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Chapter 1

Introduction

Ian W. Rodger

Pain is a wholly tormenting, disagreeable, multifactorial sensory experience. It is defined by the 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"*. Pain intensity can vary from mild to severe. Its duration can be transient, acute, intermittent or persistent. Several distinct, but frequently overlapping, types of pain are recognized: nociceptive/physiological, inflammatory and neuropathic. All pain is initially detected by a highly specialized sensory apparatus, the nociceptor, located on sensory nerve terminals. Once activated by a noxious stimulus the nociceptor transduces the signal into an electrical impulse (action potential) that travels up the primary sensory neuron *en route* to the brain. Given the extensive neural and neurochemical processes that are involved in pain signaling it is apparent that there are abundant points at which chemical/drug interference with these processes can occur. The vast array of analgesics and analgesic adjuncts that we have available today all have one thing in common; they interfere with the pain signaling cascade in delivering their analgesic effect(s).

Today healthcare providers are faced with a bewildering number of analgesics and adjunct agents in addressing different pain conditions in their patients. Indeed, the variety of analgesic agents available is also frequently mystifying to experts in the field. Furthermore, the intensity of pain research has accelerated dramatically in recent years given the recognition that there is an enormous unmet medical need for improved pain therapies, especially for those difficult to treat, intractable pain states. Thus, under the glare of this spotlight the complex molecular, genetic and pathophysiological mechanisms underlying different types of pain are steadily being unraveled. With this understanding has come the consequent realization that improved pain control is entirely feasible not only with the analgesics available today but also with those that are on the horizon for tomorrow. That said, however, today we work with analgesics that have unique sites of action. They work peripherally and/or centrally, frequently have several sites of action, come in a variety of dose strengths and formulations and have a wide variety of durations of action. It is no surprise, therefore, that many analgesics also come burdened with a far less than desirable side-effect profile and significant potential for interactions and toxicity.

In this textbook the editors have chosen to divide the subject literature available into twelve sections, each with a particular focus. Section 1 concentrates on setting the stage for an understanding of analgesic action. Thus, it describes the definitions and characteristics of different types of pain, the various pain pathways including mechanisms underlying both peripheral and central sensitization (aspects of wind-up) and other elements of analgesic theory. Sections 2 through 11 describe the essence of commonly prescribed acute and chronic pain medications. As a deliberate policy, and for both convenience and continuity, the editors have opted to list each analgesic according to its drug class. The final section (12) deals with new and emerging therapies. This section provides details of how existing therapies are being re-engineered and reformulated to provide superior analgesic control. It also provides a glimpse of the future by identifying new molecular targets that hold promise for the discovery and development of novel analgesics with completely new mechanisms of action.

In the final analysis this textbook provides a host of welcome information, tightly packaged, that provides a much needed reference source on analgesia and analgesics. It will benefit all healthcare professionals tasked with the responsibility of optimizing the control, and ideally the elimination, of pain and suffering.

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Section 1
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Pain Definitions

Pain definitions and assessment

Raymond S. Sinatra

Introduction

Pain is among the most common of patient complaints encountered by health professionals and it remains the number one cause of absenteeism and disability. Each year, more than 60 million trauma-related pain episodes occur in the USA, as well as acute pain related to over 40 million surgical procedures [1]. Pain has been defined by the International Association for the Study of Pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage" [2]. In clinical settings, it has been suggested that presence of pain and the intensity of discomfort are whatever the patient says they are unless proven otherwise by poor adherence to an agreed treatment plan [3–5]. We now recognize that in addition to the ethical and humanitarian reasons for minimizing discomfort and suffering, pain-related anxiety, sleeplessness and release of stress hormones or catecholamines may have deleterious effects upon post-surgical outcome, and may lead to the development of chronic pain [6–8].

Classification of pain

Pain is a complex physiological process that can be classified in terms of its intensity (mild, moderate, severe) its duration (acute, convalescent, chronic), its mechanism (physiological, nociceptive, neuropathic), and its clinical context, (post-surgical, malignancy-related, neuropathic, degenerative, etc.) [2]. Pain detection, or nociception, requires the activation of specialized transducers called nociceptors, which are the peripheral endings of A-delta (Aδ) and (C) sensory fibers. Nociceptors are activated following thermal, mechanical or chemical tissue injuries, and initiate afferent transmission of action potentials to the dorsal horn of the spinal cord. Pain perception follows activation of second-order sensory neurons which relay noxious signals to higher thalamic and cortical centers (Figure 2.1).

The mechanistic classification of pain is as follows [2,4,5]. (1) Physiological pain is defined as brief, rapidly perceived, non-traumatic discomfort that identifies a potentially dangerous stimulus. This adaptive alerting response involves cortical perception and localization and a reflex withdrawal that prevent and/or minimize tissue injury. Physiological pain is also associated with learned avoidance and adaptation that can modify future behavior. (2) Nociceptive pain results from the activation of physiologically normal nerve fibers in response to tissue injury. In addition to cellular damage and neural irritation, humoral mediators and peripheral inflammatory responses play a major role in its initiation and progression. Nociceptive pain can be further divided into somatic and visceral pain subtypes. Somatic nociceptive pain is well localized, sharp, crushing, or tearing pain that follows traumatic injury to dermatomally inervated structures. It includes cutaneous, muscular and ligamentous pain, but also includes headache and osteogenic pain. In contrast, visceral nociceptive pain is poorly localized non-dermatomal specific discomfort that is usually described as dull, cramping, or colicky. Visceral pain includes discomfort related to bowel obstruction, first-stage labor, dilatation of hollow viscus, early appendicitis and peritoneal irritation. Visceral pain is mediated by free nerve endings in gastro intestinal organs and peritoneum that respond to irritation or distention. Referred pain is a special form of visceral pain that radiates in a somatic dermatomal pattern. Referred pain may be explained by convergence of spinal input theory, or reflex response theory [2].(3) Neuropathic pain results from irritation, infection, degeneration, transaction or compression injury to nervous tissue. It is usually characterized as burning, electrical and/or shooting in nature. Pain following injury to sensory nerves is termed causalgia or chronic regional pain syndrome II. Pain associated with injury or abnormal activity

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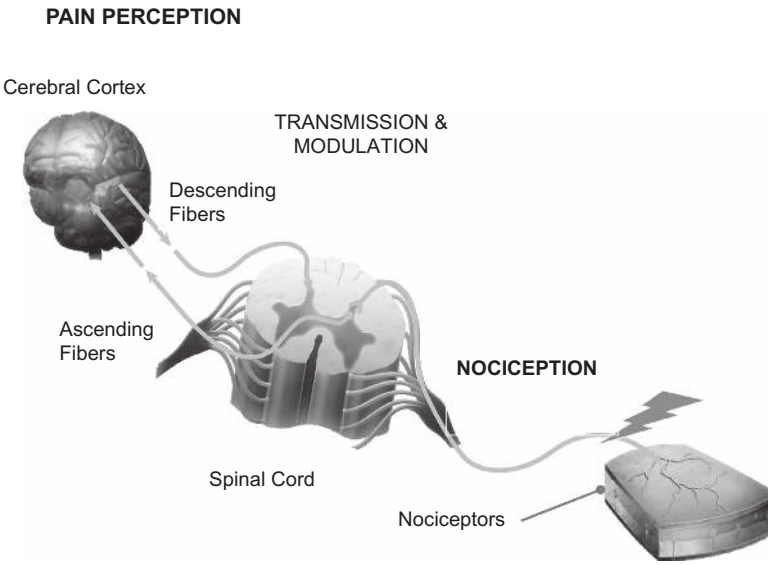

Figure 2.1. A mechanistic representation of nociception and pain perception.

Table 2.1.

Category	Cause	Symptom	Examples
Physiological	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 impacting on intact nervous tissue	Moderate to severe pain, described as crushing or stabbing; usually worsens after the first 24 hours	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, chronic regional pain syndrome, postherpetic neuralgia
Mixed	Combined somatic and nervous tissue injury	Combinations of symptoms; soft tissue pain plus radicular pain	Low back pain, back surgery pain

of sympathetic fibers is termed reflex sympathetic dystrophy or chronic regional pain syndrome I. Neuropathic pain is often associated with peripheral and central sensitization, secondary hyperalgesia and alterations in sympathetic tone and regional perfusion. A common characteristic of neuropathic pain is the coexistence of sensory deficits or sensory abnormalities in the setting of increased pain sensation. These abnormalities include hyperpathia, or increased or exaggerated pain intensity with minor stimulation; allodynia, in which non-noxious sensory stimulation is perceived as painful; dysesthesia/paresthesia, which are unpleasant sensations at rest or following touch and movement. Differences between physiological, nociceptive and neuropathic pain are described in Table 2.1.

Hyperalgesia

Hyperalgesia describes a state of increased pain sensitivity and enhanced perception following acute injury which is related to peripheral release of intracellular or humoral noxious mediators [7,9–11]. Primary hyperalgesia (peripheral sensitization) describes an altered state of sensibility in which the intensity of painful sensation induced by noxious and non-noxious

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stimulation is greatly increased. Hyperalgesia results in dynamic or "effort-dependent" pain, in which discomfort during ambulation, coughing and physical therapy is significantly increased [10]. Continued activation of nociceptors secondary to neural compression, stretch, infection, hematoma, and edema can result in prolonged disability and impaired rehabilitation. Secondary hyperalgesia (central sensitization) is related to ongoing noxious transmission and "sensitization" of second-order neurons in the dorsal horn [11]. Clinical alterations associated with secondary hyperalgesia include allodynia, multi-segmental flexion reflexes (splinting, muscle spasm) and alterations in sympathetic tone and regional perfusion. As a result, discomfort may be perceived at dermatomes above and below the site of trauma. The duration of central sensitization generally outlasts the initial barrage of high-threshold input and may become independent of further depolarization [6,7].

Pain temporality and duration

Acute pain

Acute pain is an adaptive physiological response that follows traumatic injuries and surgery. It has two primary components. (1) The sensory discriminative component describes the location and quality of the stimulus. It is characterized by rapid response, short latency to peak response, and short duration of action. Noxious information is conveyed by rapidly conducting A-delta fibers, and monosynaptic transmission to the sensory cortex [10,12]. This component rapidly identifies the site of injury or potential injury, and initiates reflexive/cognitive withdrawal responses. (2) The affective-motivational component underlies suffering and the emotional components of pain and is responsible for learned avoidance and other adaptative and non-adaptative behavioral responses.

The affective motivational component is mediated by slowly conducting c-fibers, and polysynaptic transmission to the limbic cortex [10,12]. It is responsible for continued pain perception, suffering, pain-related behaviors, hyperalgesia, reflex spasm (splinting behavior). It is also responsible for immobilization, and protection of the injury site.

In general, acute pain is limited in duration (1–14 days) and is associated with temporal reductions in intensity. Optimally controlled acute pain may be mild–moderate at rest but generally worsens during movement (effort-dependent or incident pain). Poorly controlled acute pain is associated with peripheral sensitization, spinal facilitation, hypothalamic/adrenal responses, and emotional/behavioral changes [7,9,12].

Rehabilitative/convalescent pain

A subacute pain state associated with convalescence and rehabilitation may persist for 1–2 months after surgery or traumatic injury. Patients may experience moderate to severe incident pain and require opioid analgesics for sleep and mobilization. Severe rehabilitative pain has a negative impact on physical therapy, return to normal functionality and quality of life.

Chronic pain

Chronic pain refers to persistent or progressively increasing discomfort beyond the normal time frame of healing [2,10]. An alternative definition is moderate to severe discomfort persisting 3 months or more following tissue injury (post-operative pain syndromes) or initial symptoms of cellular degeneration (osteoarthritic disease). The etiological classification of chronic pain refers to the clinical context in which pain perception takes place, and can be categorized as benign, malignancy-related, post-surgical, neuropathic, degenerative, or mixed.

Chronic pain is often associated with sensitization and plasticity changes in the peripheral and central nervous system that facilitate pain transmission and impair intrinsic noxious modulatory mechanisms [7,9,13]. Transition from acute pain to chronic pain involves ongoing peripheral and central sensitization, persistent hyperalgesia, the development of neuropathic symptoms and maladaptive emotional responses (pain behavior) [10]. Patients with chronic pain may be troubled by a persistent pain state that remains constant or gradually increases in frequency and intensity (malignancy-associated pain, osteoarthritis), or an intermittent pain state that has peaks (flare) and troughs in intensity (vasculopathic pain, gout, low back pain). Others may present with a combination of persistent pain plus intermittent flare, and complain of pain that is constant or gradually increasing, with episodes of increased intensity or flare (rheumatoid arthritis, neuropathic pain).

Chronic pain may also be characterized by its localization. Peripheral pain is is associated with

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Table 2.2.

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 months 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

Table 2.3.

Temporal	Onset, duration, periodicity
Variability	Constant, effort-dependent, waxing and waning, episodic "flare"
Intensity	Average pain, worst pain, least pain, pain with activity of living
Topography	Focal, dermatomal, diffuse, referred, superficial, deep
Character	Sharp, aching, cramping, stabbing, burning, shooting
Exacerbating/relieving	Worse at rest, with movement or no difference
Quality of life	Interferes with movement, ambulation, daily life tasks or work

ongoing nociceptor sensitization, neuropathic injury and stimulation of sympathetic efferents. Myelopathic pain is associated with spinal injuries and includes localized irritative and compression-related pain, radicular pain and skeletal muscular irritability. Central pain describes pain syndromes that follow CNS injury (post-stroke, CNS tumor) that are generally ill defined or poorly localized and difficult to treat. While some forms of chronic pain have an unclear etiology and unpredictable course, most begin as acute inflammatory or neuropathic pain. An increasing body of evidence suggests that severe acute pain, analgesic undermedication, nerve injury and genetic variabilities are responsible for the development of chronic pain [13,14].

Although acute and chronic pain have distinguishing characteristics, there is often overlap, making the diagnosis and management of pain challenging. Differences between acute and chronic pain are outlined in Table 2.2.

Qualitative aspects of pain perception

Appreciating the clinical features of the different types of pain not only helps properly classify pain and its etiology, but also helps guide the often complex multimodal medical management that accompanies pain management [10,13,14]. The healthcare provider must be detailed in attaining the qualitative factors and history associated with a patient's pain. The McGill Pain Questionnaire may be used to measure the quality, character, and intensity of acute and chronic pain. The qualitative aspects of pain perception are outlined in Table 2.3.

Finally, it is well recognized that certain acute traumatic and chronic pain conditions are associated with a mixture of noiciceptive inflammatory and neuropathic pain. For example, tissue injury and a marked inflammatory response following laparotomy or thoracotomy initiates a somatic nociceptive component responsible for incisional and muscular pain, while peritoneal or pleuritic irritation is responsible for a visceral nociceptive component. Neural injury related to retraction or transection initiates a neuropathic component. Clinical pain complaint, intensity of symptoms, pain characteristics and choice of analgesic are related to the extent of inflammation, visceral versus somatic nociception, and neural tissue injuries.

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Section 1 Chapter 3

Pain Definitions

Pain pathways and pain processing

Amit Mirchandani and Shamsuddin Akhtar

Introduction

Understanding the anatomical pathways and key neurochemical mediators involved in noxious transmission and pain perception is fundamental to optimizing the management of patients with acute and chronic pain. In this chapter we will outline the basic anatomy of the pain pathway and identify key neurochemical mediators involved in pain modulation.

Nociception

The conduction of pain does not simply involve conduction of impulses from the periphery to the cortical centers in the brain. Transmission of pain or nociception is a complex phenomenon and involves multiple stages that can be grouped broadly into three processes: (1) activation of specialized peripheral nerve endings; (2) conduction of noxious impulses to the spinal cord; and (3) transmission of impulses from the spinal cord to the supra-spinal and cortical centers. The culmination of these processes results in the localization and perception of pain. At each of these stages, nociceptive impulses can be suppressed by local interneurons or by descending inhibitory fibers and modulated by a variety of neurotransmitters and neuromodulators. Any abnormality of peripheral and central pain pathways including pathological activation, or the imbalance of activation and inhibitory pathways, may increase the severity of acute pain and contribute to the development of persistent pain [1].

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Activation of sensory end organs and/or nerve endings

The nociception begins with the activation of peripheral sensory afferent receptors, also known as nociceptors, which are widely distributed throughout the body. Nociceptors are the peripheral endings of pseudo-unipolar neurons, whose cell bodies are located in the dorsal root ganglia (DRG). The nociceptor central ending terminates in the spinal cord and transmits noxious impulses to the dorsal horn [1,2].

Nociceptors convey noxious sensation, either externally (i.e. skin, mucosa) or internally (i.e. joints, intestines). They can be activated by any noxious insult, most of which can be categorized as either mechanical, chemical, or thermal in nature. Nociceptor activation is associated with a depolarizing Ca^{2+} current or a "generator potential". Once a certain threshold is met, the distal axonal segment depolarizes via an inward Na^{+} current, and an action potential is conducted centrally.

Noxious stimuli are conducted from peripheral nociceptors to the dorsal horn via both unmyelinated and myelinated fibers. Nociceptive nerve fibers are classified according to their degree of myelination, diameter, and conduction velocity. For instance, A-delta axons are myelinated and allow action potentials to travel at a very fast rate of approximately 6–30 meters/second towards the central nervous system. They are responsible for "first pain" or "fast pain", a rapid (1 second) well-localized, discriminative sensation (sharp, stinging) of short duration [1,2]. Perception of first pain alerts the individual of actual or potential tissue injury and initiates the reflex withdrawal mechanism. The more slowly conducting non-myelinated C fiber axons conduct at speeds of about 2 meters/second. These unmyelinated C-fibers (termed polymodal-nociceptive fibers) respond to mechanical, thermal, and chemical injuries. C-fibers mediate the sensation of "second pain", which has a delayed latency (seconds to minutes) and is described as a diffuse burning or stabbing sensation that persists for a prolonged period of time. Larger A-beta axons, which respond to maximally light touch and/or movement stimuli, typically do not produce pain, except in pathological conditions [1,2].

Multiple receptors located on the primary afferent nerves are involved in specific transduction of particular noxious stimuli. Vanilloid receptors (VRI) and vanilloid receptor like-1 are excited by heat. VRI and acid-sensing ion channels are also stimulated by mechanical stimuli. Inotropic purinergic (P2X) receptors are excited by stretch and modulated by low pH [1,3]. Temperature is sensed by receptors called transient receptor potential (TRP) channels. An important TRP channel termed the TRPV-1 receptor has been widely studied. Capsacian and other TRPV-1 blockers initially activate and then deactivate nociceptors for prolonged periods of time. These compounds may provide long-term blockade of nociceptor function and prolonged suppression of acute pain.

A number of inflammatory and noxious mediators are involved in peripheral pain transduction [1] (Figure 3.1).

1. Substance P is a neuropeptide released from the unmyelinated primary afferent fibers, and its role in nociception is well established. Its effects can be blocked by treatment with the neurotoxin capsaicin, which destroys afferent nerve terminals. The pro-inflammatory effects of substance P include: vasodilatation and plasma extravasation, degranulation of mast cells, resulting in histamine release, chemo-attraction and proliferation of leukocytes, and cytokine release.
2. Bradykinin is a markedly algesic (pain-producing) substance that has direct activating effects on peripheral nociceptors.
3. Histamine is stored in mast-cell granules and is released by substance P and other noxious mediators. The effects of histamine are mediated by its interaction with specific receptors, resulting in vasodilatation and edema and swelling resulting from the enhanced permeability of postcapillary venules.
4. Serotonin or (5-hydroxytryptamine; 5-HT) is stored in the dense-body granules of platelets. 5-HT enhances microvascular permeability.
5. Prostaglandins (PGs) play a substantial role in the initial activation of nociceptors and exacerbate inflammation and tissue swelling at the site of injury. Up-regulation of cyclooxygenase-2 leads to rapid conversion of arachidonic acid from injured cell membranes into a variety of prostanoids (PGs and thromboxane A2).
6. Cytokines and interleukins released as part of the peripheral inflammatory response can circulate to and increase production of PGs in the brain. The accumulation of noxious mediators at the site of injury results in ongoing nociceptor stimulation, nociceptor recruitment and development of primary hyperalgesia.

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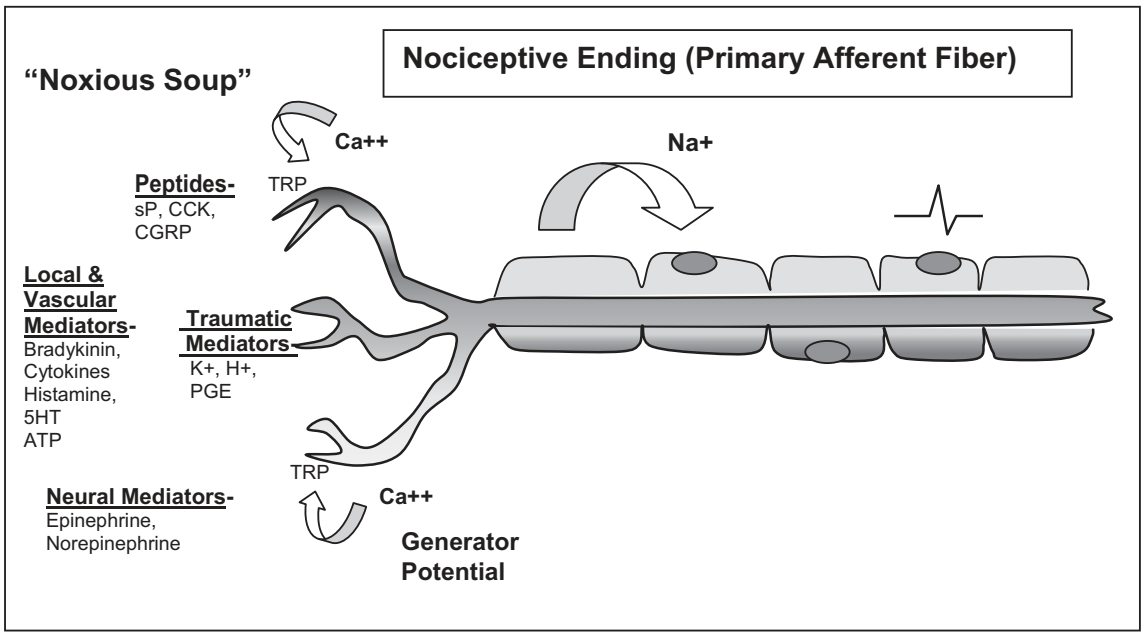

Figure 3.1. Nociceptive ending (primary afferent fiber). From: Sinatra RS. Pain pathways. In Sinatra RS, Viscusi G, de Leon-Casasola O, Ginsberg B, eds. *Acute Pain Management*. Cambridge University Press, 2009.

Conduction of pain to the spinal cord (and medulla)

Nearly all sensory afferents, regardless of peripheral origin, terminate in the dorsal horns of the spinal cord and medulla. Unmyelinated C fiber nociceptors terminate principally in lamina II (substantia gelatinosa). Small myelinated A-delta nociceptors terminate lamina I of the dorsal horn. The terminal endings of the primary afferent neurons in the spinal cord transmit pain signals to second-order neurons via several neurotransmitters, including glutamate and substance P. The second-order neurons involved in the pain pathway are principally of two types; (1) nociceptor-specific neurons that respond exclusively to inputs from A-delta and C fibers, and (2) wide-dynamic-range (WDR) neurons that respond to both noxious and non-noxious stimuli [1,4,5]. Higher-frequency stimulation leads to NMDA receptor activation, gradual increases in WDR neuronal discharge and a sustained burst of activity termed "wind-up". In this situation, WDR neurons become sensitized and hyperresponsive and transmit normal tactile responses as painful stimuli [1,5]. These central sensitizing changes are responsible for secondary hyperalgesia which increases the intensity of acute pain (refer to Chapter 5: hyperalgesia).

Reflexive intraspinal pathways connect primary nociceptor afferents to motor neurons and the autonomic efferents. Activation of these pathways leads to reflex skeletal muscular responses (muscle splinting/spasm) and autonomic responses (increased vascular tone hypertension, tachycardia, adrenal activation) [3].

A number of neurotransmitters, neuromodulators and their respective receptors are involved in the neurotransmission at the dorsal horn. They can be broadly classified into two groups.

1. Excitatory transmitters that are released from the primary afferent nociceptors or interneurons within the spinal cord.
2. Inhibitory transmitters that are released by interneurons within the spinal cord or supraspinal sources.

Most often more than one neurotransmitter is released at the same time. Aspartate and glutamate are excitatory amino-acids (EAAs) involved in pain transmission [4,5]. Glutamate is the main excitatory CNS neurotransmitter and mediates rapid, short-duration depolarization of second-order neurons. Peptides such as substance P and neurokinin are responsible for delayed long-lasting depolarization. EAAs act on various receptors, which principally include alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic

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acid (AMPA) receptors, *N*-demethyl-D-asprtate (NMDA) receptors, kaniate receptors (KA) and metabotropic glutamate receptors [3, 4]. EAAs activate AMPA receptors, which mediate sodium influx, cell depolarization and rapid priming of NMDA receptors. Substance P and other peptides bind to neurokinin receptors, leading to the activation of second messengers, culminating in changes in protein synthesis, genomic activation and slow activation of NMDA receptors (Figure 3.2). Activation of the NMDA receptor is associated with Ca^{2+} mobilization, and causes large and prolonged depolarization in the already partially depolarized neurons. Increase in intracellular calcium leads to the activation of multiple downstream pathways triggering second messengers including PG, inositol triphosphate (IP_3), cGMP, eicosanoids, nitric oxide and protein kinase C [4,5] (Figure 3.3). Persistent pathological activation of these pathways leads to central sensitization and potential chronic pain conditions. Metabotropic glutamate receptors are a family of receptors that are coupled to G-protein. Though they do not appear to be involved in acute pain, there is compelling evidence that they play a modulatory role in nociceptive processing, central sensitization and pain behavior.

Afferent impulses arriving in the dorsal horn are tempered and modulated by inhibitory mechanisms. Inhibition occurs through local inhibitory interneurons and descending pathways from the brain.

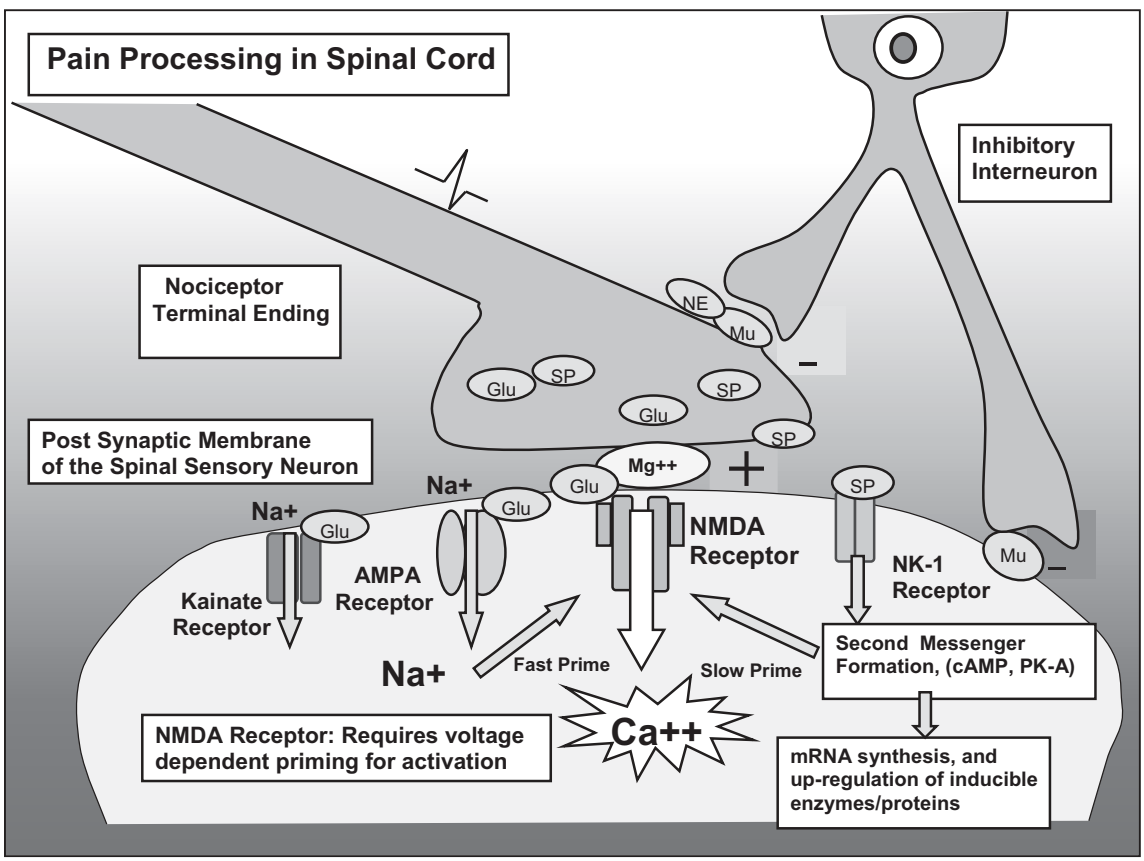

Figure 3.2. Targets of excitatory noxious mediators on second-order cells. Glutamate is the primary excitatory agonist for noxious transmission. Glutamate activates specific binding sites located on AMPA, kainate, and NMDA receptors. Ion channels on activated AMPA and kainate receptors allow Na^+ to enter and depolarize the cell. Changes in intracellular voltage rapidly prime the NMDA receptor and allow 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 up-regulates second messengers including cAMP and PKA which slowly prime and maintain excitability of NMDARs. Activation of second messengers in turn up-regulates inducible enzymes, initiates transcription of mRNA, and mediates synthesis of acute reaction proteins. These changes increase neuronal excitability and underlie subsequent plasticity. From: Sinatra RS. Pain pathways. In Sinatra RS, Viscusi G, de Leon-Casasola O, Ginsberg B, eds. *Acute Pain Management*. Cambridge University Press, 2009.

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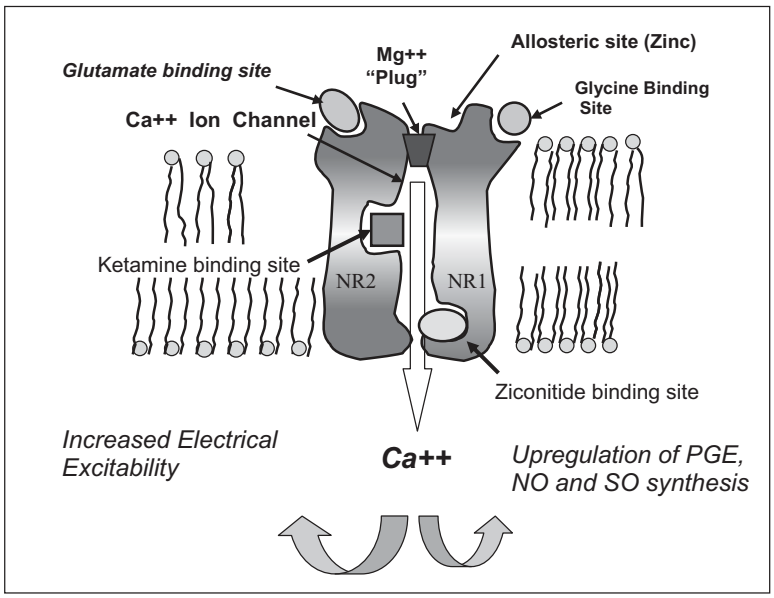

Figure 3.3. The NMDA receptor is a four-subunit, voltage-gated ligand-specific ion channel. The four subunits include two NR-2 units which contain glutamate binding sites and two NR-1 units which contain glycine binding sites and an allosteric site that is sensitive to zinc ions. Glutamate is the primary agonist of NMDR while 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. From: Sinatra RS. Pain pathways. In Sinatra RS, Viscusi G, de Leon-Casasola O, Ginsberg B, eds. *Acute Pain Management*. Cambridge University Press, 2009.

GABAergic and glycinergic interneurons are involved in tonic inhibition of nociceptive input and loss of these neurons is implicated in the development of chronic and neuropathic pain [5]. Endogenous opioids and noradrenergic pathways are also involved in inhibitory pain modulation.

Transmission of impulses from the spinal cord to the supraspinal structures

Several ascending tracts are responsible for transmitting nociceptive impulses from the dorsal horn to supraspinal targets. These include spinothalamic, spinoreticular, spinomesencephalic and spinolimbic tracts. The spinocervicothalamic and post-synaptic dorsal column are also involved in nociception. Of these, the spinothalamic tract is considered the primary perception pathway [1]. Axons traveling in the spinothalamic tract (STT) travel to several regions of the thalamus where pain signals diverge to broad areas of the cerebral cortex. The STT is divided into two tracts: the lateral neo-spinothalamic tract (nSTT) and the more medial paleo-spinothalamic tract (pSTT). The nSTT projects directly to the neothalamus. The neothalamus is a highly somatotopically organized region with cells conveying nociceptive impulses directly to the somatosensory cortex for rapid perception (localization) and prompt withdrawal from the noxious stimulus [1,5]. The lateral tracts are also discriminative and account for sensory qualities, such as throbbing or burning. The pSTT is a slow multisynaptic pathway that projects to the reticular activating system (RAS), periaqueductal gray (PAG), and medial thalamus. The medial thalamus is not somatotopically organized, and its cells project to the frontal and limbic cortex. The pSTT is associated with prolonged acute pain and chronic pain, and is responsible for diffuse, unpleasant feelings, and suffering long after an injury has occurred. Nociceptive impulses transmitted by the pSTT lead to persistent supraspinal responses affecting circulatory, respiratory, and endocrine function and underlie emotional and behavioral responses such as fear, anxiety, helplessness, and learned avoidance [1,5].

Descending control of pain

Descending neural pathways inhibit pain perception and efferent responses to pain. The cerebral cortex, hypothalamus, thalamus and brainstem centers (periaqueductal gray [PAG], nucleus rhaphe magnus [NRM] and locus coeruleus [LC]) send descending axons to the brainstem and spinal cord that modulate pain transmission in the dorsal horn. These axonal terminals either inhibit release of noxious neurotransmitters from primary afferents, or diminish the response of second-order neurons to the noxious input. Several neurotransmitters play critical roles in

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