SECTION I

Pain Physiology and Pharmacology

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Pain Pathways and Acute Pain Processing

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Understanding the anatomical pathways and neurochemical mediators involved in noxious transmission and pain perception is key to optimizing the management of acute and chronic pain. The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." Although acute pain and associated responses can be unpleasant and often debilitating, they serve important adaptive purposes. They identify and localize noxious stimuli, initiate withdrawal responses that limit tissue injury, inhibit mobility thereby enhancing wound healing, and initiate motivational and affective responses that modify future behavior. Nevertheless, intense and prolonged pain transmission,[1] as well as analgesic undermedication, can increase postsurgical/traumatic morbidity, delay recovery, and lead to development of chronic pain (see also Chapter 11, Transitions from acute to persistent pain). This chapter focuses on the anatomy and neurophysiology of pain transmission and pain processing. Particular emphasis is directed to mediators and receptors responsible for noxious facilitation, as well as to factors underlying the transition from acute to persistent pain.

CLASSIFICATION OF PAIN

Pain can be categorized according to several variables, including its duration (acute, convalescent, chronic), its pathophysiologic mechanisms (physiologic, nociceptive, neuropathic),[2] and its clinical context (eg, postsurgical, malignancy related, neuropathic, degenerative). Acute pain[3] follows traumatic tissue injuries, is generally limited in duration, and is associated with temporal reductions in intensity. Chronic pain[4] may be defined as discomfort persisting 3–6 months beyond the expected period of healing. In some chronic pain conditions, symptomatology, underlying disease states, and other factors may be of greater clinical importance than definitions based on duration of discomfort.[5] Clinical differentiation between acute and chronic pain is outlined in Table 1.1.

With regard to a more recent classification, pain states may be characterized as physiologic, inflammatory (nociceptive), or neuropathic. *Physiologic* pain defines rapidly perceived nontraumatic discomfort of very short duration. Physiologic pain alerts the individual to the presence of a potentially injurious environmental stimulus, such as a hot object, and initiates withdrawal reflexes that prevent or minimize tissue injury.

Nociceptive pain is defined as noxious perception resulting from cellular damage following surgical, traumatic, or disease-related injuries. Nociceptive pain has also been termed *inflammatory*[6] because peripheral inflammation and inflammatory mediators play major roles in its initiation and development. In general, the intensity of nociceptive pain is proportional to the magnitude of tissue damage and release of inflammatory mediators.

Somatic nociceptive pain is well localized and generally follows a dermatomal pattern. It is usually described as sharp, crushing, or tearing in character. Visceral nociceptive pain defines discomfort associated with peritoneal irritation as well as dilation of smooth muscle surrounding viscus or tubular passages.[7] It is generally poorly localized and nondermatomal and is described as cramping or colicky. Moderate to severe visceral pain is observed in patients presenting with bowel or ureteral obstructions, as well as peritonitis and appendicitis. Visceral pain radiating in a somatic dermatomal pattern is described as referred pain. Referred pain[8] may be explained by convergence of noxious input from visceral afferents activating second-order cells that are normally responsive to somatic sensation. Because of convergence, pain emanating from deep visceral structures may be perceived as well-delineated somatic discomfort at sites either adjacent to or distant from internal sites of irritation or injury.

The process of neural sensitization and the clinical term *hyperalgesia*[9] describe an exacerbation of acute nociceptive pain, as well as discomfort in response to sensations that normally would not be perceived as painful. These changes, termed *hyperpathia*[10] and *allodynia*,[11] although common following severe or extensive injuries, are most pronounced in patients developing persistent and neuropathic pain. Hyperalgesia can be

Table 1.1: Clinical Differentiations between Acute and Chronic Pain

Acute Pain	*Chronic Pain*
1. Usually obvious tissue damage	1. Multiple causes (malignancy, benign)
2. Distinct onset	2. Gradual or distinct onset.
3. Short, well characterized duration	3. Persists after 3–6 mo of healing
4. Resolves with healing	4. Can be a symptom or diagnosis.
5. Serves a protective function	5. Serves no adaptive purpose
6. Effective therapy is available	6. May be refractory to treatment

classified into primary and secondary forms (Table 1.2). Primary hyperalgesia[12] reflects sensitization of peripheral nociceptors and is characterized by exaggerated responses to thermal stimulation at or in regions immediately adjacent to the site of injury. Secondary hyperalgesia[13] involves sensitization within the spinal cord and central nervous system (CNS) and includes increased reactivity to mechanical stimulation and spread of the hyperalgesic area.[13] Enhanced pain sensitivity extends to uninjured regions several dermatomes above and below the initial site of injury. The stimulus response associated with primary and secondary hyperalgesia is outlined in Figure 1.1.

Neuropathic pain is defined by the International Association for the Study of Pain as "pain initiated or caused by a pathologic lesion or dysfunction" in peripheral nerves and CNS. Some authorities have suggested that any chronic pain state associated with structural remodeling or "plasticity" changes should be characterized as neuropathic.[1] Disease states associated with classic neuropathic sysmptoms include infection (eg, herpes zoster), metabolic derangements (eg, diabetic neuropathy), toxicity (eg, chemotherapy), and Wallerian degeneration secondary to trauma or nerve compression. Neuropathic pain is usually constant and described as burning, electrical, lancinating, and shooting. Differences between the pathophysiologic aspects of physiologic, nociceptive, and neuropathic pain are outlined in Table 1.3.

A common characteristic of neuropathic pain is the paradoxical coexistence of sensory deficits in the setting of increased noxious sensation.[14] By convention, symptoms related to peripheral lesions are termed *neuropathic*, whereas symptoms related to spinal cord injuries are termed *myelopathic*.[15] Causalgia or

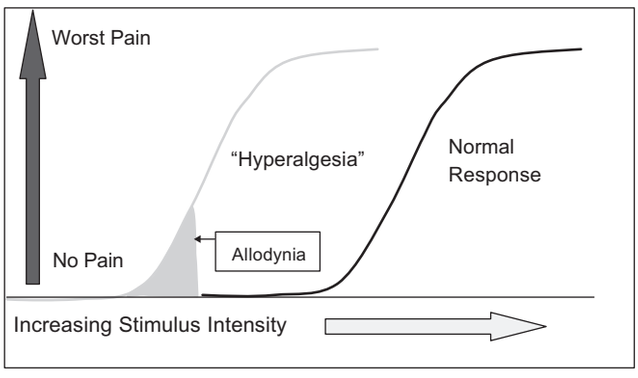

Figure 1.1: Stimulus response alteration observed with hyperalgesia.

Table 1.2: Characteristics of Hyperalgesia

Hyperalgesia

Defines a state of increased pain sensitivity and enhanced perception following acute injury that may persist chronically.

The hyperalgesic region may extend to dermatomes above and below the area of injury and is associated with ipsilateral (and occasionally contralateral) muscular spasm/immobility.

(Hyperalgesia is may be observed following incision, crush, amputation, and blunt trauma.)

Primary hyperalgesia

Increased pain sensitivity at the injury site

Related to peripheral release of intracellular or humoral noxious mediators

Secondary hyperalgesia

Increased pain sensitivity at adjacent, uninjured sites

Related to changes in excitability of spinal and supraspinal neurons

Abnormal sensations associated with hyperalgesia

Hyperpathia (increased or exaggerated pain intensity with minor stimulation)

Allodynia (nonnoxious sensory stimulation is perceived as painful)

Dysesthesia (unpleasant sensation at rest or movement)

Paresthesia [unpleasant often shock-like or electrical sensation precipitated by touch or pressure (CRPS-II causalgia)]

chronic regional pain syndrome II[16] describes pain following injury to sensory nerves, whereas discomfort associated with injury or abnormal activity of sympathetic fibers is termed *reflex sympathetic dystrophy* or *chronic regional pain syndrome I*.[17]

Finally, it is well recognized that certain acute traumatic and chronic pain conditions are associated with a mixture of nociceptive and neuropathic pain. Symptoms are proportional to the extent of neural versus nonneural tissue injuries. Clinical appreciation of the qualitative factors of the pain complaint helps guide the caregiver in differentiating between pain categories (Table 1.4).

PAIN PERCEPTION

A number of theories have been formulated to explain noxious perception.[18] One of the earliest ideas, termed the *specificity theory*, was proposed by Descartes.[19] The theory suggested that specific pain fibers carry specific coding that discriminates between different forms of noxious and nonnoxious sensation. The *intensity theory*, proposed by Sydenham,[20] suggested that the intensity of the peripheral stimulus determines which sensation is perceived. More recently, Melzack and Wall[21] proposed the *gate control theory* and suggested that sensory fibers of differing specificity stimulate second-order spinal neurons (dorsal horn transmission cell or wide dynamic range [WDR] neuron) that, depending on their degree of facilitation or inhibition, fire at varying intensity. Both large- and small-diameter afferents can activate "transmission" cells in dorsal horn; however, large sensory fibers also activate inhibitory substantia gelatinosa (SG) cells.[22] Indeed, it is the neurons and circuitry within the substantia gelatinosa that determine whether the "gate" is opened

Table 1.3: Pathophysiologic Representation of Pain

Category	*Cause*	*Symptom*	*Examples*
Physiologic	Brief exposure to a noxious stimulus	Rapid yet brief pain perception	Touching a pin or hot object
Nociceptive/inflammatory	Somatic or visceral tissue injury with mediators having an impact on intact nervous tissue	Moderate to severe pain, described as crushing or stabbing	Surgical pain, traumatic pain, sickle cell crisis
Neuropathic	Damage or dysfunction of peripheral nerves or CNS	Severe lancinating, burning or electrical shock like pain	Neuropathy, CRPS. Postherpetic Neuralgia
Mixed	Combined somatic and nervous tissue injury	Combinations of symptoms; soft tissue plus radicular pain	Low back pain, back surgery pain

Table 1.4: Qualitative Aspects of Pain Perception

1. Temporal: onset (when was it first noticed?) and duration (eg, acute, subacute, chronic)
2. Variability: constant, effort dependent (incident pain), waxing and waning, episodic "flare"
3. Intensity: average pain, worst pain, least pain, pain with activity of living
4. Topography: focal, dermatomal, diffuse, referred, superficial, deep
5. Character: sharp, aching, cramping, stabbing, burning, shooting
6. Exacerbating/Relieving: worse at rest, with movement or no difference; incident pain is worse with movement (stretching and tearing of injured tissue); intensity changes with touch, pressure, temperature
7. Quality of life: interfere with movement, coughing, ambulation, daily life tasks, work, etc.

or closed.[23] Substantia gelatinosa cells close the gate by directly suppressing transmission cells. In contrast, increased activity in small-diameter fibers decreases the suppressive effect of SG cells and opens the gate. Peripheral nerve injuries also open the gate by increasing small fiber activity and reducing large fiber inhibition.[24] Finally, descending inhibition from higher CNS centers and other inhibitory interneurons can also suppress transmission cells and close the gate. Some aspects of the gate control theory have fallen out of favor; nevertheless, pain processing in dorsal horn and, ultimately, pain perception are dependent on the degree of noxious stimulation, local and descending inhibition, and responses of second-order transmission cells. A schematic representation of the gate control system is presented in Figure 1.2.

Woolf and coworkers have proposed a new theory to explain pain processing.[27] They suggest that primary and secondary hyperalgesia as well as qualitative differences among physiologic, inflammatory, and neuropathic pain reflect sensitization of both peripheral nociceptors and spinal neurons (Figure 1.3). Noxious perception is the result of several distinct processes that begin in the periphery, extend up the neuraxis, and terminate at supraspinal regions responsible for interpretation and reaction. The process includes nociceptor activation, neural conduction, spinal transmission, noxious modulation, limbic and frontal-cortical perception, and spinal and supraspinal responses. The process of central sensitization, particularly within the SG, appears to be the key that unlocks the dorsal horn gate, thereby facilitating pain transmission. Identifying mediators that increase or diminish spinal sensitization and help close the gate will be important targets for treating pain in the near future.[23] The anatomic pathways mediating pain perception are outlined in Figure 1.4.

TRANSDUCTION

Transduction[27] defines responses of peripheral nociceptors to traumatic or potentially damaging chemical, thermal, or mechanical stimulation. Noxious stimuli are converted into a calcium ion– (Ca^{2+}) mediated electrical depolarization within the distal fingerlike nociceptor endings. Peripheral noxious mediators are either released from cells damaged during injury or as a result of humoral and neural responses to the injury. Cellular damage in skin, fascia, muscle, bone, and ligaments is associated with the release of intracellular hydrogen (H^+) and potassium (K^+) ions, as well as arachadonic acid (AA) from lysed cell membranes. Accumulations of AA stimulate and upregulate the cyclooxygenase 2 enzyme isoform (COX-2) that converts AA into biologically active metabolites, including prostaglandin E_2 (PGE_2), prostaglandin G_2 (PGG_2), and, later, prostaglandin H_2 (PGH_2). Prostaglandins[28] and intracellular H^+ and K^+ ions play key roles as primary activators of peripheral nociceptors. They also initiate inflammatory responses and peripheral sensitization that increase tissue swelling and pain at the site of injury.

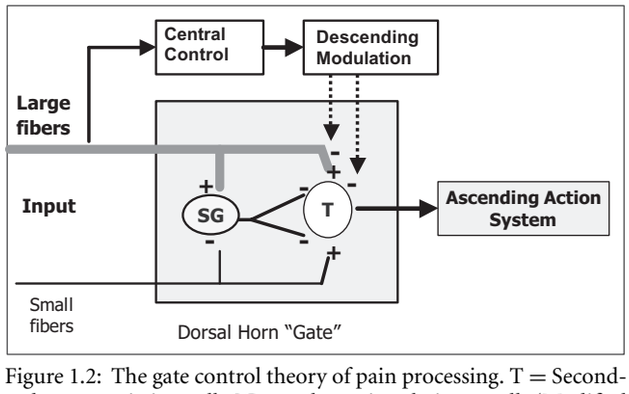

Figure 1.2: The gate control theory of pain processing. T = Second-order transmission cell; SG = substantia gelatinosa cell. (Modified from Melzack R and Wall PD, *Science*. 1965;150(699):971–979.).[21]

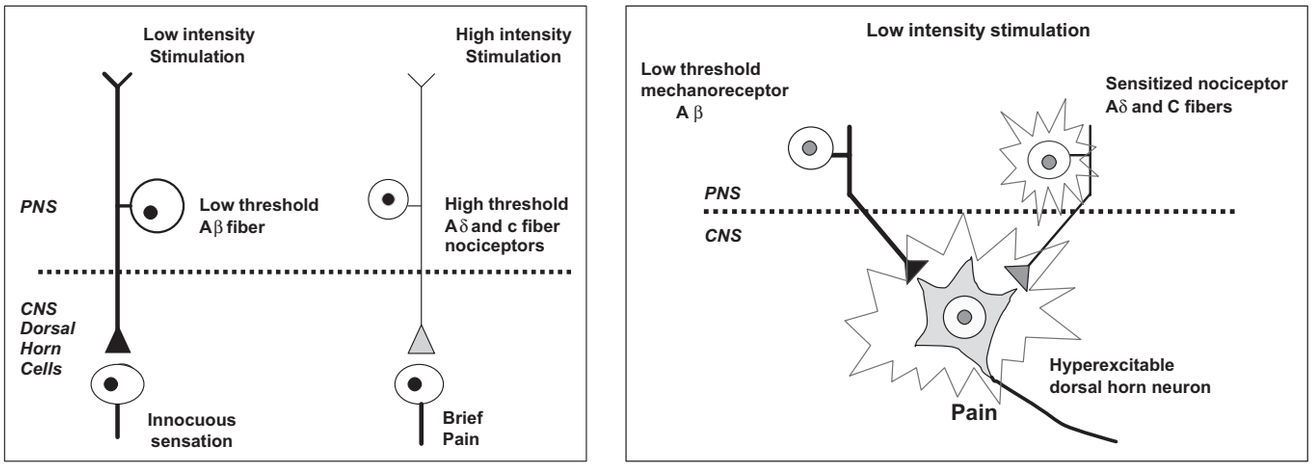

Figure 1.3: (a) The sensitization theory of pain perception suggests that brief high-intensity noxious stimulation in the absence of tissue injury activates the nociceptive endings of unmyelinated or thinly myelinated (high-threshold) fibers, resulting in physiologic pain perception of short duration. Other low-threshold sensory modalities (pressure, vibration, touch) are carried by larger-caliber (low-threshold) fibers. Large and small fibers make contact with second-order neurons in the dorsal horn. (b) Following tissue injuries and release of noxious mediators, peripheral nociceptors become sensitized and fire repeatedly. Peripheral sensitization occurs in the presence of inflammatory mediators, which in turn increases the sensitivity of high-threshold nociceptors as well as the peripheral terminals of other sensory neurons. This increase in nociceptor sensitivity, lowering of the pain threshold, and exaggerated response to painful and nonpainful stimuli is termed *primary hyperalgesia.* The ongoing barrage of noxious impulses sensitizes second-order transmission neurons in dorsal horn via a process termed *wind-up*. Central sensitization results in secondary hyperalgesia and spread of the hyperalgesic area to nearby uninjured tissues. Inhibitory interneurons and descending inhibitory fibers modulate and suppress spinal sensitization, whereas analgesic under medication and poorly controlled pain favors sensitization. In certain settings central sensitization may then lead to neurochemical/neuroanatomical changes (plasticity), prolonged neuronal discharge and sensitivity (long-term potentiation), and the development of chronic pain. (Modified from Woolf CJ, Salter MW. Neuronal plasticity: increasing the gain in pain. *Science.* 2000;288(5472):1765–1769.)[1]

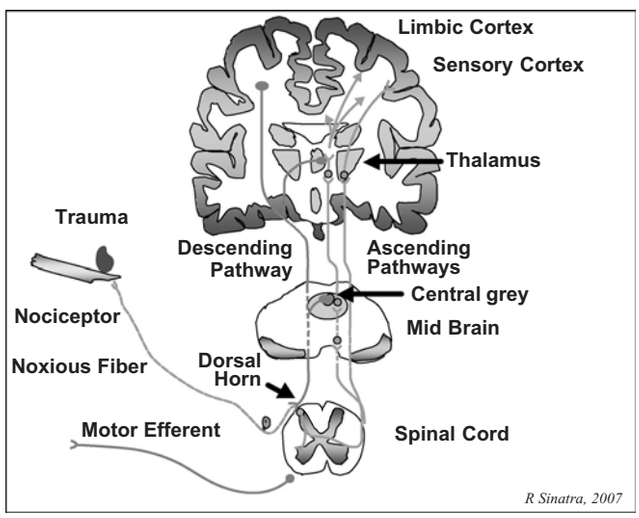

Figure 1.4: An anatomical overview of pain pathways. Noxious information is conveyed from peripheral nociceptors to the dorsal horn via unmeylinated and myelinated noxious fibers. Second-order spinal neurons send impulses rostrally via two distinct pathways, the neospinothalamic and paleospinothalamic tracts. These cells also activate motor and sympathetic efferents within the spinal cord. Ascending tracts make contacts in the brainstem and midbrain, central gray, and thalamus. Projections are then made with the frontal and limbic cortex. Descending fibers emanating from cortex, hypothalamus, and brainstem project to the spinal cord to modulate pain transmission.

In addition to PGEs, leukotrienes,[29] 5-hydroxytryptamine (5-HT),[30] bradykinin (BK),[31] and histamine[32] released following tissue injury are powerful primary and secondary noxious sensitizers. 5-hydroxytryptamine released after thermal injury sensitizes primary afferent neurons and produces mechanical allodynia and thermal hyperalgesia via peripheral 5-HT2a receptors.[33] Bradykinin's role in peripheral sensitization is mediated by G-protein-coupled receptors,[1] B1 and B2, that are expressed by the primary nociceptors. When activated by BK and kallidin, the receptor-G-protein complex strengthens inward Na^+ flux, whereas it weakens outward K^+ currents, thereby increasing nociceptor excitability. These locally released substances increase vascular permeability, initiate neurogenic edema, increase nociceptor irritability, and activate adjacent nociceptor endings. The resulting state of peripheral sensitization is termed *primary hyperalgesia.*

In addition to locally released and humoral noxious mediators, neural responses play an important role in maintaining both peripheral sensitization and primary hyperalgesia. Bradykinin, 5-HT, and other primary mediators stimulate orthodromic transmission in sensitized nerve endings and stimulate the release of peptides and neurokinins, including calcitonin gene-related protein (CGRP),[34] substance P (sP),[35] and cholocystokinin (CCK),[36] in and around the site of injury. Substance P, via a feedback loop mechanism, enhances peripheral sensitization by facilitating further release of bradykinin, histamine from mast cells, and 5-HT. Calcitonin gene-related protein is a 37-amino-acid peptide found in the peripheral and central terminals of more than 50% of C fibers and 35% of *Aδ* fibers.[37]

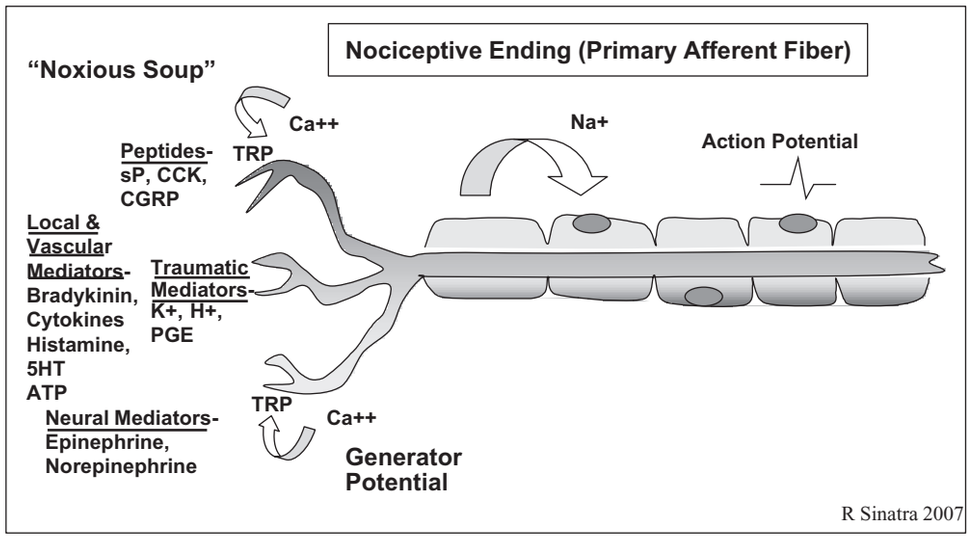

Figure 1.5: Pain is detected by unmyelinated nerve endings, termed *nociceptors*, that innervate skin, bone, muscle, and visceral tissues. Nociceptor activation initiates a depolarizing Ca^{2+} current or generator potential. Generator potentials depolarize the distal axonal segment and initiate an inward Na^{+} current and self-propagating action potential. Following tissue injury, cellular mediators (potassium, hydrogen ions, and prostaglandin released from damaged cells, as well as bradykinin [BK] released from damaged vessels) activate the terminal endings (nociceptors) of sensory afferent fibers. Prostaglandin (PGE), synthesized by cyclooxygenase 2, is responsible for nociceptor sensitization and plays a key role in peripheral inflammation. Orthodromic transmission in sensitized afferents leads to the release of peptides (substance P (sP), cholycystokinin (CCK), and calcitonin gene-related peptide (CGRP) in and around the site of injury. Substance P is responsible for further release of BK and also stimulates release of histamine from mast cells and 5HT from platelets, which further increases vascular permeability (neurogenic edema) and nociceptor irritability. The release of these mediators and others, such as serotonin (5HT) and cytokines, creates a "noxious soup" that exacerbates the inflammatory response, recruits adjacent nociceptors, and results in primary hyperalgesia. Reflex sympathetic efferent responses may further sensitize nociceptors by releasing noradrenaline and, indirectly, by stimulating further release of BK and sP and leading to peripheral vasoconstriction and trophic changes.

Like sP, CGRP[38] is produced in the cell bodies of primary nociceptors located in the dorsal root ganglion. Following axonal transport to peripheral and central terminals, these substances initiate mechanical and thermal hyperalgesia. When released at peripheral endings, CGRP enhances PGE[39] and histamine-induced vasodilation and inflammatory extravasation. It also prolongs the effect of sP by inhibiting its peripheral metabolic breakdown.[40] Finally, reflex-sympathetic efferent responses also sensitize nociceptors by releasing norepinephrine, which produces peripheral vasoconstriction at the site of injury. Norepinephrine also stimulates release of BK and sP and leads to atrophic changes in bone and muscle.

Peripheral sensitization is also associated with release of nerve growth factor, which alters intracellular signaling pathways and initiated posttranslational regulatory changes, including phosphorylation of tyrosine kinase and G proteins. These alterations markedly increase the sensitivity and excitability of distal nociceptor terminals.[41] For example, nociceptors are activated at lower temperatures ($< 40^{\circ}C$) and in response to lower concentrations of PGE_2 and other primary mediators.

Acute tissue injury results in an increased synthesis and extravasation of humoral proinflammatory cytokines, such as interleukin- (IL) 1β and IL-6. These cytokines play an important role in exacerbating edematous and irritative components of inflammatory pain.[42] Studies have shown that elevated levels of IL-1β result in allodynia and the development of persistent pain,[42] whereas effective postoperative analgesia decreases proinflammatory cytokines levels.[43,44] According to Bessler et al,[42] genetic polymorphisms influence production of proinflammatory cytokines and may contribute to observed interindividual differences in postoperative pain intensity scores and variations in morphine consumption.

The inflammatory mediators and proinflammatory cytokines described above activate transducer molecules such as the transient receptor potential (TRP) ion channel.[1] At least 8 different TRP ion channels have been identified and respond differentially to thermal, traumatic, and chemical 14 evoked mediators within the microenvironment. The TRP-VI/capsaicin ion channel has been well described. This 4-unit receptor contains a central ion channel that permits inward Ca^{2+} and Na^{+} currents following stimulation by H^{+} ions, heat, and direct application of capsaicin,[45] the active chemical compound found in hot pepper. The inward flux of Ca^{2+} via TRP ion channels is responsible for the generator potential.[31] Generator potentials summate and depolarize the distal axonal segment and the resulting action potential is then conducted centrally to terminals in the dorsal horn. The "noxious soup" of local humoral and neural mediators released following acute tissue injury as well as the nociceptor response to peripheral injury are summarized in Figure 1.5.

Table 1.5: Classification of Primary Afferent Nerve Fibers

Characteristic	Aβ	Aδ	C fibers
Diameter size	Largest	Small	Very small
Degree of myelination	Myelinated	Thinly myelinated	Unmyelinated
Conduction velocity	Very Fast	Fast	Slow
	30–50 m/s	5–25 m/s	<2 m/s
Threshold level	Low	High	High
Activated by	Light touch movement and vibration	Brief noxious stimulation; also intense and prolonged noxious stimuli	Intense and prolonged noxious stimuli
Located in	Skin, joints	Skin and superficial tissues; deep somatic and visceral structures	Skin and superficial tissues; deep somatic and visceral structures

CONDUCTION

Conduction refers to the propagation of action potentials from peripheral nociceptive endings via myelinated and unmyelinated nerve fibers. Central terminals of these fibers make synaptic contact with second-order cells in the spinal cord. Nociceptive and nonnoxious nerve fibers are classified according to their degree of myelination, diameter, and conduction velocity (Table 1.5). The largest-diameter sensory fibers, termed Aβ fibers, are generally nonnoxious special sensory axons that innervate somatic structures of the skin and joints. Two classes of nociceptive fibers include the thin myelinated Aδ and unmyelinated C fibers that innervate skin and a wide variety of other tissues. The Aδ fibers transmit the "first pain," a rapid-onset (<1 s) well-localized, sharp or stinging sensation of short duration. This perception of "first pain" alerts the person to actual or potential injury, localizes the site of injury, and initiates reflex withdrawal responses. The unmyelinated C fibers, also termed *high threshold polymodal nociceptive fibers*, respond to mechanical, chemical, and thermal injuries. They are responsible for the perception of "second pain," which has a delayed latency (seconds to minutes) and is described as a diffuse burning, stabbing sensation that is often prolonged and may become progressively more uncomfortable.[46] Ion channels found in nociceptive axons as well as their terminal endings appear to have selective roles in noxious conduction. Axonal Na^+ ion channels have been classified as being either sensitive or resistant (TTX-r) to the puffer fish biotoxin tetrodotoxin. The TTX-r isoform is upregulated in sensitized nerve fibers. Currently available local anesthetics block both forms; however, development of specific TTX-r channel blockers may provide more selective therapy for neuropathic and chronic inflammatory pain. Axonal conduction in nociceptive fibers culminates in the release of excitatory amino acids (EAAs) and peptidergic transmitters from presynaptic terminal endings in the dorsal horn. Neuronal-type (N-type) calcium channels are concentrated in these terminal endings and open in response to action potential induced depolarization. Following depolarization, these 4-subunit voltage-gated channels allow a rapid influx of Ca^{2+} ions that facilitates release of EAAs. N-type calcium channels may be blocked by conotoxins such as ziconotide. Specific ion channels that facilitate or suppress pain transmission are presented in Table 1.6.

TRANSMISSION

Transmission refers to the transfer of noxious impulses from primary nociceptors to cells in the spinal cord dorsal horn. Aδ and C fibers are the axons of unipolar neurons that have distal projections known as nociceptive endings. Their proximal terminals enter the dorsal horn of the spinal cord, branch within Lissauer's tract, and synapse with second-order cells located predominantly in Rexed's laminae II (substantia gelatinosa) and V (nucleus proprius). The second-order dorsal horn neurons are of two main types. The first type, termed *nociceptive-specific neurons* (NS), are located in lamina I and respond exclusively to noxious impulses from C fibers. The second type, known as *WDR*, are primarily localized in lamina V and respond to both noxious and innocuous stimuli. Wide dynamic range neurons have variable response characteristics such that low-frequency C fiber stimulation results in nonpainful sensory transmission, whereas higher frequency stimulation leads to gradual increases in WDR neuronal discharge and transmission of painful impulses.[47] WDR neurons can also be suppressed by local inhibitory cells and descending synaptic contacts. The inhibitory actions of SG cells, as well as the ability of WDR neurons to function as "transmission cells" that differentially process noxious and innocuous stimuli, provide the physiologic foundation of the gate control theory. Synaptic connections made within the spinal cord are presented in Figure 1.6.

Excitatory amino acids such as glutamate (Glu) and aspartate are responsible for fast synaptic transmission and rapid neuronal depolarization. Excitatory amino acids activate ionotropic amino-3-hydroxyl-5-methyl-4-propionic acid (AMPA) and kainite (KAR) receptors that regulate Na^+ and K^+ ion influx and intraneuronal voltage. AMPA and KAR are relatively impermeable to Ca^{2+} and other cations.

Each AMPA receptor contains 4 subunits with integral glutamate binding sites that surround a central cation channel. Agonist binding at two or more sites activates the receptor, opening the channel and allowing passage of Na^+ ions into the cell.[48] This brief increase in Na^+ ion flux depolarizes second-order spinal neurons, allowing noxious signals to be rapidly transmitted to supraspinal sites of perception. Kainate receptors are also involved in postsynaptic excitation. The KAR cation channel regulates both Na^+ and K^+ flux; however, unlike AMPA,

Table 1.6: Receptors Associated with Noxious Transmission in the Dorsal Horn

Receptor	*Type*	*Ligand*	*Voltage Gated*	*Action*	*Function*	*Onset*
AMPA	Ionotropic	Glu	No	Excitatory	Na^+ flux	Rapid
NMDA	Ionotropic	Glu	Yes	Excitatory	Ca^2 flux	Delayed
KAR	Ionotropic	Glu	No	Excitatory	Na^+, K^+ flux	Rapid
NK-1	Metabotropic	sP	No	Excitatory	Activates 2nd messengers	Delayed
Glycine	Ionotropic	Gly	No	Inhibitory	Cl- Flux	Rapid
GABA	Iontropic	GABA	No	Inhibitory	Inhibits K^+ flux	Rapid
ENK	Metabotropic	ENK	No	Inhibitory	Inhibits K^+ flux and 2nd messengers	Rapid

Abbreviations: Glu = glutamate; sP = substance P; Gly = glycine; GABA = γ-aminobutyric acid; ENK = enkephalin.

these receptors appear to play a minor role in synaptic signaling following brief noxious stimulation. Once activated, KARs may improve synaptic efficacy by increasing the likelihood of second-order neuronal discharge in settings of ongoing stimulation.

In the setting of continued high-frequency noxious stimulation, activated AMPA and KAR receptors initiate voltage mediated priming of *N*-methyl-D-aspartic acid (NMDA) receptors.[49,50] The NMDA receptor is a 4-subunit (2 NR1 subunits and 1 NR2A and 1 NR2B subunit) membrane protein that regulates inflow of Na^+ and Ca^{2+} and cellular outflow of K^+ via an intrinsic ion channel. The extracellular portion of NR2 subunit contains a Glu binding site, whereas a glycine (Gly) binding site is located on the NR1 subunit. Each subunit has an extensive cytoplasmic portion that can be modified by protein kinases and an external allosteric portion that may be altered by zinc ions. NMDA receptors are both ligand dependent and voltage gated. Activation requires AMPA-induced membrane depolarization and a positive change in intracellular voltage, as well as binding of glutamate or aspartate to the receptor (Figure 1.7).

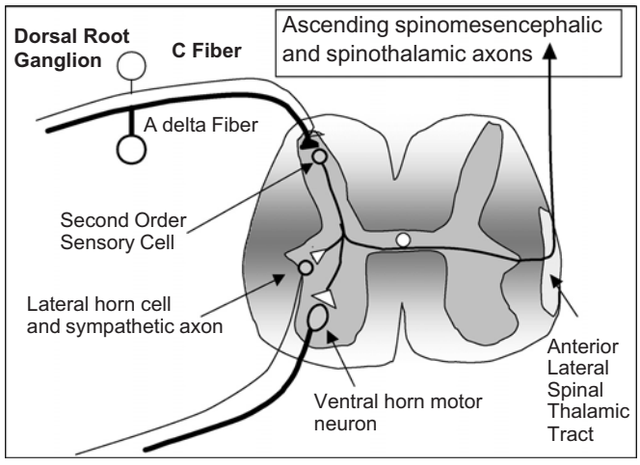

Figure 1.6: Synaptic contacts and pain transmission between primary afferent fibers and second-order cells in the dorsal horn. Projections from second-order cells contact efferent motor and sympathetic cell bodies in the spinal cord and also ascend to supraspinal sites.

Activated AMPA receptors initiate slow excitatory postsynaptic potentials (EPSPs) lasting several hundred milliseconds.[51] These <5-Hz potentials accumulate and produce a summated depolarization that in turn dislodges a magnesium ion "plug" that normally blocks the NMDA ion channel. Following dislodgement of Mg^{2+}, a rapid influx of Ca^{2+} ions is initiated. Activated NMDA receptors (NMDARs) are further sensitized by direct effects of glutamate at the glutamate binding site.[52]

Accumulation of intracellular Ca^{2+} initiates a series of neurochemical and neurophysiologic changes that influence acute pain processing. Second-order spinal neurons become highly sensitized and fire rapidly and independently of further sensory stimulation. This process, termed *wind-up*, refers specifically to transcription-independent excitation of dorsal horn neurons. (Refer to section on transition from acute to chronic pain.)

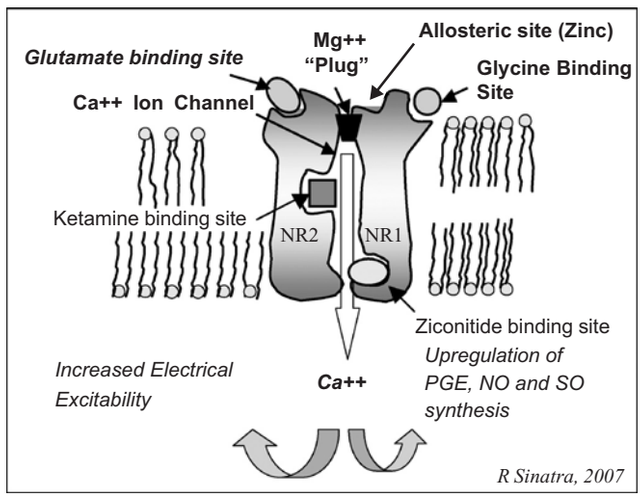

Figure 1.7: The NMDA receptor is a 4-subunit, voltage-gated ligand specific ion channel. The 4 subunits include 2 NR2 units, which contain glutamate binding sites, and 2 NR1 units, which contain glycine binding sites and an allosteric site that is sensitive to zinc ions. Glutamate is the primary agonist of NMDA, whereas glycine functions as a modulator. The central ion channel is normally blocked by a magnesium ion. Once dislodged, Ca^{2+} ions can pass through the channel and induce neuronal excitability.

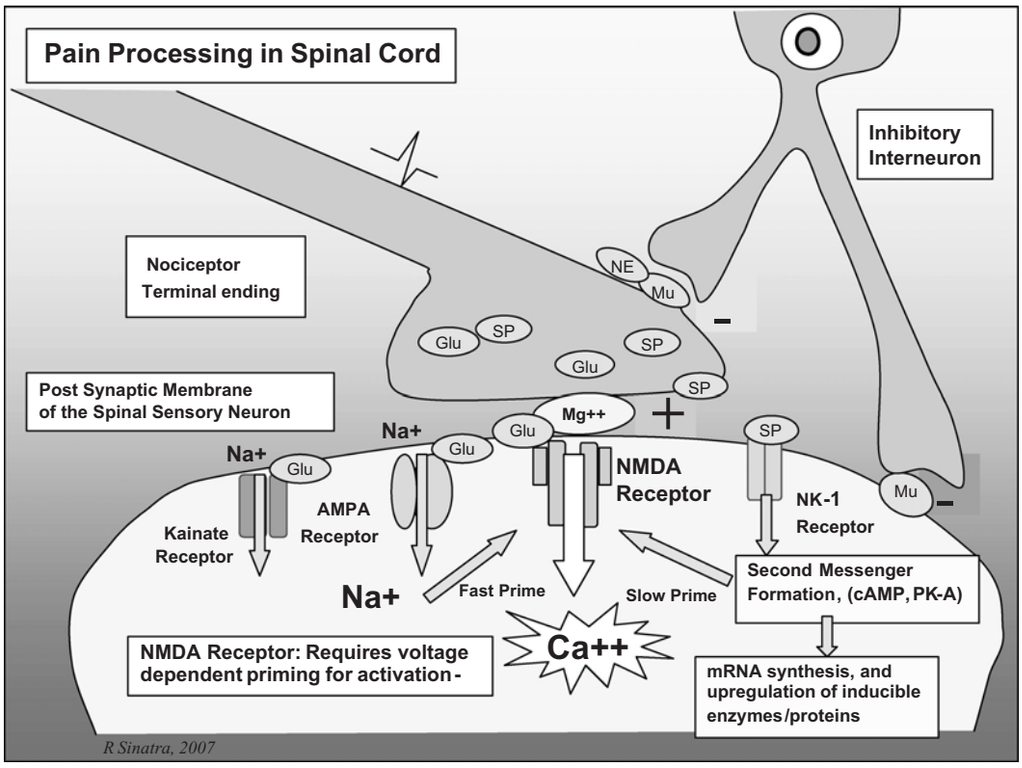

Figure 1.8: Targets of excitatory noxious mediators on second-order cells. Glutamate is the primary excitatory agonist for noxious transmission. Glutamate activates specific binding sites located on AMPA, kainate, and NMDA receptors. Ion channels on activated AMPA and kainate receptors allow Na^+ to enter and depolarize the cell. Changes in intracellular voltage rapidly prime the NMDA receptor and allows an Mg^{2+} plug to be dislodged. Following dislodgement, an inward flux of Ca^{2+} is initiated. Glutamate binding to NMDARs maintains the inward Ca^{2+} flux. Substance P binds and activates NK-1 receptors. This receptor upregulates second messengers, including cAMP and PKA, which slowly prime and maintain excitability of NMDARs. Activation of second messengers in turn upregulates inducible enzymes, initiates transcription of mRNA, and mediates synthesis of acute reaction proteins. These changes increase neuronal excitability and underlie subsequent plasticity.

Woolf and others have shown that NMDA activation, wind-up, and central sensitization are responsible for clinical hyperalgesia and can occur following nerve injury as well as trauma and inflammation,[1] Central sensitization is also observed in supraspinal regions of the CNS, including rostroventral medulla, amygdala, and anterior cingulate gyrus.[53]

Intracellular Ca^{2+} ions also activate inducible enzymes, including nitric oxide synthase (NOS) and COX-2. Peptides such as sP and CGRP are responsible for delayed and long-lasting depolarization of second-order dorsal horn neurons. Substance P binding at metabotrophic neurokinin 1 (NK-1) receptors synergistically activates NMDARs and appears necessary for the development of long-term potentiation (LTP).[54] Following activation of NK-1, second messengers cyclic adenosine monophosphate (cAMP) and phosphokinase A (PKA) are synthesized and mediate a number of cellular changes, including slow priming of NMDARs, second-messenger cascades, and genome activation. Synthesis of acute phase proteins together with increased intracellular and extracellular PGE and NO are responsible for transcription-dependent central sensitization and associated neural plasticity changes and responses that facilitate pain transmission. The process of NMDA activation and its consequences are presented in Figure 1.8.

MODULATION

The concept of modulation refers to pain-suppressive mechanisms within the spinal cord dorsal horn and at higher levels of the brainstem and midbrain. In the spinal cord, this intrinsic "breaking mechanism" inhibits pain transmission at the first synapse between the primary noxious afferent and second-order WDR and NS cells, thereby reducing spinothalamic relay of noxious impulses. Spinal modulation is mediated by the inhibitory actions of endogenous analgesic compounds released from spinal interneurons and terminal endings of inhibitory axons that descend from central gray locus ceruleus and other supraspinal sites. Endogenous analgesics, including enkephalin (ENK), norepinephrine (NE), and γ-aminobutyric acid (GABA), activate opioid, alpha adrenergic, and other receptors that either inhibit release of Glu from primary nociceptive afferents or diminish postsynaptic responses of second-order NS or WDR neurons (Figure 1.9). The balance between excitatory mediators and the inhibitory effects of endogenous analgesics adjusts K^+ ion flux and the firing frequency of dorssal horn cells.[55]

Endogenous opioids, including the ENKs and endorphins, modulate pain transmission by activating pre- and postsynaptic

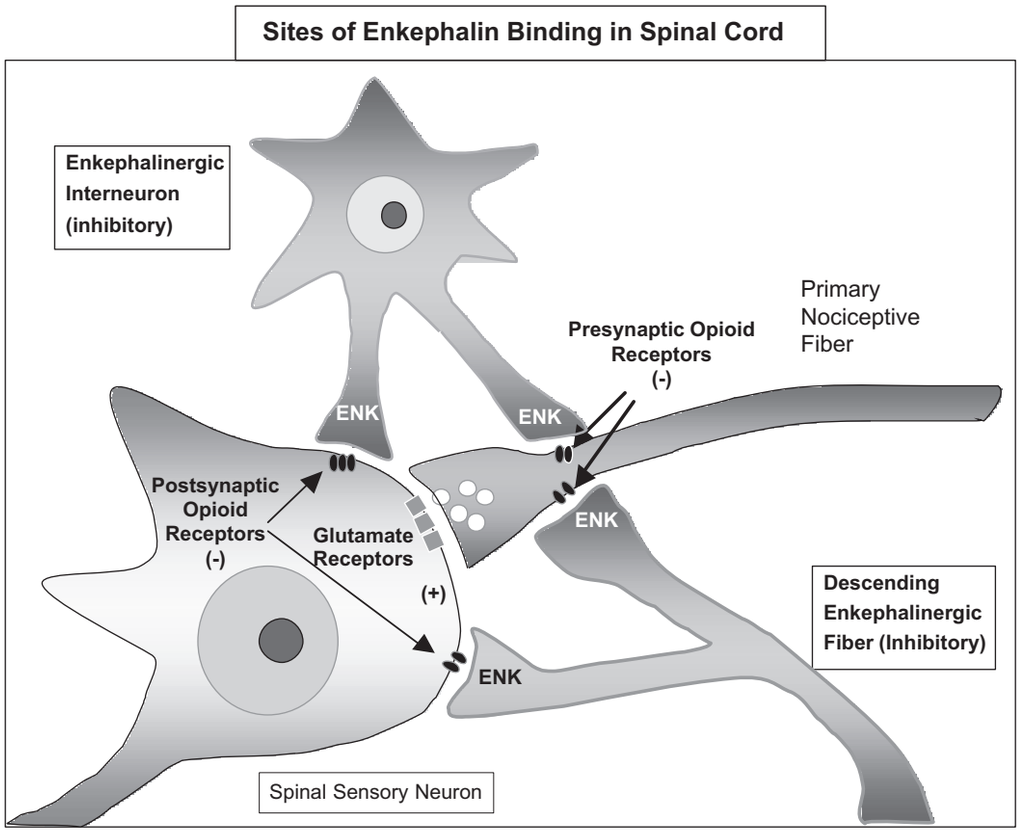

Figure 1.9: Enkephalinergic modulation of noxious transmission. Both local interneurons and descending axons suppress synaptic transmission between the primary nociceptor and second-order sensory cells. Enkephalins activate both pre- and postsynaptic opioid receptors. Opioid receptors inhibit either release of noxious transmitters such as glutamate or second-order responses.

μ-, κ-, and δ-receptor subtypes. These subtypes belong to a large superfamily of transmembrane-spanning G-protein-coupled receptors.[56] μ-opioid receptors are primarily responsible for mediating spinal and supraspinal analgesia, euphoria, and respiratory depression. Kappa subtypes mediate spinal analgesia, as well as sedative/hypnotic effects of opioids. Delta receptors appear to potentiate mu-mediated analgesia, whereas activation of σ receptors may be responsible for dysphoria.[57] Opioid binding at μ receptors activates coupled G proteins (Gi/o), which in turn inhibit the neuronal cAMP pathway. Adenylate cyclase is suppressed, and production of cAMP PKA are markedly reduced. Reductions in cAMP and inhibition of potassium (K^+) influx decrease neuronal excitability (Figure 1.10). The structure of μ-opioid receptors (μ-opioid receptor peptide or MOP) is coded by the MOP gene, which is part of the opioid receptor μ 1 (*OPRM1*) gene. The *OPRM1* gene has 4 exons that determine the amino acid constituents and tertiary configuration of the external and internal portions of the MOP.[29] At least 10 single nucleotide polymorphisms (SNP) in the coding or open reading frames and more than 100 polymorphisms in the noncoding frames of the human *OPRM1* gene have been identified.[58] Polymorphic variations influence transcriptional regulation, expression, and functionality of the mu receptor.[59] With regard to expression, polymorphisms of *OPRM1* neither influence the conformation of the external binding site nor affect the binding affinity of opioid ligands. They do, however, alter the internal segment and c-terminus of MOP and may influence secondary proteins, such as G proteins and adenylate cyclase, that modulate receptor efficacy.[60] In clinical settings, these polymorphisms may explain interindividual differences in opioid

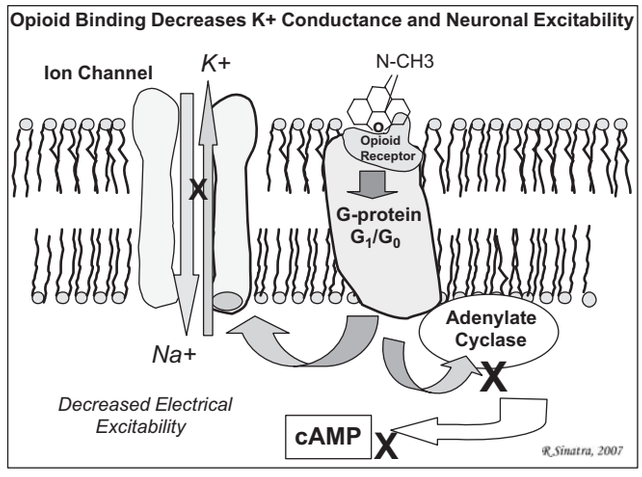

Figure 1.10: Opioid receptors activate specific G proteins that decrease neuronal excitability either by inhibiting K^+ ion conductance or decreasing intracellular cAMP.