of gabapentin, is increased in DRG neurons after peripheral nerve injury.

Transmission of sensory information from periphery to the CNS is normally subjected to either pre- or postsynaptic inhibitory control maintained by activity in sensory afferents, dorsal horn interneurons, and descending pathways. In the spinal cord, the sensory afferent terminals undergo plasticity that reflects changes occurring in their cell bodies in the DRG. Peripheral nerve injury also trans-synaptically causes the molecular modification in neurons and glia cells in the dorsal horn of the spinal cord, including ion channels, receptors, and signal transduction-related molecules. The plastic changes in the dorsal horn neurons include expanded or novel receptive fields, ongoing activity, afterdischarges, and in some cases, hypersensitivity. The overall excitatory drive in the dorsal horn may be increased, and there is strong evidence that inhibitory control in the spinal cord is compromised after nerve injury. The endogenous opioid peptides and their receptors represent another important spinal inhibitory system on nociception. Morphine and other opioid analgesics are very effective in treating nociceptive or inflammatory pain, but their inhibitory effects are reduced in neuropathic pain. This may be due to injury-induced reduction of μ-opioid receptors on afferent terminals of and/or dorsal horn interneurons. In addition, the decreased sensitivity to opioid analgesics may be involved in the modulation of several anti-opioid systems, including an increased expression of CCK and its receptors.

Some of these plastic changes in the pain pathway are correlated with the current therapy for neuropathic pain. For a long time, several antidepressants, antianxiety drugs, and anticonvulsants are used during the treatment of neuropathic pain, although the pharmacological mechanisms for such a treatment are largely unclear. Gabapentin, which is regarded as an anticonvulsant, has been used as a first-line...
drug for the treatment of neuropathic pain. The nerve injury-induced upregulation of Ca\textsuperscript{2+} channel \(\alpha2\delta1\) in both the DRG and the dorsal spinal cord could be a molecular basis for using gabapentin in neuropathic pain treatment.

In fact, the functions of most molecules with marked up- or down-regulation remain to be determined. For example, only a few DRG neurons express pancreatitis-associated proteins (PAPs) and lectin-related secretory proteins. Recent studies show that both inflammation and peripheral nerve injury trigger the expression of PAPs in DRG neurons, suggesting that PAPs may play potential roles in pathological pain. However, the functions of PAPs in the pain pathway remain unclear, and the receptors for PAPs have not been identified. Furthermore, the complexity of neuropathic pain could be added by the modification of protein processing and trafficking in the neurons. The progress of cell biology suggests that the trafficking of receptors and ion channels could be highly regulated by not only the neuronal activity but also their interacting proteins. For instance, a loss of protachykinin-A might result in a reduced axonal transport of \(\delta\)-opioid receptors (DORs) after peripheral nerve injury because the trafficking of DORs in the regulated secretory pathway in small DRG neurons is dependent on the DOR/protachykinin-A interaction (Zhang et al. 2010).

Taken together, although it is generally accepted that the nerve injury-induced plastic changes in neurochemical substrates along the somatosensory pathways, especially at the nociceptor level, are associated with development of nerve injury-related pain, mechanisms underlying other types of neuropathic pain such as postherpetic neuralgia, diabetic neuropathic pain, poststroke pain, and multiple sclerosis-associated pain, etc., remain largely unknown and require to be further studied.

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### The Spinal Cord Dorsal Horn

#### Organization of the Dorsal Horn

**Primary Afferents to the Dorsal Horn** The spinal dorsal horn is the major site of termination for primary nociceptive afferent axons (Basbaum and Jessell 2000; Willis and Coggeshall 2004; McMahon and Koltzenburg 2006; Basbaum et al. 2009). They are distributed in an orderly way based on fiber size and sensory modality. Most small afferents with either fine myelinated (A-\(\delta\)) or unmyelinated (C) axons are nociceptors, and these terminate predominantly in lamina I and II, although a few reach deeper laminae (Figs. 28.2, 28.3). Most large (A-\(\beta\)) cutaneous afferents function as low-threshold mechanoreceptors, and each type has a characteristic pattern of arborization in the deeper laminae (III–VI) of the dorsal horn (Figs. 28.2, 28.3). In the dorsal horn of spinal cord, the central terminals of primary afferents make synapses either with the projection neurons in their respective laminae or with spinal interneurons that synthesize glutamate, \(\gamma\)-aminobutyric acid (GABA), opioid peptides, and other modulators. The processed signals are then transmitted to higher levels of the brain to contribute to pain perception.
As aforementioned, there are several “neurochemical markers” that can be used to track tracing the projection site of the nociceptive primary afferents. For example, the peptidergic (SP, CGRP) and TrkA-expressing C nociceptors send their central terminals to lamina I, outer lamina II (IIo), and the dorsal part of the inner lamina II (Ii) of the spinal cord (Figs. 28.2, 28.3). The nonpeptidergic IB4-positive and Ret-expressing subset of C nociceptors send their central terminals to lamina Iii of the spinal cord (Figs. 28.2, 28.3).

Unlike somatic tissue, the viscera are unique. They are dually innervated by two sets of primary afferents that appear to contribute to different aspects of visceral pain and hyperalgesia. Upon entering the dorsal horn, the central projections and terminal arborization of these visceral afferents are highly divergent. They cover the mediolateral and dorsoventral extent and extend rostrocaudally for 5–10 segments of the spinal cord. This extremely divergent terminal arborization likely contributes to the poor localization of visceral pain.

**Spinal Pain Sensory Neurons**

It is widely known that there are three classes of sensory neurons in the spinal cord dorsal horn according to their response characteristics to natural mechanical stimuli applied to their cutaneous receptive fields (Willis and Coggeshall 2004), namely, (1) class 1 (also known as low-threshold mechanoreceptive – LTM) neurons, mostly evoked by innocuous or non-painful stimulation; (2) class 2 (also known as multireceptive or WDR) neurons, evoked by both noxious and non-noxious stimulation with the response stronger to noxious stimulation; and (3) class 3 (also known as NS) neurons, only evoked by noxious stimulation. Anatomically, NS neurons are mainly distributed in lamina I and lamina IIo of the Rexed lamination of the spinal cord. WDR neurons are mainly located within laminae IV–VI with the lamina V most densely populated. LTM neurons are interneurons in nature and mainly located within lamina III, the proper layer of the spinal cord dorsal horn. The three classes of neurons can also be identified in the caudal subnucleus of the spinal tract nucleus of the trigeminal nerves which innervate the head and orofacial area. Both WDR and NS neurons are second-order neurons relaying painful information through synaptic connection with the central terminals of the nociceptive primary sensory neurons in the DRG where, as shown above, various kinds of proteins (TRPV1, etc.) are synthesized and transported to their peripheral terminals serving as pain sensors (Fig. 28.2). Most of WDR and NS neurons are the spinothalamic tract cells projecting their axonal fibers to the thalamic ventrobasal complex (ventroposterior lateral nucleus and ventroposterior medial nucleus) through ventrolateral system. A number of dorsal horn nociceptive sensory neurons send axonal fibers to the brain stem where the spinoreticulothalamic tract is formed and projects to the intralaminar nuclei of the thalamus. Moreover, among the three classes of dorsal horn sensory neurons, there are reliable lines of evidence showing that the majority of WDR neurons, but not NS neurons, are intercalated in the spinal circuitry responsible for the nociceptive flexion reflex (NFR).

**Nociceptive Flexion Reflex**

NFR (also known clinically as the nociceptive withdrawal reflex) is believed to be mediated by a spinally organized neural circuitry which mainly includes a central-processing site of sensory information
in the spinal cord dorsal horn and a central-processing site for motor output in the ventral horn (Willis and Coggeshall 2004). Both the dorsal horn and the ventral horn have been extensively studied, and they are known to be subject to various sources of modulation (inhibition or facilitation) from supraspinal, propriospinal, and segmental inputs. The NFR is a useful and powerful tool for the evaluation of pain (nociceptive) responses and effects of endogenous or exogenous antinociceptive drugs in both human and animal experimental studies. Electrophysiological studies have revealed that peripheral cutaneous or deep tissue injury and inflammation can result in hyperexcitability or central sensitization in the spinal dorsal horn nociceptive neurons as well as a temporal or spatial facilitation of the NFR in both human and animal experimental models of pain hypersensitivity. The hyperexcitable states known as windup (a progressive increase in response to repetitive electrical C fiber stimulation; for details, see below) or long-term potentiation (LTP) of postsynaptic efficacy (for details, see below) can also be induced by conditioned electrically noxious stimulation in the dorsal horn of spinal cord as well as in the ventral horn motor units mediating the NFR in intact or spinal, anesthetized animals as well as in human subjects. However, the interactions between the sensory dorsal horn and motor ventral horn of the spinal cord and the spinal circuitry of the NFR are less known due to lack of experimental models or direct evidence to link the individual sensory events with concomitant motor events following nociceptive sensory stimulation.

**Ascending Pain-Signaling Pathways**

Molecular markers (e.g., c-Fos) of the functional activity of nociceptive neurons and retrograde-tracing techniques have been used to characterize the ascending pathways of noxious information in animals. Spinal cord dorsal horn neurons directly or indirectly receive noxious inputs of majority of body (except for face) from thinly myelinated A-δ fibers and unmyelinated C fibers of DRG neurons. Their axonal fibers curve medially to cross the midline and ascend in anterolateral system within spinal cord white matter. Based on the terminating locations, the projecting fibers are divided into the spinothalamic, spinoreticular, spinomesencephalic, spinotectal, and spinohypothalamic tracts (Fig. 28.6, also see Millan 1999; Basbaum and Jessell 2000; Willis and Coggeshall 2004; McMahon and Koltzenburg 2006; Basbaum et al. 2009). Approximately 15% of nociceptive fibers project directly to the thalamus, whereas 85% project to the thalamus via a relay in the reticular formation or midbrain. In the direct pathway, nociceptive signals relayed from the spinal cord are directly transmitted to the ventroposterior lateral, the ventroposterior inferior, and the intralaminar nuclei of the thalamus via the spinothalamic tract. In contrast, in the indirect pathway, nociceptive signals are transmitted to the reticular formation or midbrain and then transmitted to the intralaminar nuclei of the thalamus (which functions to arouse the organism in response to nociceptive input) and to the hypothalamus and the amygdala (which induces autonomic, reflex, and emotional responses to pain stimuli). The signals that relay in the thalamus are finally transmitted to the somatosensory cortex (including the primary (S1) and secondary (S2) somatosensory cortices), where pain localization, intensity, quality, and sensory integration are processed. The S1 cortex also sends projections to the S2 cortex,
Fig. 28.6 Anatomy of the pain pathway. Primary afferent nociceptors convey noxious information to projection neurons within the dorsal horn of the spinal cord. A subset of these projection neurons conveys information to the somatosensory cortex via the thalamus, providing information about the location and intensity of the painful stimulus. Other projection neurons engage the cingulate and insular cortices via connections in the brain stem (parabrachial nucleus) and amygdala, contributing to the affective component of the pain experience. This ascending information also accesses neurons of the rostral ventral medulla and midbrain periaqueductal gray to engage descending feedback systems that regulate the output from the spinal cord (From Fig. 2 of Basbaum et al. Cellular and molecular mechanisms of pain. Cell, 2009, 139:267–284. With permission from Elsevier)
which is believed to have an important function in the memory of pain input. Cerebral imaging studies on human subjects have demonstrated that nociceptive signals are not only processed in the S1 and S2 cortices but also in the anterior cingulate cortex and anterior insular cortex. The latter two regions are connected with the limbic cortex and are involved in the emotional aspect of pain.

It should be mentioned that the neurons of the trigeminal spinal nucleus receive facial noxious inputs from thinly myelinated A-δ fibers and unmyelinated C fibers of TG neurons and possess axons that cross the midline and ascend in the trigeminal lemniscus to the contralateral thalamus, from which it is relayed to somatosensory cortex through ventroposterior medial nucleus.

**Descending Pain-Modulating Pathways** In addition to receiving noxious information through the ascending pain pathway, the brain modulates pain sensation through the descending pathways (Fig. 28.6, see Basbaum and Fields 1984; Millan 2002; Fields 2004). Studies have suggested that the descending pathways have inhibitory effects on pain signals. Electrical stimulation or local administration of agonists or antagonists into defined brain regions elicits antinociception. However, more and more evidence indicates that this pathway may also facilitate pain sensation under some pathological state (for details, see below). These inhibitory and facilitatory influences on spinal pain signals may originate from the same brain regions. The best example is that two types of neurons in the rostral ventromedial medulla (RVM), the so-called ON- and OFF-cells, contribute to the determination of descending facilitation and inhibition, respectively. Descending pathways arise from a number of supraspinal sites, including cerebral cortex, limbic structures, hypothalamus, parabrachial nucleus, nucleus tractus solitarius, midbrain periaqueductal gray (PAG)-RVM system, locus coeruleus (LC), and dorsal reticular nucleus. Of those, the PAG-RVM system has been well established. The PAG projects to the RVM (including the nucleus raphe magnus, the nucleus reticularis gigantocellularis pars α, and the nucleus paragigantocellularis lateralis). Neurons in the RVM directly project to the spinal cord dorsal horn through spinal dorsolateral funiculus that synapse with dorsal horn interneurons and modulate pain response. Some neurotransmitters (e.g., endogenous opioid and anti-opioid peptides, noradrenaline, and serotonin) have been shown to participate in inhibition and facilitation of pain transmission through binding to their respective receptor subtypes.

**Spinal Mechanisms of Hyperalgesia and Allodynia**

**Windup of Pain-Sensing Cells** As early as in the 1960s, animal studies showed that spinal cord dorsal horn neurons become increasingly excitable following repeated electrical stimulation at sufficient intensity to recruit activities of peripheral C fibers (Mendell and Wall 1965). These progressively increased activities of spinal sensory neurons are termed “windup” and considered as a result of artificial responses involving central temporal summation that is dependent on the frequency (0.3–5 Hz), with less extent to the modalities, of noxious stimuli. Within the dorsal
horn of the spinal cord, deep WDR, but not superficial NS, neurons have been suggested to mediate “windup” phenomenon. In addition to the spinal dorsal horn, “windup” can also be evoked in the spinal ventral horn motoneurons by repeated stimulation (Herrero et al. 2000). Utilizing simultaneous recording approach, “windup” of spinal nociceptive withdrawal reflexes are highly correlated with the occurrence of spinal dorsal horn WDR neuronal responses, suggesting existence of central sensory-motor integration (You et al. 2003). Physiologically, this accumulative facilitation of spinal cord dorsal horn neuronal responses may lead to increased nociception and pain reported as allodynia, hyperalgesia, and “windup”-like pain in animals as well as in humans. Experimental data have been documented that “windup” of spinal sensory and motor neurons is mediated by NMDA receptors and can be modulated by activation of opioid receptors and others. Although “windup” phenomenon is commonly considered as central plastic changes relative to pain sensitization, this short-term (less than minutes), reversible central plasticity is, however, critically questioned, namely, “windup” is not equal to the long-term manifestations of central hypersensitivity, that is, central sensitization, during the exposure to painful stimuli (Woolf 2011).

Long-Term Potentiation LTP in spinal dorsal horn is used to serve as a synaptic model of hyperalgesia or pain hypersensitivity (Liu and Sandkuhler 1995; Drdla and Sandkuhler 2008). LTP, referred to as a long-lasting increase in efficacy of synaptic transmission, is a common mechanism of memory storage in the CNS. In spinal dorsal horn, LTP at C fiber synapses is induced by intensive noxious stimulation, such as high-frequency (100 Hz) or low-frequency (2 Hz) electrical stimulation, nerve injury, and tissue inflammation. LTP-inducible stimulation can produce long-lasting hyperalgesia in both rodents and in humans. The drugs that attenuate hyperalgesia, such as clonidine, ketamine, etc., are also able to inhibit spinal LTP. Recently, it has been shown that spinal LTP can also be induced by abrupt withdrawal of opioids. Therefore, the spinal LTP may contribute to persistent hyperalgesia produced by both noxious events and opioid withdrawal. The molecular mechanisms of spinal LTP are similar to LTP in the hippocampus due to the following data: (1) Induction of LTP depends on the rise in intracellular Ca\textsuperscript{2+} produced by opening of NMDA receptor and VGCCs, and the subsequent activation of intracellular PKA, PKC, CaMKII, PLC, and release of NO. (2) Late-phase (>3 h), but not early phase (<3 h), LTP is dependent on de novo protein synthesis. Local application of BDNF into the hippocampus or spinal dorsal horn directly induces late-phase LTP. (3) In recent years, accumulating evidence has demonstrated that activation of glial cells regulates synaptic plasticity by releasing pro-inflammatory cytokines. Interestingly, the effects of glial cells and pro-inflammatory cytokines on spinal LTP and hippocampal LTP are totally different. Activation of microglia in the hippocampus inhibits LTP, while in spinal dorsal horn microglial activation is essential for LTP induction by high-frequency stimulation and by BDNF. TNF-\textgreek{z} inhibits hippocampal LTP but not spinal LTP in na"ive animals. In animals with neuropathy, however, TNF-\textgreek{z} induces spinal LTP. Therefore, the drugs targeting at glial cells and TNF-\textgreek{z} may not only attenuate chronic pain but also improve memory in hippocampus.
Disinhibition refers to a reduction of GABAergic and/or glycinergic inhibitory neurotransmission in the CNS (Basbaum et al. 2009; Sandkuhler 2009). Loss of inhibitory modulation of projection neuron activity would be expected to favor hypersensitivity of spinal nociceptive circuits to both A-β and C fiber sensory inputs manifesting as allodynia and hyperalgesia. For example, tactile allodynia may result from a loss of inhibition of excitatory interneurons that convey low-threshold mechanoreceptive inputs to lamina I projection neurons, leading to a miscoding of the information by cells that normally only detect painful stimuli. Several mechanisms involving the release of GABA and/or glycine or their post-synaptic actions could lead to disinhibition. (1) Nerve injury-induced cell death of GABA and/or glycine containing interneurons (Scholz et al. 2005). (2) Depletion of GABA (or glycine) from axons of inhibitory interneurons as suggested by the evidence that one isoform of GAD is downregulated after peripheral nerve injury. (3) Reduced synaptic efficacy resulted from altered GABA receptor subunit expression. The above-mentioned mechanisms have been challenged by recent studies showing that no significant neuronal loss or altered GABA receptor expression was detected in spinal dorsal horn after nerve injury (Todd 2010). (4) Attenuation of GABAergic and/or glycinergic inhibition induced by downregulation of the potassium chloride transporter KCC2. This attractive hypothesis, however, does not explain why spinal administration of GABA_A receptor agonists reduces allodynia or hyperalgesia in neuropathic pain models. (5) Alteration of the primary afferent inputs to spinal inhibitory interneurons. Different types of spinal interneurons receive synaptic input from specific classes of primary afferent fibers. Loss of synaptic inputs of inhibitory interneurons may differ in the extent after peripheral nerve injury.

Changes in Descending Pain Modulation Descending circuitries linking the PAG, RVM, or LC, and the spinal dorsal horn are well characterized in brain stem pain modulatory pathways and play a critical role in the endogenous pain modulatory systems by inhibiting or facilitating nociceptive transmission at the level of the spinal cord (Basbaum and Fields 1984; Millan 2002; Porreca et al. 2002). Descending modulatory pathways mediate morphine analgesia (Fields 2004) and allow integrated emotional and cognitive outputs from higher cortical areas including anterior cingulate, insular cortex, and amygdala to influence spinal pain message processes. Turning on from earlier address on descending pain inhibition responsive to acute pain or transient noxious stimuli, recent studies have demonstrated that after tissue or nerve injury the descending pain circuitries exhibit tremendous plasticity, which results in both enhanced descending net inhibition and facilitation (Porreca et al. 2002). However, when prevailing over the parallel anti-pain actions, the enhanced facilitation outlives its biological significance, serving as a warning system or protective role in the setting of persistent injury, and instead significantly accounts for the development of chronic pain. It is now recognized that the establishment and perpetuation of chronic pain are dependent to a large degree on the imbalance induced by the maladaptive changes in the endogenous pain modulatory system. Recent studies have paid attention to the involvement of the RVM of the circuits in experimental chronic pain condition at
the base of its relay between the PAG and the spinal cord and its 5-HT-rich descending projection neurons for the final net output of the top-down modulation to persistent pain states.

Neuronal hyperexcitability and functional switch in the RVM have been found after inflammation. RVM lesions or silences prevent or abolish tissue or nerve injury-induced pain hypersensitivity including hyperalgesia and allodynia. This might be related to the contribution of some chemically characterized neurons in the RVM in the maintenance of neuropathic pain, such as demonstrated by knockdown of RVM neurons expressing µ-opioid receptor or CCK receptor and molecular depletion of 5-HT in RVM neurons. Furthermore, such integrative intercellular-signaling cascades, as excitatory amino acid and its receptors AMPAR and NMDAR, neuronal BDNF-TrkB system, and proinflammatory cytokines released by hyperactivated glia cells and their receptors in neurons, in the RVM appear to be involved in molecular mechanisms underlying the inappropriate hyperexcitability and play a fundamental role in the enhanced descending pain facilitation after inflammation or nerve injury. Additionally, recent evidence indicates that the descending pain facilitation is required for the central sensitization or hypersensitivity in spinal neurons after injury by a spinal-bulbo-spinal loop in the spinal cord. Although the inhibitory or facilitatory effect of descending-released 5-HT depends on the spinal 5-HT receptor subtypes activated, 5-HT3 receptor expression in the spinal dorsal horn may dominantly mediate descending pain facilitation and contributes to the enhanced nociceptive processing and persistent pain states.

Roles of Glial Cells

Recent studies have indicated that glial cells (microglia and astrocytes) in the spinal cord play important roles in initiation and maintenance of pain (De Leo et al. 2007; Ren and Dubner 2010). First, the glial cells in the spinal cord dorsal horn can be activated by various nociceptive stimulations (physical, chemical, biological, etc.). Once activated, the resting glial cells switch into an active state and show changes in morphology, gene expression, function, and numbers. These changes correlate reliably with the animals’ behavioral responses. Second, the neurotransmitters/modulators, for example, ATP, excitatory amino acids, BDNF, neuropeptides (SP, CGRP), NO, opioids, etc., released from presynaptic terminals may also reach their corresponding receptors on the glial cells, like P2X2/3, P2X4, P2X7, NMDA or AMPA subunit, TrkB, neurokinin 1, µ-opioid receptors, and toll-like receptor 4 (TLR4), to produce glial activation. Third, activation of glial cells initiates cellular signal transduction pathways, for example, Ca\(^{2+}\), mitogen-activated protein kinases (MAPKs) (ERK and p38), NF-κB, transcription 1 and 3 (Stat1/3), etc., which lead to the release of a variety of substances including inflammatory cytokines, prostaglandins, BDNF, ATP, NO, D-serine, TNF-α, and glutamate. These mediators in turn modulate neuronal activity and facilitate pain transmission. Fourth, the animals with inflammatory or neuropathic pain can be treated with anti-inflammatory cytokines (IL-2, IL-4, IL-10, TGF-β), glial cell modulators or inhibitors (fluorocitrate, minocycline, TLR4, CNI-1493), or some receptor antagonists (TNF-bp, Brilliant Blue G, PPADS, NF449, NF023, A-740003, A438079, A-839977) to resolve pathological
pain and to inhibit the responses of glial cells. Thus, glial cells may be a potential therapeutic target for neuropathic pain in the future.

**Tripartite Synaptic Model of Central Sensitization** Classic synaptic transmission refers bipartite synapses consisting of presynaptic and postsynaptic components and a synaptic cleft, by which information transfers from one to another neuron. However, based on the discovery of the existence of bidirectional neuronal-astrocytic signaling, the new concept “tripartite synapse” was proposed by Parpura and colleagues (Fig. 28.7, see Parpura et al. 1994). Besides the traditional perspective that astrocytes anatomically enwrap the synapses and functionally serve housekeeping roles, emerging evidence has indicated that the structural and functional coordination of neurons with neighboring glia actively processes synaptic information and contributes to synaptic plasticity (Perea et al. 2009; Halassa et al. 2010). As active elements in the synapse, astrocytes can be triggered by synaptic activity through activation of multiple membrane-bound receptors expressed by astrocytes. Astrocytic calcium elevations evoke the release of gliotransmitters, including glutamate, ATP, and d-serine, and in turn, regulate the synaptic transmission to impact neuronal function. Although many aspects of the neuronal-glial relationship are still to be elucidated in the CNS mechanisms of acute and persistent pain, recent evidence is shedding light on the critical role of glial cells in central sensitization at the level of synapses, local circuits, and pain behavior with a specific focus on imbalances of nociceptive processing in tripartite synapses in the spinal dorsal horn (Ren and Dubner 2010). Spinal glial activation is now considered as an important component in the development and maintenance of allodynia and hyperalgesia after inflammation and nerve injury. Understanding the intercellular interactions among astrocytes, microglia, and neurons in this novel synaptic model of persistent pain has major implications for the development of novel analgesic drugs.

Behavioral pain hypersensitivity is encoded by enhanced efficacy of synapses between terminals of primary nociceptive afferents and spinal dorsal horn neurons. Enhancement of excitatory synaptic transmission in pain-signaling pathway is a key neural substrate underlying persistent pain and is also associated with a robust and prolonged hyperactivation of glial cells and increased release of proinflammatory cytokines in the spinal dorsal horn. After tissue and nerve injury, increased release of transmitters, such as glutamate, SP, and CGRP, from terminals of small primary afferents induces not only strong and frequent activation of postsynaptic receptors and amplification of postsynaptic currents but high probability of spinal neuronal firing as well. Meanwhile, the neurotransmitters also activate the nearby receptors expressed on glial profiles including astrocytic processes in the synapses, and subsequently the initial increase in intracellular calcium leads to the activation of calcium-dependent signaling cascades in glial cells (Woolf and Salter 2000). Accumulating data have demonstrated that microglial activation with a preferential increase of MAPKs pathway p-p38 and p-ERK1/2 precedes prolonged activation of astrocytes with the elevation of p-JNK in the spinal dorsal horn during the development of neuropathic pain. The activated signaling cascades could be involved in the transcriptional and posttranslational regulation of multiple genes encoding for proinflammatory cytokines including TNF-α, IL-1β, IL-6, and matrix
Fig. 28.7 Central sensitization and synaptic plasticity. Hypothetical scheme shows central sensitization or synaptic plasticity occurring at an excitatory tripartite synapse in the spinal cord dorsal horn. Both glial cells and neurons are involved in the processing due to peripheral persistent pain state. Upon transient pain stimulation, neurotransmitters glutamate (Glu) and some neuromodulators (e.g., substance P (SP)) are released from the central terminals of the primary afferent neurons and evoke postsynaptic glutamate AMPA subunit receptor (GluAR) and NK1 receptor, respectively, on pain-signaling neurons in the dorsal horn and finish nociceptive signal transmission at the first synapse of the sensory processes. Meantime, released glutamate act on neighboring spinal astrocytes to wake up glutamate transporter (GluT) system for cleaning glutamate in synaptic cleft and keeping normal homeostasis. However, following peripheral tissue and nerve injury, beside enhanced astrocytic activation, some active mediators including ATP, fractalkine, and CCR2 are also released from sensitized C and A-δ fiber terminals activate spinal microglia by binding to purinoreceptors (such as P2X4 and P2X7) or cytokine receptors as neuron-to-microglial cross talk. Afterward, hyperactivated microglia produce and secrete proinflammatory cytokines, such as interleukin (IL)-1β, IL-6, tumor necrosis factor (TNF)-α, and IL-18, and they act on their receptors expressed on astrocytes as microglia-to-astrocyte signals for a long-lasting hyperactivation of astrocytes, which continue to produce and release proinflammatory cytokines, including IL-1β and TNF-α, and chemokines, such as CCR2, and further act back their receptors expressed on dorsal horn neurons as astrocyte-to-neuron interaction, facilitating pain transmission by enhancing the function of NMDA receptors (GluNR) and GluARs and resulting in neuronal hyperexcitability. In addition, hyperactivated astrocytes also secrete D-serine, which binds to the glycine-binding site of postsynaptic GluNRs and thereby increases the activity-dependent synaptic strength. The glial GluT including GLT-1 and GLAST are downregulated in spinal astrocytes after inflammation and nerve injury, also amplifying excitatory synaptic transmission and subsequently, in local circuitry level, central sensitization.
metalloproteinase-9 (MMP9). Experimentally, intrathecally selective blockade of spinal glial function and its intracellular-signaling cascades can attenuate hyperalgesia and allodynia, supporting that spinal glial hyperactivation contributes to the mechanisms underlying inflammatory and neuropathic pain (Ren and Dubner 2010). Upon glial activation, released or secreted cytokines mainly are pro-inflammatory or pro-nociceptive and are considered as an important key of the positive feedback loops engaged in enhanced excitatory synaptic transmission. For example, activation of the cytokine receptors expressed on the dorsal horn neurons, such as receptors for TNF-α or IL-1β, primarily induces a quick enhancement of functional expression of VGSCs and increased NMDAR phosphorylation as well as downregulation of GABA receptor expression on dorsal horn neurons, and long lasting alters gene transcription and protein synthesis and consequently results in neuronal hyperexcitability. In addition, it has been reported that the astrocytic expression of the glutamate transporters including GLT1 is dramatically reduced by pro-inflammatory cytokines such as TNF-α, which indirectly facilitates excitatory synaptic transmission through increasing glutamate concentration in synaptic sites. Neutralization of the endogenous cytokines in the spinal cord significantly prevents injury-induced neuronal hyperexcitability and behavioral pain hypersensitivity, supporting that chemical mediators contribute to the mechanisms of central sensitization and persistent pain.

Additionally, microglial cells are extremely hyperactivated in the dorsal horn quickly by immune challenges. Some signaling molecules, such as ATP and chemokine fractalkine (CX3CL1), released from the primary afferent terminals and intrinsic neurons can activate spinal microglia through expressing P2X receptors (Tsuda et al. 2010) and CX3CR1 receptor (Milligan and Watkins 2009), respectively, and intracellular-signaling cascades p38 MAPK, ERK1/2, and src-family kinases. Upon activation, besides proinflammatory cytokines, microglia also release some neuroactive substances such as BDNF, NO, and prostaglandins and consequently decrease GABAergic inhibitory tone or enhance functional NMDA receptor expression to increase neuronal excitability (Woolf and Salter 2000; Ren and Dubner 2010), contributing to the induction and maintenance of neuropathic pain by altering neuronal function. In addition, TLRs are a family of pattern recognition receptors that mediate innate immune responses to stimuli from pathogens or endogenous signals. TLRs expression on microglia appear to be the most relevant in triggering and tailoring microglial activation in the dorsal horn following tissue and nerve injury and are critically involved in immune-mediated pain signaling in the dorsal horn (Guo and Schluesener 2007). Furthermore, new data has demonstrated that there are time course-dependent upregulation of MMPs

Fig. 28.7 (continued) related to pathological pain. See text for further details. AQP4 aquaporin 4, BDNF brain-derived neurotrophic factor, CCR2 cysteine-cysteine chemokine receptor, ERK extracellular signal-regulated kinase, JNK c-Jun N-terminal kinase, MMP matrix metalloprotease, NK1R neurokinin-1 tachykinin receptor, NF-κB transcription factor nuclear factor-κ B, p- phosphorylated form, p-38 p-38 mitogen-activated protein kinase, PGE2 prostaglandin E2, TLRs toll-like receptors (With permission from Feng Wei)
in both neurons and glia in the DRG and in the dorsal horn neuron after spinal nerve ligation. MMP-9 induces neuropathic pain through IL-1β cleavage and microglial activation at early times, whereas MMP-2 maintains neuropathic pain through IL-1β cleavage and astrocyte activation at later times (Kawasaki et al. 2008). Neutralization of endogenous cytokines blocks pain hypersensitivity after injury, supporting that glial activation and released cytokines are both necessary and sufficient causal for creating pathological pain (Ren and Dubner 2010). Blockade of glial-signaling cascades and cytokines represents a major avenue for therapeutic intervention for inflammatory and neuropathic pain. Figure 28.6 is a schematic drawing of synaptic plasticity at an excitatory tripartite synapse that illustrates interactions between spinal glial cells and neurons underlying central sensitization and persistent pain.

**Cortical and Subcortical Processing of Pain**

**Multimodal Neuroimaging for Human Pain Studies**

Modern neuroimaging has opened new avenues to noninvasively unveil brain mechanisms implicated in various acute and chronic pain conditions of both experimental and clinical settings. Multimodal neuroimaging employed for pain research can be divided into four major categories: (1) functional neuroimaging, including functional magnetic resonance imaging (fMRI), magnetoencephalography (MEG), electroencephalography (EEG), and functional near-infrared spectroscopy (fNIRS); (2) structural neuroimaging using MRI; (3) biochemical neuroimaging, including magnetic resonance spectroscopy (MRS), positron emission tomography (PET), and single-photon emission tomography (SPECT); and (4) receptor neuroimaging, including PET and SPECT (Casey and Bushnell 2000; Apkarian et al. 2011).

Functional neuroimaging, measuring regional cerebral blood flow and electromagnetic brain signals, mandates both high spatial and temporal resolutions to elucidate the dynamic scenario of brain processing (Fig. 28.8). Exploiting various experimental paradigms and types of experimental pain (e.g., thermal, mechanical, chemical, and electrical) for brain activation study, regions of brain engaged in multidimensional (discriminative, affective, and cognitive) processing of pain have been consistently identified by functional neuroimaging and coined as “pain matrix” that subserves the conscious experience of pain (Melzack 2005) (Fig. 28.9). The structural organization constitutes the pain circuitries involves S1 and S2 cortices, insula, anterior cingulate cortex (ACC), and prefrontal cortices as well as the thalamus. Other regions include the basal ganglia, cerebellum, amygdala, hippocampus, and areas within the parietal and temporal cortices (Fig. 28.9). The actual expression of the pain matrix is highly dependent upon the particular set of circumstances and psychophysiological state for the individual suffering from specific pain in the context of type and nature as well as chronicity.
Structural neuroimaging employed various imaging and modeling techniques to macroscopically study gray matter density (voxel-based morphometry, VBM), cortical thickness (surface-based morphometry, SBM), fiber integrity (diffusion tensor imaging, DTI), and fiber tract density (tractography) that can crucially disclose neuroplastic information. VBM, a common approach for various structural neuroimaging modalities, computes the differences in local biological parameters of brain through a voxel-wise comparison of multiple brain images. Most VBM studies found related areas with significant decreases but not increases of gray matter density and cortical thickness. This has led to the notion of maladaptive brain atrophy that may be responsible for development and maintenance of the pain state. On the contrary, acute nociceptive infliction in healthy individuals has been associated with “adaptive plasticity,” manifested as regional hypertrophy in pain-related areas.

Biochemical neuroimaging probes the brain metabolism (e.g., glucose) and energetics (e.g., glutamate, glycine, N-acetyl aspartate, and GABA) underlying the neurochemical mechanisms for the brain activity. MRS and PET measure the concentrations or synthesis rates of neurotransmitters, energy turnover/consumption, and neurochemical disruption that might discriminate chronic pain state of patients from normal controls. Receptor neuroimaging provides critical insight for neuromodulator changes in response to an acute or a chronic pain condition. Rewarding system is associated with experiential aspect of pain. In this context,
studies on dopaminergic, opioiergic, and serotonergic systems can be crucial to unveil hitherto unexplored mechanisms underlying the comorbidities of chronic pain and psychiatric problems, for example, depression.

With the enormous knowledge of pain processing in the brain that can be obtained from pain imaging, a cohesive and profound understanding of pain can be achieved to enhance clinical intervention and drug discovery for pain treatment.

**Brain “Matrix” of Pain**

In the past two decades, a large number of studies have been taken to map pain-related regions in the human brain using functional neuroimaging techniques as aforementioned. It is likely that a network of brain areas can be consistently activated by a variety of painful stimuli such as acute thermal, mechanical, and chemical modalities (Casey and Bushnell 2000; Apkarian et al. 2011). Thus, the concept of the “pain matrix” has been used as a brain signature for an activity pattern associated with pain. The brain areas that can be activated by painful stimuli include S1/S2, insula, orbital cortex, ACC, amygdala, thalamus, hypothalamus, cerebellum, etc. (Fig. 28.9). However, more recent studies suggest that the concept of “pain matrix” is only valid in healthy subjects and only for acute pain, but not for chronic
pain of various pathological conditions (Apkarian et al. 2011). Thus, alternatively a new concept referred to as “salience detection system” is recently proposed to represent a basic mechanism for detection of significant events of the body’s integrity, regardless of the sensory channel through which these events are conveyed (Legrain et al. 2010). The “salience detection system” represents a functional state that the brain network only responds to the occurrence of salient sensory events (visual, auditory, tactile somatosensory, and nociceptive somatosensory) by which attention can be oriented toward and actions can be taken to react so as to survive and escape from harmful stimuli. Thus, the concept of brain “matrix” of pain described here is only limited to physiological or acute pain conditions.

S1/S2 Areas The role of S1 area in pain processing remains controversial (Casey and Bushnell 2000). Brain imaging studies do not consistently reveal pain-related activation of S1. Similarly, studies of cortical lesion/stimulation in humans did not uncover a clear role of S1 in the pain experience. Possible reason for this phenomenon may be that (1) S1 activation is strongly modulated by cognitive factors modulating pain perception, including attention and expectation; (2) focal areas may be activated in S1 due to the precise somatotopic organization, which are degraded by individual variability when averaged across subjects; (3) the effects of nociceptive input to S1 may be mixed excitatory and inhibitory and could be disparately represented in different experimental paradigms; and (4) variation in experimental designs, instructions to subjects, and statistical methods may also induce inconsistent results. Taken together, the current evidence strongly supports a prominent and highly modulated role for S1 cortex in the sensory aspects of pain, including localization and discrimination of pain intensity.

S2 area has also been shown to participate in human pain processing. MEG studies found that S2 activity was an S-shaped intensity-response function to laser pain with a sharp increase in amplitude only at stimulus intensities well above pain threshold. This suggests a role in cognition and attention rather than a significant contribution to the sensory-discriminative aspects of pain perception. Monitoring of the attentional level revealed that evoked S2 activity increased markedly from the low-attention task to the mid-level-attention task, but not further. This saturation function of the pain relevance also suggests a possible attentional involvement. Conversely, an fMRI study revealed an increased activation of S2 during mechanical impact on pain compared with heat pain. This activation was significantly correlated with the intensity but not affective scores in the mechanical impact pain, which may physically attract more attention. Thus, evidence suggests an important role of S2 in the sensory dimension of pain, integrated with cognitive factors such as attention.

Insula This is a major structure in the lateral sulcus linking temporal lobe and frontal lobe, plays diverse functions linking to emotions and bodily regulation of homeostasis. Insular was first noted in 1988 in the asymbolia for human pain, as a sensory-limbic disconnection syndrome (Berthier et al. 1988). Subsequent PET imaging and fMRI supported the involvement of insular in human pain. Three lines of studies support the role of insular in the processing of human pain. (1) Insula has been proposed to be associated with the genesis of human pain perception because it can be activated by a variety of painful stimulations. (2) Direct insular stimulation
has been shown to result in responses associated with sensory, motor, pain, auditory, oropharyngeal, speech disturbances, and neurovegetative phenomena, such as facial reddening, generalized sensations of warmth or cold, hypogastric sensations, anxiety attacks, respiratory accelerations, sensations of rotation, and nausea. Insula has bilateral receptive fields and shows some degree of somatotopic organization in the human insula for pain representation. (3) PET-fMRI neuroimaging shows multiple somatotopic representations for pain within the operculo-insular region in humans.

**Orbital Cortex** The ventrolateral orbital cortex (VLO) locates in the prefrontal cortex and receives major projections from the trigeminal subnucleus caudalis and the spinal dorsal horn lamina I via the thalamic nucleus submedius (Sm). Most neurons in the VLO respond specifically to noxious stimuli and have very large and bilateral receptive fields. The neurons receive widespread convergent inputs from noxious stimulation of the skin, muscles, and viscera, and the neuronal responses were not well graded to increasing stimulation intensities. These findings suggest that the VLO may be involved in the affective and motivational aspects of pain.

Of considerable interest is the finding that the VLO contains neurons that project to the PAG, a region that has been extensively implicated in descending pain modulation (Tang et al. 2009). Therefore, the VLO and PAG may constitute a pain modulatory pathway, activation of which leads to activation of the PAG-brain stem-descending inhibitory system and suppression of nociceptive inputs in the spinal cord and trigeminal nucleus. A number of studies have provided with evidence for this hypothesis. Microinjection of inhibitory neurotransmitter GABA bilaterally into the VLO was shown to facilitate the spinal nocifensive reflex, while electrical stimulation of the VLO or microinjection of excitatory neurotransmitter glutamate into the VLO resulted in suppression of the spinal nocifensive reflex and nerve injury-evoked painful hypersensitivity. These antinociceptive effects can be eliminated by lesions or functional blockade of the PAG or the VLO. Multiple types of neurotransmitters and their corresponding receptors are now known to be involved in the VLO-induced descending antinociception, such as opioid, 5-HT, dopamine, glutamate, and GABA. Further studies have demonstrated that antinociception mediated by µ-opioid, 5-HT1A, and D2 receptors is produced by disinhibition of GABAergic interneurons from the VLO output neurons projecting to the PAG, while that mediated by 5-HT2 receptors is produced by presynaptic facilitation of the excitatory glutamatergic synaptic transmission. In contrast, D1 receptors in the VLO exhibited a tonic facilitatory effect on the nociception that is likely to be produced by presynaptic facilitation of the inhibitory GABAergic synaptic transmission.

**ACC** has been proposed to be associated with emotional aspect of pain (Zhuo 2008). Early work showed that lesions of the medial frontal cortex including the ACC significantly increased acute nociceptive responses as well as injury-related aversive memory behaviors. Electrophysiological recordings from both animals and humans demonstrate that neurons within the ACC respond to noxious stimuli. Neuroimaging studies further confirm these observations and show that the ACC, together with other cortical structures, are activated by acute noxious stimuli, psychological pain, and social pain. One key cellular model for chronic pain is
LTP. Such potentiation or excitation persists for a long period of time and consequently may generate abnormal neuronal spike activity in the brain without obvious peripheral sensory stimulation. At synaptic level, at least three different phases of plastic changes are proposed: early phase (I), late phase (II), and enduring phase (III). In early phase (I), excitatory synaptic transmission may undergo rapid potentiation such as LTP, which can last for hours to days. Changes in presynaptic releases and postsynaptic receptor modifications are the likely key mechanisms for early changes. Calcium-stimulated adenylyl cyclase subtype 1 (AC1) is critical for the induction of LTP. PKMζ is critical for maintaining ACC LTP. In late phase (II), translational events become involved. These include synthesis of key synaptic-signaling proteins such as NMDA NR2B receptor, novel signaling messengers, as well as other proteins that are required for prolonged structural changes. In enduring phase (III), reorganization of the cortical networks happens, which can take years to occur, resulting in the formation of new structural connections within the cortex, as well as between cortical areas. Integrative physiological and molecular approaches provide powerful tools for revealing novel drug target proteins such as AC1 and NR2B for chronic pain and its related emotional disorders.

Amygdala This is a forebrain multinuclear structure composed of several distinct nuclei including the lateral (LA), basolateral (BLA), and central (CeA) nuclei and is activated in both humans and rodents during pain. Within the amygdala, the CeA is well positioned to link noxious stimuli to defense responses. It receives nociceptive information through the spino-parabrachio-amygdaloid pain pathway and polymodal information through the LA and BLA. The CeA, the output nucleus for the major amygdala functions, in turn, projects to the hypothalamus, substantia inominata dorsalis, and various brainstem nuclei that mediate defense behavioral responses. Within the CeA, the laterocapsular division (CeLC) has been identified as a putative pain regulatory center. Electrophysiological recordings indicate that noxious stimuli activate the amygdaloid neurons, and most of these noxious-responsive neurons are located in the CeLC. Furthermore, these noxious-responsive neurons undergo persistent changes in excitability and synaptic strength during persistent visceral pain and chronic inflammatory pain conditions. Behavioral studies in rodents have demonstrated that the amygdala is necessary for some types of analgesia without affecting responses to acute noxious stimuli, suggesting that the amygdala may contribute to persistent pain. Chronic persistent pain has been associated with negative emotions, anxiety, and depression. Some behavioral studies using a conditioned place aversion test reveal that the amygdala also mediates the negative affective component of pain. Lesion or inactivation of the amygdala decreases emotional pain reactions, without affecting normal behavior or baseline nociceptive responses. Biochemical experiments demonstrate that activation of metabotropic glutamate receptors 5 and its downstream, ERKs, in the CeA may be critical to nociceptive processing. However, β- and α2-adrenoceptors within the CeA play a pivotal role in the negative affective, but not sensory, component of visceral pain. Differently, corticotropin-releasing factor (CRF) and its CRF1 and CRF2 receptors in amygdala may have dual effects on sensory and emotional aspects of neuropathic pain.
**Thalamus** The involvement of the thalamus in pain perception was first recognized in patients with thalamic pain syndrome, the clinical signs of which include ongoing pain, a paradoxical loss of cutaneous pain sensitivity, and thermosensory dysfunction. The lateral thalamus and medial thalamus are suggested to be involved in discriminative pain and affective aspects of pain, respectively. The thalamus is an important relay of ascending nociceptive pathways and is intimately interconnected with the cerebral cortex. The function of the thalamus in pain cannot be considered in isolation and must include multiple forebrain regions and pathways. Ventral posterior thalamic nuclei are the main thalamic somatosensory nuclei. They relay a somatotopic representation of cutaneous mechanoreceptors from dorsal column nuclei and the principal trigeminal nucleus to the S1 area (3b and 1). Nociceptive neurons, including NS and WDR cells, exist among the many mechanoreceptive neurons in ventral posterior thalamic nuclei where the spinothalamic tract terminates in monkeys, cats, and rodents. Rats with experimentally induced arthritis or neuropathy have an increased activity and number of WDR thalamic cells. Ventral posterior thalamic nuclei are involved in the localization and intensity discrimination aspects of pain sensation. In the medial thalamus, lamina I spinothalamic tract inputs terminate in the ventral caudal part of the medial dorsal nucleus, which projects to the ACC in the monkey. Cats and rats have indirect spinal inputs to the medial thalamus by way of parabrachial nuclei. In monkeys, cats, and rats, responses to noxious electrical, mechanical, or thermal stimuli have been recorded throughout the intralaminar thalamus, particularly central lateral and parafascicular nuclei. Clinical studies reported the existence of thalamic neurons in chronic pain patients that fired in a bursting pattern similar to low-threshold calcium spike-mediated bursting activity, suggesting that such abnormal burst firing may be associated with chronic pain.

**Hypothalamus** It is well known that the hypothalamus is the main center for neuroendocrine and autonomic regulations in the central nervous system. The hypothalamus is involved in hormone synthesis, thermoregulation, determining biological rhythms, and the cardiovascular regulation. The hypothalamus receives nociceptive input from the spinal cord or nuclei in the brain stem, then the hypothalamus may take part in the modulation of pain responses by release of neurotransmitters and hormones. The arcuate nucleus (ARC), one of the main nuclei of the hypothalamus, contains most of the β-endorphinergic neurons synthesizing β-endorphin in the brain. The major fiber bundles terminate in the PAG, which plays an important role in descending antinociceptive pathway. Administration of β-endorphin to various brain areas, including the PAG and the ARC, results in strong analgesic effects. In addition, the concentration of β-endorphin in the cerebrospinal fluid is increased when the ARC is applied with either electrical stimulation or chemical stimulation by glutamate. At the same time, these stimuli are shown to induce antinociceptive effects, indicating an involvement of β-endorphin in antinociception through descending antinociceptive system. Recent studies report that both inflammation- and nerve injury-induced pain induce changes in hypothalamic function, especially the function of the hypothalamus-pituitary-adrenal axis. It has been reported that inflammation-induced hyperalgesia
increases the concentration of \( \beta \)-endorphin in the hypothalamus in rats, while intra-ARC administration of antiserum against \( \beta \)-endorphin results in reduction in inflammatory pain hypersensitivity. Interestingly, intra-ARC administration of \( \beta \)-funaltrexamine, the selective antagonist against the \( \mu \)-opioid receptor, induces enhancement of hyperalgesia, while the \( \delta \)- and \( \kappa \)-opioid receptor antagonists show no significant effects. The results indicate that there may be a tonic release of endogenous opioid peptides that activate the \( \mu \)-opioid receptor in the ARC, thereby exerting an antinociceptive effect.

**Cerebellum** It is known that the cerebellum is one of the important brain structures playing modulation roles in motor functions. The cerebellum receives projections from the brain and the spinal cord and sends projections to different brain regions related to motor functions. Recent studies find that the cerebellum is not only involved in motor control but also involved in memory, associative learning, cognition, as well as somatosensory processing. Neuroanatomical and electrophysiological studies demonstrate that the afferent input of nociceptive information transmits to the cerebellum directly or indirectly, leading to activation of the neuronal activity in the cerebellum. It has been shown that the mossy fibers can be activated by \( C \) nociceptor activation. Injection of morphine into the anterior portion of the cerebellum induces acute analgesia that can be reversed by opioid receptor antagonist naloxone. It has also been reported that administration of D, L-homocysteic acid, a nonspecific glutamate receptor agonist, to the cerebellar fastigial nucleus results in visceral nociceptive responses in rats, suggesting an involvement of the cerebellum in pain modulation at the brain stem level. Neuroimaging studies by fMRI further confirmed that noxious thermal stimulation in humans resulted in widespread activation of the cerebellum including the deep cerebellar nuclei, anterior vermis, and bilateral cerebellar hemispheric lobule VI. However, it is still not known whether the cerebellum plays an active or passive roles in nociceptive information processing (Moulton et al. 2010).

**Modulation of Clinical Pain**

**Placebo Modulation of Pain**

The beneficial effects of the administration of placebo in the perception of pain are widely known. A significant proportion of the research has been conducted in the fields of pain and analgesia, and the placebo analgesia appears to be the best-understood model of placebo mechanisms (Zubieta and Stohler 2009; Tracey 2010). A review of 44 clinical trials shows that placebo has analgesic effects in the treatment of pain. Human functional neuroimaging techniques can be used to study how the intact human brain responds to placebo. It has been shown by fMRI and PET that placebo analgesia is related to decreased neural activities in pain-modulatory brain regions, such as the rostral ACC (rACC), insula, thalamus, and brain stem including PAG and ventromedial medulla. The endogenous opioid system, specifically activation of \( \mu \)-opioid receptors, is thought to mediate the
observed effects of placebo. The μ-opioid receptor-selective radiotracer-labeled PET studies show that placebo effects are accompanied by reduction in activation of opioid neural transmission in pain-sensitive brain regions, including rACC, prefrontal cortex, insula, thalamus, amygdala, nucleus accumbens (NAC), and PAG. Additional PET studies with dopamine D2/D3 receptor-labeled radiotracer demonstrate that basal ganglia including NAC are related to placebo analgesic responses. Activation of NAC dopamine release is observed under placebo analgesia and related to expectation of analgesia. These data indicate that aforementioned brain regions and neurotransmitters, such as endogenous opioid and dopamine systems, contribute to placebo analgesia. Although neuroimaging studies have proved that placebo has actual neurobiological effects on the brain in both experimental and clinical pain, further studies are required to unravel the underlying molecular and cellular neurobiological mechanisms of placebo analgesia that will be beneficial to research design in clinical trials of analgesics.

**Acupuncture Modulation of Pain**

Acupuncture, an age-old healing art in the TCM, has been widely accepted to effectively treat diverse diseases by inserting needles into the specific “acupuncture points” (acupoints) on the patient’s body (Zhao 2008; Han 2011; Han and Ho 2011). The 361 acupoints are based on the ancient meridian theory. The meridians are referred to as channels “Jing” and their branches “Luo” to link acupoints via “Qi” (energy) streaming. However, no convincing evidence shows the existence of novel structures serving as the anatomical foundations of meridians. Therefore, the meridians might be a functional, but not an anatomical, concept that includes a summation of multiple physiological functions, including the nervous, circulatory, endocrine, and immune systems. The “acupoint” is an anatomically small locus rather than a tiny point on the skin, which may be muscle/skin-nerve complexes with high density of nerve endings expressing multireceptors. Among acupuncture therapies, the acupuncture-induced analgesic effect has been used widely to alleviate diverse pains, particularly chronic pain, and is termed “acupuncture analgesia” that is manifested only when the acupuncture-induced intricate feeling (soreness, numbness, heaviness, and distension) in patients occurs following acupuncture manipulation. The acupuncture manipulations mainly include the following: (1) manual acupuncture (MA) is the insertion of an acupuncture needle into acupoint followed by the twisting of the needle up and down by hand (in MA, all types of afferent fibers (A-β, A-δ, and C) are activated); (2) in electrical acupuncture (EA), a stimulating current via the inserted needle is delivered to acupoints (electrical current intense enough to excite A-β and part of A-δ fibers can induce an analgesic effect); and (3) the electrical acupuncture-like stimulation (EALS) – current via surface electrodes activates A-β and partial A-δ afferent fibers induces analgesia.

Acupuncture signals ascend mainly through the spinal ventrolateral funiculus to the brain. Segmental mechanism in the spinal cord contributes to the functionally
relative specificity of acupoints. Many brain nuclei composing a complicated network are involved in processing acupuncture analgesia, including the nucleus raphe magnus (NRM), PAG, LC, ARC, preoptic area, nucleus submedius, habenular nucleus, accumbens nucleus, caudate nucleus, septal area, amygdala, etc. Acupuncture analgesia is essentially a manifestation of integrative processes at different levels in the CNS between afferent impulses from pain regions and impulses from acupoints. Acupuncture analgesia has a well-established neurochemical basis. Diverse signal molecules are demonstrated to contribute to acupuncture analgesia, such as ATP and adenosine A1 receptors, opioid peptides (\(\mu\)-, \(\delta\)-, and \(\kappa\)-receptors), glutamate (NMDA and AMPA/KA receptors), 5-HT, and cholecystokinin octapeptide (CCK). Among these, the opioid peptides and their receptors in ARC-PAG-NRM-spinal dorsal horn pathway play a pivotal role in mediating acupuncture analgesia. The release of opioid peptides evoked by EA is frequency dependent (Han 2011). EA at 2 and 100 Hz produce release of enkephalin and dynorphin in the spinal cord, respectively. CCK-8 antagonizes acupuncture analgesia. PTX-sensitive G\(i/o\) protein- and MAPK-mediated signaling pathways as well as the downstream events NF-kB, c-Fos, and c-Jun play important roles in EA analgesia. The individual differences of acupuncture analgesia are associated with inherited genetic factors and the amount of CCK receptors. The brain regions associated with acupuncture analgesia identified in animal experiments were confirmed and further explored in the human brain by means of functional imaging. Increasing evidence shows that EA analgesia is likely associated with its counter-regulation to spinal glial activation.

Neuromodulation of Pain

Neuromodulation is defined as direct electrical stimulation of nervous tissue for modulation of nervous functions. In a broader sense, neuromodulation includes peripheral transcutaneous electrical nerve stimulations (TENS), spinal cord stimulations (SCS), and deep brain stimulations (DBS). Several recent major reviews contend the scientific rationale, indications, surgical techniques, and outcomes of intracranial neuromodulation procedures for the treatment of chronic pain, but few provide specific systematic reviews. There lacks the issues of patients selection, stimulation parameters, and objective methods in the outcome evaluation. To date, a major meta-analysis of DBS in pain relief includes stimulation to the midbrain PAG, sensory thalamus, and internal capsule. The long-term pain alleviation rate was highest with DBS of the PVG/PAG (79%) or the PVG/PAG plus sensory thalamus/internal capsule (87%). Stimulation of the sensory thalamus alone was less effective (58% long-term success). DBS was more effective for nociceptive than deafferentation pain (63% vs. 47% long-term success). Moreover, motor cortex stimulation is an effective alternative for relief of intractable, drug-resistant neuropathic pain. Future efforts in this field require the implementation of “data-based medicine” to generate sufficient reliability and proof of valid therapeutic modality in neuromodulation of human pain.
**Psychological Modulation of Pain**

Along many modalities in human pain modulation, the “top-down” psychological methods prove to be intuitive and appear most direct. Psychological modulation includes mainly (1) distraction, (2) placebo, (3) hypnosis, and (4) belief. Distraction of pain by way that activation of PAG appeared to be predictive of human pain modulation. Appeal of positive coping, including distraction, reduced symptom associated pain report, and the cognitive coping by distraction rendered highlighted ventromedial prefrontal cortex (VMPFC) and PAG activation. Expectation and placebo showed that expectations regarding pain radically change the strength of spinal nociceptive responses in humans. Expectation of a pain increase in the nocebo group led to an increase in cortisol. Placebo-induced belief would activate the prefrontal cortex with downstream effects on these dopamine systems as well as on PAG opioid output neurons. Dynamic changes in prefrontal areas during placebo-conditioning and hypnotic analgesia were also related to parietal, insular, and cingulate pain-related clusters. Pain modulation by hypnosis indicates that pain intensity is reduced by approximately 50% compared to the resting state. The hypnosis-induced reduction in affective and sensory responses to noxious thermal stimuli was modulated by the activity in the midcingulate cortex. The opioidergic and dopaminergic systems play an important role in the mediation of the placebo response. Finally, belief also enables pain modulation in that the control belief subscales explained a significant amount of the variance in distress and disability of human pain. Confidence in beliefs is an important determinant of expectancy effects on pain perception. The right VMPFC is shown to influence the ventral midbrain in a religious belief framework.

**Drug Modulation of Pain**

In the past several decades, although neurobiological mechanisms of pain have been greatly achieved, development of novel analgesics that are proven to be with higher efficacy and safety for chronic pain patients is still challenging (Woolf 2010). The pharmacological agents that can affect the pain modulation system represent the main option for treatment of pain. However, it is widely accepted that the function of the pain modulatory circuits appears to be disturbed in many pathological conditions. Practically, traditional analgesics such as opioids continue to provide an important choice for the treatment of moderate to severe pain clinically. They relieve pain by activating descending pain inhibitory circuits, as well as by modifying affective and somatosensory aspect of the pain experience through activities at cortical and subcortical sites (Ossipov et al. 2010). A recent fMRI study demonstrated that pain-related response in primarily sensory-related brain region (S1, S2, etc.) is linearly attenuated with increasing dosages of opioid (e.g., alfentanil). In contrast, the affective dimensions of pain-related activation disappeared with the lowest dose of alfentanil, which may explain why when applied clinically, low dose of opioids reduce only the affective but not the sensory
dimension of pain. It is important to mention that exposure to opioids may also induce the change in pain sensitivity (e.g., hyperalgesia) regardless of their tolerance and addiction side effects. NSAIDs (nonsteroidal anti-inflammatory drugs) exert their therapeutic effect on inflammatory pain by inhibition of PGE2 synthesis, thus reducing peripheral and central sensitization. Although the therapeutic effects of NSAIDs have been known for many years, our understanding of molecular mechanisms underlying NSAIDs analgesia is gained by the discovery of two isoenzymes cyclooxygenases (COX-1 and COX-2). Recent studies also indicate that inhibition of COXs in the PAG promotes an opioid-mediated descending pain inhibition. In addition to the drugs directed against known mechanisms especially of opioids and NSAIDs, tricyclic antidepressants and anticonvulsants have been shown to relieve various types of neuropathic pain. The δ2-binding agents, pregabalin and gabapentin, are effective in the treatment of neuropathic pain by interacting with VGCCs. A recent fMRI study indicates that the most robust gabapentin effect during central sensitization is the reduction of stimulus-induced brain deactivation that is different from nociceptive pain which causes increased activity in the brain (Iannetti et al. 2005).

Nonetheless, a few new drugs targeting the recently discovered molecular identities are subject to clinical trials. Tanezumab, as the most advanced monoclonal antibody against NGF, is currently undergoing phase III trial for knee pain from osteoarthritis based on the sequestration of NGF or the inhibition of the activation mechanism via TrkA. Ziconotide that blocks N-type VGCC via pore-forming α1 subunit reduces severe and chronic pain with intrathecal administration. TRPV1 antagonist effectively reduces osteoarthritis pain in phase II trials, but much remains to be understood about the role of this channel in thermoregulation since the selective TRPV1 channel blocker leads to significant hyperthermia. The road to success in research and development of novel analgesics for relief of chronic pain, especially neuropathic pain, is still challenging, and this may change our strategies from hypothesis-driven research to patient-based research (Woodcock et al. 2007; Woolf 2010).

### Gene Therapy and Stem Cells Used in Pain Treatment

For the majority of patients with chronic pain, particularly neuropathic pain, much of currently available clinical treatments are only partially effective, and many are limited by off-target effects or have the potential of abuse. Analgesics that are highly effective in the management of pain often provide only very short-term relief. In recent years, significant progress has been made in the fundamental understanding of the neurobiology of pain. The local production of neurotransmitters achieved by therapeutic gene transfer may be used to achieve desired outcomes while avoiding the side effects that would result from activation of the same receptors in other pathways by a systemic administration of drugs. The most commonly used viral vectors in studies of pain treatment are based on recombinant adenovirus, adeno-associated virus, lentivirus, or herpes simplex virus (HSV) to express endogenous opioid peptides (enkephalin, endomorphin), glutamate
decarboxylase 67, or anti-inflammatoiy cytokines (soluble TNF receptor, interleukin 4 and 10) in the inflammatory or neuropathic pain models in animal. HSV vector-based gene therapy takes advantage of the natural biology of virus to transduce exogenous genes into the host cells. Namely, knockdown of genes encoding molecules that are essential to activation and hypersensitization of spinal pain-related neurons can be obtained by using viral vector that expresses siRNA of the target gene. Non-viral gene transfer expressing interleukin 10 also reduces chronic pain in animals. The first human trial of gene therapy for chronic pain, a phase-I study of a nonreplicating HSV-based vector engineered to express preproenkephalin in patients with intractable pain from cancer, began in December 2008 at the University of Michigan.

Stem cells are characterized by the ability to renew themselves through mitotic cell division and to differentiate into a diverse range of specialized cell types. Highly plastic adult stem cells from a variety of sources, including umbilical cord blood and bone marrow, are routinely used in medical therapies. Stem cell therapy for chronic pain is attractive and promising. Mesenchymal stem cells (MSCs) are known anti-inflammatory cytokine and growth factor producers. CD34 cells produce angiogenic factors and in some cases have been demonstrated to differentiate into neurons directly. Intrathecal administration of MSCs and CD34 cells, isolated from the placental matrix and umbilical cord blood, respectively, significantly reduced spinal injury-induced neuropathic pain in human.

Outlook

Changing the Definition of Pain

Pain was officially defined by International Association for the Study of Pain (IASP) as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” (Merskey and Bogduk 1994). Although this scientific definition of pain helps scientists a lot to study nociceptive mechanisms at peripheral and spinal levels, it is obscure somewhat for clinicians who are coping with pain problems because it is sometimes impossible to link the pain of patients with any tissue injury on the body such as headache, abdomen ache, and some chronic pain states. Thus, the concept or definition of pain is required to be changed with the emergence of translational science from bench to bedside. The IASP’s definition of pain has been challenged by D. D. Price who proposed a new definition of pain as “a somatic perception containing (1) a bodily sensation with qualities like those reported during tissue-damaging stimulation, (2) an experienced threat associated with this sensation, and (3) a feeling of unpleasantness or other negative emotion based on this experienced threat” (Price 1999). The new definition proposed by D. D. Price has great significance: (1) patients and clinicians do not need to directly demonstrate an association between biological tissue damage and the sensation of pain and (2) highlighting the roles of the brain dysfunctions in chronic pain that might be caused by previously
experienced tissue damage of a part or parts of the body that may not presently exist in chronic pain patients. However, this change in pain idea requires a more dynamic shift of research work from spinal level toward the brain level.

**Understanding the Brain Mechanisms of Pain**

There are tremendous amounts of brain imaging studies in both human and animal subjects supporting that pain is a complex experience associated with various brain functions such as sensory discrimination, affective motivation, and cognitive evaluation (Price 1999; Casey and Bushnell 2000). Now it has been gradually known that noxious information caused by tissue or nerve damage is processed by a widely distributed, hierarchically interconnected neural network, referred to as pain matrix, in the brain (Melzack 2005; Casey and Bushnell 2000). Therefore, understanding of chronic pain as a multidimensional experience requires more studies on the inherent characteristics between pain experience and structural or functional state of the brain network. However, looking back to the past 46 years since the appearance of the *gate-control theory* of pain proposed by R. Melzack and P. D. Wall (1965), identifying multiple neural networks subserving these functional aspects of pain and use of this knowledge to manipulate pain clinically in new and beneficial ways is still a challenging task. There is now a consensus on the idea that pain, when becomes persistent or chronic, may cause not only sensory dysfunction (spontaneous pain, hyperalgesia, and allodynia) but also various functional brain disorders such as anxiety, loss of sleep, amnesia, and depression (Crombie et al. 1999). These comorbidities of chronic pain make it necessary to extend the pain research from lower levels below the spinal cord into the higher level of cortical and subcortical brain structures (Apkarian et al. 2011). However, the knowledge of pain perception, emotion, and cognition is surprisingly poor and requires to be gained by experimental research using multiple approaches at the cortical levels (Merskey et al. 2005). Moreover, it is also widely aware that research and development and the therapeutic strategies of pain, especially those of neuropathic pain, clinically are more underdeveloped than other areas due to lack of patient- or disease-based model and hypothesis of pain (Farrar 2010; Woolf 2010).

Thus, in the remaining twenty-first century, development of brain models of pain and hypothesis will be critical for understanding and translating the basic concept of pain into the clinical use, namely, from bench to bedside.

**Glossary**

**Acupuncture** Is a traditional Chinese preventative or therapeutic method for treatment of different symptoms including pain (Schmidt and Willis 2007). (Traditionally, thin, solid silver needles are inserted into proposed specific points, referred to as *acupuncture points* or *acupoints*, on the body. Contemporary, many modifications of the method have been described, such as
electro-acupuncture through which a variety of frequencies ranging from 2 to 100 Hz are used for different purposes of therapy. Transcutaneous electrical nerve stimulation (TENS) is an acupuncture-like method that can be used in treatment of muscle pain.)

**Acute Pain** Is defined as “pain of recent onset and probable limited duration. It usually has an identifiable temporal and causal relationship to injury or disease” (Schmidt and Willis 2007). (Perception of acute pain requires transduction of noxious mechanical, thermal, or chemical stimuli by nociceptive neurons, integration, and modulation at the level of the spinal cord and ultimately transmission to the cortical structures.)

**Algogen** Is defined as a chemical substance with the ability to induce pain and hyperalgesia. (Endogenous algogens include protons, adenosine triphosphate (ATP), 5-hydroxytryptamine (5-HT), histamine, potassium, and bradykinin. Exogenous algogens are probably countless in number or type, but those that have been experimentally well established are few, including paraformaldehyde, capsaicin, melittin or bee venom, scorpion venom, etc.) (Schmidt and Willis 2007).

**Allodynia** Is a nociceptive reaction and/or pain due to a stimulus that does not normally evoke pain (Merskey and Bogduk 1994; Schmidt and Willis 2007). (*Allo* means “other” in Greek. *Odynia* means “pain” that is derived from the Greek word “*odune*” or “*odyne*.” The term *allodynia* was originally introduced to separate from hyperalgesia and hyperesthesia, the conditions seen in patients with lesions of the nervous system where touch, light pressure, or moderate cold or warmth evokes pain when applied to normal skin. Now, the term is also taken to apply to conditions which may give rise to sensitization of the skin, for example, sunburn, inflammation, and trauma. Allodynia is believed to be based on sensitization of spinal central neurons with increased excitability to A-β fiber input and is critically dependent on the ongoing activity of nociceptive afferent.)

**Analgesia** Is a reduced or absent sense of pain response to stimulation that would normally be painful (Merskey and Bogduk 1994; Schmidt and Willis 2007). (It can also be described as a situation in which the intensity of the stimulus required to evoke an escape or avoidance response is increased above normal, or the time required for an animal to respond to a noxious stimulus is increased above normal.)

**Antinociception** Is a state of attenuation of nociceptive processing in the nervous system and the reduction of inhibition of nociceptive transmission (Schmidt and Willis 2007). (Antinociception is often used to describe a decrease in an animal response to a stimulus that is perceived as painful to humans.)

**Cancer Pain** A malignant pain, arises from tumor cells which invade soft tissue and/or bony structures, or occur as a result of therapeutics used to treat cancer (Schmidt and Willis 2007).

**Chronic Pain** Unlike acute pain, rarely has an identifiable temporal and causal relationship to injury or disease in the body. Unlimited duration of 3 months or more that pain lasts or persists is believed to be essential for diagnosis of a chronic pain (Schmidt and Willis 2007).
**Hyperalgesia** Is traditionally defined as the psychophysical correlate of sensitization of either peripheral or central nociceptive system that is characterized by decreased pain threshold (the IASP definition of “allodynia”) and increased pain to suprathreshold stimuli (the IASP definition of hyperalgesia as “increased painful response to a stimulus which is normally painful”). Specifically, increased pain sensitivity at a site of tissue damage is referred to as primary hyperalgesia; while increased pain sensitivity in normal skin surrounding a site of tissue damage is referred to as secondary hyperalgesia (Merskey and Bogduk 1994; Schmidt and Willis 2007). (Because both hyperalgesia and allodynia represent “a leftward shift of the stimulus–response function that relates magnitude of pain to stimulus intensity,” there is no need to separate the two phenomena by two terms. Thus, it is recently suggested that the IASP narrow definition should be replaced by an umbrella term as the traditional definition.)

**Hypersensitivity** Is an increased sensation of stimuli or increased scores of symptoms in response to standard stimuli (Schmidt and Willis 2007).

**Hypoalgesia** Is defined by IASP as “diminished pain in response to a normally painful stimulus” that is characterized as decreased perception of noxious stimuli or raised threshold to painful stimuli (Merskey and Bogduk 1994; Schmidt and Willis 2007).

**Inflammatory Pain** Is that which is associated with chronic inflammation (e.g., arthritis, back pain, or temporomandibular joint disorders) (Schmidt and Willis 2007).

**Mechanonociceptor** Is a subpopulation of sensory afferents activated only by strong mechanical stimulation, most effectively by sharp objects (Schmidt and Willis 2007).

**Migraine** Is a common, episodic neurovascular headache disorder characterized by unilateral pulsating moderate to severe headache, typically lasting 4–72 h, of throbbing quality and with associated symptoms of light and sound sensitivity, nausea and vomiting, and phono- and/or photophobia (Schmidt and Willis 2007).

**Myalgia** Is muscle pain or pain of muscular origin, without regard to cause (e.g., fibromyalgia, and myofascial pain syndrome) (Schmidt and Willis 2007).

**Neuropathic Pain** Is redefined as pain “arising as a direct consequence of a lesion or disease affecting the somatosensory system” (Treede et al. 2008; Haanpää et al. 2011). The current IASP definition is pain “initiated or caused by a primary lesion or dysfunction of the nervous system” (Merskey and Bogduk 1994). (The new definition proposed by NeuPSIG (Neuropathic Pain Special Interest Group of the IASP) replaces “dysfunction” with “disease” to distinguish neuropathic pain from pain caused by neural plastic changes in response to strong nociceptive stimulation. The term “nervous system” is replaced by the “somatosensory system” to distinguish neuropathic pain from pain caused by lesions in other parts of the nervous system, e.g., pain associated with muscular spasticity associated with lesions of the central motor pathways.) (Treede et al. 2008; Haanpää et al. 2011).
Nociception  Is the transduction, encoding, and transmission of neural information about tissue damage, or impending tissue damage, which would occur if a stimulus was maintained over time (Schmidt and Willis 2007). (The term is derived from the Latin word “nocere,” which means “to injure.”)

Nociceptive Neuroplasticity Denotes the changes in the nervous system processing resulting from nociceptive inputs, including both functional and structural changes that are reversible or irreversible (Schmidt and Willis 2007).

Nociceptive Pain  Is caused by ongoing activation of A-δ and C nociceptors in response to a noxious stimulus of somatic or visceral structures such as inflammation, trauma, or disease (Schmidt and Willis 2007).

Nociceptive Pathways Are referred to as the neural circuits, including long sensory tracts, which convey information related to noxious stimuli (Schmidt and Willis 2007). (The consequences of nociceptive processing can include pain sensation, motivational-affective responses, reflex behavior, endocrine changes, and learning and memory of painful events.)

Nociceptive Primary Afferents Are primary sensory neurons that respond to tissue damaging stimuli (Schmidt and Willis 2007). (Nociceptive primary sensory neurons are specialized sensory nerve fibers innervating peripheral tissues that are normally only activated by noxious stimuli or not innocuous stimuli.)

Nociceptive Reflex Is a reflex that is elicited by noxious stimuli, mediated by nociceptive (A-delta and C) afferents, and exerts a defense reaction (Schmidt and Willis 2007).

Nociceptive Stimulus Is referred to as a stimulus modality (mechanical, thermal, chemical) that can elicit pain or pain behaviors such as withdrawal, vocalization, etc., and might be potentially or overtly injurious (Schmidt and Willis 2007). Noxious stimulus is defined by the IASP as “one which is damaging to normal tissue” (Merskey and Bogduk 1994).

Nociceptive Thresholds Are usually defined in experimental animals as the threshold (temperature, mechanical force) at which a withdrawal response is evoked, measured either by active withdrawal of a limb or tail, for example, or measurement of the electrical activity of a muscle in an anesthetized animal (Schmidt and Willis 2007).

Nociceptive Withdrawal Reflexes Denote an integrated reflex to avoid potential tissue injury. It is dependent upon stimulus site, stimulus intensity, and functional context (Schmidt and Willis 2007).

Nociceptron (Shortened from “Noci-Receptor”) Is currently defined by the IASP as a receptor preferentially sensitive to a noxious stimulus or to a stimulus which would become noxious if prolonged (Merskey and Bogduk 1994). (Note: use of terms like pain receptor, pain pathway, etc., should be avoided.) Nociceptron is originally based on the concept of nociception proposed by Charles Sherrington (1906), a Nobel laureate of 1932 in medicine. He suggested that events producing disruption of tissue or representing a physical threat to its integrity could be labeled noxious regardless of their natures. Nociceptron is suggested to be classified into at least four categories (Perl 1996): (1) high threshold
mechanoreceptor that responds vigorously to noxious mechanical stimulation applied to the skin; (2) polymodal nociceptor that responds to noxious heat, mechanical, and irritant chemicals; (3) mechano-heat nociceptor that responds to both noxious mechanical and heat applied to the glabrous skin; (4) mechano-cold nociceptor that responds to both noxious low skin temperature and noxious mechanical stimuli. Additionally, a “silent” nociceptor is evidenced to exist because it can only be excited by mechanical stimuli when sensitized by local inflammation (or histamine). Since the first cloning of transient receptor potential vanilloid receptor 1 (TRPV1) in 1997, cellular and molecular mechanisms of thermal nociception have been gradually unraveled. TRPV1, a nonselective cation channel with higher Ca\textsuperscript{2+} permeability, is also known as capsaicin receptor and thermal nociceptor that can be activated by capsaicin (an ingredient of hot chili peppers), noxious heat (>42˚C), and proton. The genes encoding TRPV1 is highly expressed in the primary sensory neurons innervating A-δ and C fibers of dorsal root ganglia and trigeminal ganglia. TRPV2, another defined thermal nociceptor, is characterized by a property of activation by temperature higher than 52˚C and insensitivity to capsaicin. The cellular and molecular mechanisms underlying cold nociception and mechanical nociception are not as clear as what we know for the thermal nociception. TRPA1 and TRPM8 are believed to be candidates of cold nociceptors, while TRPV1, ATP receptors (P2X3 and P2Y1), and acid sensing ion channels (ASICs), etc., are likely to be the candidates of chemical nociceptors.

**Nociceptor Generator Potential** Is referred to as a local change in membrane potential caused by the opening of ion channels in the peripheral terminals of nociceptive neurons, when natural stimuli (mechanical, thermal, chemical) activate their transduction mechanisms (Schmidt and Willis 2007).

**Pain** Is defined by the IASP earlier as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage (Merskey and Bogduk 1994). It is later suggested that “The inability to communicate verbally does not negate the possibility that an individual is experiencing pain and is in need of appropriate pain-relieving treatment” (Schmidt and Willis 2007).

**Pain Behaviors** Refer to overt, observable, and measurable expression and manifestations of pain and include distorted ambulation, facial/audible expressions of pain, expressions of affective distress, and seeking help (Schmidt and Willis 2007).

**Pain Threshold** Is currently defined by the IASP as the least experience of pain which a subject can recognize (Merskey and Bogduk 1994). However, in contrast, in the book Encyclopedia of Pain (Schmidt and Willis 2007), pain threshold is defined as the lowest stimulus intensity that reliably elicits the perception of pain. In psychophysics, pain threshold can be defined as the stimulus intensity that evokes a pain report in 50% of the trials (Schmidt and Willis 2007).

**Pain Tolerance** Is currently defined by the IASP as the greatest level of pain which a subject is prepared to tolerate (Merskey and Bogduk 1994). (Note: as
with pain threshold, the pain tolerance is the subjective experience of the individual and cannot be confused with an external stimulation.)

**Referred Pain** Is defined by the IASP as pain arising or occurring in a region of the body innervated by nerves or branches of nerves other than those that innervate the actual source of pain (Merskey and Bogduk 1994; Schmidt and Willis 2007). (Referred pain is defined elsewhere as a sensation of pain arising from a body region remote from the site of the noxious event and afferent activation, most frequently appearing as pain or hyperalgesia in muscle or skin as a result of visceral nociceptive activation.)

**Sensitization** Is an increase in the excitability and/or responsiveness of neurons in the periphery and/or the central nervous system. Peripheral sensitization refers to a hyperexcitable and/or hyperresponsive state of peripheral nerve endings of primary nociceptive sensory neurons in response to peripheral stimulation. Central sensitization refers to a hyperexcitable and/or hyperresponsive state of spinal or supraspinal nociceptive neurons in response to peripheral stimulation. Electrophysiologically, central sensitization includes increased ongoing background activity, enhancement of responsiveness, windup, long-term potentiation (LTP), and expansion of cutaneous receptive field of central (spinal) neurons. Sensitization is one phenomenon of neural plasticity that is proposed to include three processes: activation, sensitization, and modification of the nervous system (Woolf and Salter 2000).

**Silent Nociceptor** Refers to a type of cutaneous nerve terminals that are normally insensitive to even very intense mechanical stimuli. However, it becomes sensitized in the course of pathophysiological processes in the tissue and becomes responsive to formerly nonnoxious mechanical stimuli (Schmidt and Willis 2007).

**Somatic Pain** Is pain evoked by nociceptive information arising from any of the tissues that constitute the structure of the body (Schmidt and Willis 2007). (Note: The term “somatic” derives from the Greek word “σομα,” meaning “body” that is used to distinguish from visceral pain arising from internal organs of the body. A pivotal feature of somatic pain is that it is caused by the stimulation of the nerve endings of the peripheral nerves that innervate the tissues that are the source of pain. This feature distinguishes the somatic pain from neuropathic pain in which the source of nociception lies in axons of the affected nerves.)

**Somatosensory Nervous System** Is part of the nervous system that conveys sensations from the body, such as touch, pressure, vibration, position, pain, and temperature (Schmidt and Willis 2007).

**Transient Receptor Potential (TRP)** Refers to transient change in electrical potential across the cell membrane, for example, induced by activation of a TRP receptor (Schmidt and Willis 2007).

**Transient Receptor Potential (TRP) Family of Ion Channels** Are a family of at least 28 different channel proteins encoded by a family of *trp* genes. The TRP channel primary structures are six transmembrane domains, with a pore domain between the fifth and sixth segments, and both the C- and N-termini are located
intracellularly (Schmidt and Willis 2007). (Note: TRP channels are relatively nonselectively permeable to cations, including sodium, calcium, and magnesium. TRP channels were initially discovered in \textit{trp} mutant strain of the fruit fly \textit{Drosophila}. Later, TRP channels were found in vertebrates where they are ubiquitously expressed in many cell types and tissues. TRP channel family are generally divided into two broad groups: group 1 includes, TRPC (“C” for canonical), TRPV (“V” for vanilloid), TRPM (“M” for melastatin), TRPN, and TRPA. In group 2 there are TRPP (“P” for polycystic) and TRPML (“ML” for mucolipin). Many of these channels mediate a variety of sensations like the sensations of pain, hotness, warmth, or coldness, different kinds of tastes, pressure, and vision. In the body, some TRP channels are thought to behave like microscopic thermometers and used in animals to sense hot or cold. Some TRP channels activated by molecules found in spices like garlic (allicin), chili pepper (capsaicin), wasabi (allyl isothiocyanate); others are activated by menthol, camphor, peppermint, and cooling agents; yet others are activated by molecules (tetrahydrocannabinol, cannabidiol, and cannabinol) found in marijuana. Some act as sensors of osmotic pressure, volume, stretch, and vibration.) (See http://en.wikipedia.org/wiki/.)

**Visceral Pain** Is pain that is caused by nociceptive information arising from the organs (viscera) of the body, for example, the heart, stomach, intestine, bladder, and uterus (Schmidt and Willis 2007).

**Visual Analog Scale (VAS)** Is a pain intensity rating tool that is often used in human experimental studies. The VAS is comprised of a horizontal or vertical line and anchored at both ends by words indicative of extremes of magnitude, such as “no pain,” to “most intense pain sensation imaginable.” The scale can be from “0” to “10” or from “0” to “100.” Score “5” or “50” means mild and tolerable pain (Schmidt and Willis 2007).

**Windup** Refers to an electrophysiological phenomenon in which repetitive stimulation of unmyelinated C fibers can result in prolonged discharge of dorsal horn cells. It is characterized by a progressive and frequency-dependent increase in the number of action potentials elicited by each following stimulus of constant and high intensity repetitive electrical stimuli. Windup, like long-term potentiation (LTP), is believed to be an important component of central sensitization (Schmidt and Willis 2007).

**Further Reading**


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