Pathophysiology of Pain
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Nature of pain

Pain is described as an unpleasant sensation associated with a specific part of the body [1]. It is produced by processes that either damage, or are capable of damaging, the tissues. Such damaging stimuli are called “noxious” and are detected by specific sensory receptors called “nociceptors” [2]. Nociceptors are identified as C-fibers and Aδ-fibers. By definition, nociceptors respond selectively to noxious stimuli. These nociceptors are free nerve endings with cell bodies in the dorsal root ganglia and terminate in the superficial layers of the dorsal horn of the spinal cord. Here they relay messages by releasing neurotransmitters such as glutamate [3], substance P, and calcitonin gene related peptide (CGRP) [4,5]. These “pain” neurotransmitters will result in the activation of the second-order neuron via their corresponding receptor. The second-order neuron crosses the spinal cord to the contralateral side and travels up the spinothalamic tract until it reaches the thalamus. From there the third-order neuron is activated, traveling from the thalamus to the somatosensory cortex, which allows for the perception of pain. It should be mentioned that at the level of the spinal cord, second-order neurons result in the direct activation of lower motor neurons in the ventral horn of the spinal cord, provoking a reflex withdrawal from the noxious stimulus. Likewise, there are interneurons at the level of the spinal cord that will modulate the incoming pain information.

Neural processing of pain signals

Several steps can be identified in the neural processing of noxious signals that can lead to the experience of pain.
Transduction is the process by which noxious stimuli are converted to electrical signals in the nociceptors. Unlike other sensory receptors, nociceptors are not specialized from the structural point of view (in contrast to, eg, Pacinian corpuscles or Merkel’s disks), but rather exist as free nerve endings. Nociceptors readily respond to different noxious modalities such as thermal, mechanical or chemical stimuli, but nociceptors do not respond to non-noxious stimuli. Also in contrast to other types of sensory receptors, nociceptors do not adapt. That is, continued stimulation results in continuous or repetitive firing of the nociceptor and, in some cases, continued stimulation actually results in a decrease in the threshold at which the nociceptors respond (ie, sensitization of nociceptors) [6–8].

Nociceptive afferent fibers are typically pseudounipolar neurons, with a peripheral terminal and a central terminal. Neurotransmitters that are produced within the cell body (ie, in the dorsal root ganglia) are the same at both the central and peripheral ends of the nerve fiber. The neurotransmitters are released at both ends, participating in producing the pain signal peripherally, as well as in promoting events that lead to additional pain perception centrally. The release of neurotransmitters from the peripheral terminals of the afferent fibers is actually an “efferent” function of these afferent neurons. Peripheral release of neurotransmitter substances leads to the classic “axon reflex.” This reflex leads to peripheral changes that are recognized as indicators of pain: redness, swelling, and tenderness [9].

The pain produced can result from activation of the peripheral nociceptors by the released neurotransmitters, as well as by decreases in the threshold of response of the nociceptive fiber and surrounding nociceptors (nociceptor sensitization). In addition, “sleeping” or “silent” nociceptors, which are normally not active, are recruited after tissue injury has occurred and can then respond to a variety of stimulus modalities [10,11]. Once activated, these previously silent nociceptors fire persistently. When nociceptors become sensitized, they respond to noxious stimuli more vigorously, ie, the same stimulus now produces more pain. This is called hyperalgesia. Curiously, normally non-noxious stimuli can also produce pain, a phenomenon called “allodynia.”

More importantly, opioid receptors located on the peripheral nerve endings, when activated by either endogenous or exogenous opioids (ie, administration of morphine), show inhibition of afferent firing. Morphine acting at mu opioid receptors (G-protein coupled receptors) results in the indirect opening of potassium channels. Potassium with its positive charge flows out of the nociceptor leaving the inside of the neuron more negative. The enhanced intracellular negative charge hyperpolarizes the nociceptor, resulting in a decrease in nociceptor activity (ie, analgesia).

Transmission is the second stage of processing of noxious signals. Information from the periphery is relayed to the spinal cord, then to the thalamus, and finally to the cortex. Noxious information is relayed
mainly via two different types of primary afferent nociceptive neurons that conduct at different velocities.

*C-fibers* are nonmyelinated fibers that conduct in the range of 0.5 to 2 m/sec. Nociceptive C fibers transmit noxious information from a variety of modalities including mechanical, thermal, and chemical stimuli. For this reason, they are termed *C-polymodal nociceptors.*

*A-delta fibers* are thinly myelinated fibers that conduct in the range of 2 to 20 m/sec. All fibers respond to high-intensity mechanical stimulation and are therefore termed *high-threshold mechanoreceptors.* Some, but not all, A-delta fibers also respond to thermal stimuli; the latter are termed *mechanothermal receptors* [12].

These afferent fibers then synapse on a second-order neuron in the superficial layer of the spinal cord. This second-order neuron will send its axon across the midline and form the ascending spinothalamic tract that leads to the thalamus. It is in the thalamus that the second-order cell synapses with the third-order cell that projects to the sensory cortex.

The second-order cells in the spinal dorsal horn also have the capacity to change their response patterns in the circumstance of sustained discharge of afferent fibers (as would occur in the setting of an injury). Under these circumstances, these cells respond at lower thresholds and form inputs over a broader area in the periphery (ie, have expanded “receptive fields”). In other words, the second-order cells become “sensitized.” This is termed “central sensitization” and also contributes to the phenomena of hyperalgesia and allodynia [13].

Once the nociceptive afferents have terminated in the dorsal horn of the spinal cord, they transmit the signal from the periphery by releasing specific neurotransmitters that are associated with pain. One of the most important neurotransmitters for pain and the primary afferent is glutamate, which can interact with both N-methyl-D-aspartate (NMDA)-type and non-NMDA excitatory amino acid receptors. Another important transmitter associated with the transmission of pain is an 11–amino acid peptide called substance P, which interacts with the tachykinin receptor family (G-protein coupled receptors).

(3) **Modulation** is a third and critically important aspect of the processing of noxious stimuli. This process represents changes that occur in the nervous system in response to noxious stimuli and allows noxious signals received at the dorsal horn of the spinal cord to be selectively *inhibited* so that the transmission of the signal to higher centers is modified. An endogenous pain modulation system consisting of well-defined *intermediate neurons* within the superficial layers of the spinal cord and *descending neural tracts* can inhibit transmission of the pain signal [14]. Endogenous and exogenous opioids can act on the presynaptic terminal of the primary afferent nociceptor via the mu opioid receptor by *indirectly* blocking voltage gated calcium channels as well as opening potassium channels. The inhibition of calcium
entry into the presynaptic terminal as well as the efflux of potassium (hyperpolarization) results in the inhibition of pain neurotransmitter release from the primary afferent fibers, hence analgesia. Opioids have a second site of action at the level of the spinal cord. Opioid receptors on the postsynaptic nerve (the second-order neuron), when activated by an opioid, indirectly open potassium channels resulting in hyperpolarization of the nerve.

Activation of the cortical descending neural system is thought to involve the supraspinal release of neurotransmitters including beta-endorphins and enkephalins [15]. These peptides represent two families of endogenous peptides that are believed to produce pain relief, mainly under situations of stress. This is critically important to you as a physician because when you relieve your patients’ pain with narcotics, you are giving drugs that mimic the actions of these endogenous neurotransmitters.

(4) **Descending modulatory systems:** Activation of the descending system by endorphins occurs through specific receptors called “opioid receptors.” These systems are activated in and around the periaqueductal gray (PAG) region of the midbrain. Such neurons then project to sites in the medullary reticular formation and the locus ceruleus (the major source of serotonin and norepinephrine cells in the brain, respectively) through uncertain circuitry (probably through disinhibition, that is, inhibition of a tonically active inhibitory interneuron). These descending fibers then project to the dorsal horn of the spinal cord along a tract called the dorsolateral funiculus (located in the dorsolateral portion of the spinal cord) to synapse with either the incoming primary afferent neuron, the second-order pain transmission neuron, or interneurons. These descending pain modulatory neurons either (1) release neurotransmitters in the spinal cord, especially serotonin (5HT) and norepinephrine (NE) or (2) activate small opioid-containing interneurons in the spinal dorsal horn to release opioid peptides (again through disinhibition). The released NE and 5HT act to (1) directly inhibit the release of pain transmitters from the incoming nociceptive afferent signal, and (2) to inhibit the second-order pain transmission cell. Activation of the descending pain modulatory system is a good example of why subjects report not feeling pain under conditions of stress, or perhaps other situations, where even though the pain is felt, the degree appears to be greatly modulated [16–18].

**Summary of sites of opioid action:** We can identify four sites where opioids can act to relieve pain. When you give morphine or other opiates to patients you are (1) activating the opioid receptors in the midbrain and “turning on” the descending systems (through disinhibition), (2) activating opioid receptors on the second-order pain transmission cells to prevent the ascending transmission of the pain signal, (3) activating opioid receptors at the central...
terminals of C-fibers in the spinal cord, preventing the release of pain neurotransmitters, and (4) activating opioid receptors in the periphery to inhibit the activation of the nociceptors as well as inhibit cells that may release inflammatory mediators.

**Intracellular mechanisms of opioid analgesia**

Recent cloning has identified three distinct genes, one encoding for each of the three (mu, delta, kappa) opioid receptors [19–22]. All three receptors belong to the G-protein coupled receptor (GPCR) family. Agonist binding to opioid receptors leads to a conformational change in the opioid receptor itself. This conformational change results in the activation of an intracellular protein called a G-protein. The G-protein is made up of three separate protein subunits termed alpha, beta, and gamma. The alpha portion of the G-protein in an unactivated state associates with guanosine diphosphate (GDP), hence earning the name G-protein. Typically the alpha portion with its GDP will bind with the beta and gamma subunits and exist as an intracellular trimeric protein. Although there are more than 100 different types of G-protein coupled receptors, it is thought that the diversity of the G-protein subunit combinations offer diversity among agonist intracellular messages. When an opioid binds to an opioid receptor, the opioid-bound receptor undergoes a conformational change in the receptor. This results in the exchange of the GDP for a guanosine triphosphate (GTP) on the Gα subunit. It is this exchange of GDP for GTP that activates the G-protein complex. Opioid receptors typically couple to a Gαi subunit, and once the exchange of GDP for GTP has occurred, the αi subunit will dissociate from the βγ subunit and inhibit the activity of adenylate cyclase, a nearby membrane bound enzyme. Under resting conditions, adenylate cyclase converts ATP into cAMP at some basal rate. cAMP acts as a second messenger within the cell resulting in several events including the activation of protein kinases and gene transcription proteins. Opioid receptor activation by an opioid will result in the activation of the Gαi subunit and inhibit adenylate cyclase enzyme, hence significantly decreasing intracellular basal levels of cAMP. This opioid via opioid receptor–induced decrease in cAMP indirectly results in the inhibition of voltage dependent calcium channels on presynaptic neurons. These voltage dependent calcium channels are important in the release of neurotransmitter and transduction of neuronal communication. Opioid receptors located on the presynaptic terminals of the nociceptive C-fibers and Aδ-fibers, when activated by an opioid agonist, will indirectly inhibit these voltage dependent calcium channels via decreasing cAMP levels hence blocking the release of pain neurotransmitters such as glutamate, substance P, and CGRP from the nociceptive fibers resulting in analgesia.

In addition to the indirect inhibition of voltage-gated calcium channels by opioid receptors, the βγ subunit of the G-protein will open inward rectifying potassium (GIRK) channels allowing K⁺ to flow down its concentration
gradient and out of the cell carrying its (+) charge. This results in a more negatively charged environment within the cell termed hyperpolarization. This opioid-induced hyperpolarization results in a decrease in cell excitability hence attenuating neuronal transmission [23].

**Chronic pain**

Chronic pain states, typically represented as inflammatory or neuropathic in origin, are characterized by enhanced perception of pain to a nociceptive stimulus (ie, hyperalgesia) and the novel perception of a normally innocuous stimulus as being painful (ie, allodynia). Our understanding of the mechanisms that drive these abnormal, enhanced pain states has grown considerably, and it is understood that chronic pain states depend in part on sensitization of the spinal cord, the activation of nociceptive pathways projecting to medullary and midbrain sites, and the activation of descending pain facilitatory systems. The latter appear to be essential in maintaining a sensitized state of the spinal cord.

Spinal sensitization has been thought to be a direct result of increased primary afferent discharges into the spinal cord that maintains a state of excitation. Injured nerves show spontaneous, ectopic discharges from injury-induced neuromas, and mechanical stimulation of the neuromas elicit sensations ranging from minor dysesthesias to intense pain [24–26]. Spontaneous ectopic discharge was generated in the dorsal root ganglion (DRG) of the injured nerves that remained after excision of the neuroma [27–29]. The generation of ectopic action potentials and spontaneous discharges from injured peripheral nerves increased within the immediate postinjury period and were maximal within 1 week of the injury, they declined very rapidly within 3 weeks, and were essentially lost within 10 weeks [30–32]. In contrast, behavioral manifestations of nerve injury endure for months after the initial injury [33–35]. Current evidence indicates that the initial discharges initiate a state of central sensitization, but neuroplastic changes within the central nervous system (CNS) maintain the long-term sensitized status of the spinal dorsal horn [33,36,37]. The neuroplastic activation of ascending and descending components of a pain facilitatory system is described.

**Primary afferent inputs and spinal sensitization**

The augmented primary afferent activity in the immediate aftermath of nerve injury produces a state similar to long-term potentiation, commonly referred to as spinal sensitization [38,39]. A specific type of sensitization may be suggested by the phenomenon of wind-up, which is observed as progressively increasing responses of spinal dorsal horn neurons following repetitive electrical stimulation of C-fibers [40,41]. This phenomenon implies
that an initial stimulus produces sufficient excitation of post-synaptic cells and that these cells are not fully repolarized before the next stimulus arrives, and are thus primed to produce an enhanced response. Importantly, wind-up is nociceptive-specific [40–42]. The slow depolarizations of these dorsal horn neurons allow the development of temporal summation to inputs from primary afferent C-fibers, which may translate as increased pain [43,44].

These observations correlate well with studies performed with natural stimuli. Noxious stimuli applied to the skin enhance the excitability of dorsal horn units such that responses to subsequent stimuli are exaggerated, and repetitive C-fiber conditioning stimuli caused prolonged flexion reflexes in rats [44,45]. The persistent spontaneous afferent discharges after peripheral nerve injury are also believed to produce a similar sensitized state, leading to the enhanced pain observed in the neuropathic state [39,46–48].

Evidence for increased primary afferent activity is supported by microdialysis studies showing that the release of glutamate and aspartate from primary afferents is increased in response to intradermal capsaicin, formalin, or repeated electrical stimulation of C-fibers [49–51]. In a recent study employing microdialysis, it was found that spinal administration of NMDA elicited a long-lasting release of prostaglandin PGE2 and, subsequently, of excitatory amino acids. Spontaneous and stimulus-evoked release of substance P, CGRP, and glutamate from primary afferent terminals is increased after peripheral nerve injury [52–54]. The increased release of excitatory neurotransmitters from primary afferents, including glutamate, substance P, and CGRP, promotes the sensitization of target neurons and can lead to hyperalgesia by virtue of the enhanced responsiveness of the excited cell [55,56]. Primary afferent outflow is increased by glutamate acting at excitatory presynaptic NMDA autoreceptors on the primary afferent terminals [57,58]. This increase in primary afferent outflow amplifies the activity of the second-order neurons, which release nitric oxide (NO) and PGE2 that then promote further release of glutamate and excitatory neuropeptides from primary afferent terminals [59,60]. Taken together, these studies indicate that repeated or persistent noxious stimuli can cause the enhanced outflow of excitatory neurotransmitters that may interact and potentiate their excitatory functions, setting the stage for the development of central sensitization.

**Descending pain facilitatory pathways maintain central sensitization**

The rostral medial medulla (RVM) is considered to be the final common relay with respect to nociceptive processing and modulation, and receives inputs from the spinal dorsal horn as well as from the cortex [61–63]. The RVM’s role in modulating a pain inhibitory system has long been recognized; it is now realized that the RVM also acts as a source of descending facilitation of nociceptive inputs at the level of the spinal dorsal horn [37,64–68]. Electrical stimulation applied in the nucleus raphe magnus of
the RVM and surrounding tissue elicited excitatory responses in neurons of the spinal dorsal horns [69]. Although focal electrical stimulation of the RVM at high current intensities inhibits behavioral and electrophysiologic responses to nociceptive stimuli, stimulation at low intensities actually promote nociceptive responses [70,71]. Similarly, microinjection of glutamate, neurotensin, or cholecystokinin (CCK) into the RVM promotes a perceived noxious behavioral response [70–73]. Manipulations that attenuate RVM activity have blocked enhanced nociception caused by a variety of methods. Hyperalgesia induced by naloxone-precipitated withdrawal was blocked by the microinjection of lidocaine into the RVM [74]. Taken together, these observations indicate the existence of an endogenous pain facilitatory system that arises from the RVM [75].

Converging lines of evidence suggest that the development of abnormal pain states depend on the establishment of descending facilitatory mechanisms arising from the RVM. The application of a noxious thermal stimulus applied to the tail facilitated the hindpaw withdrawal reflex, increased electrical cell activity of the RVM, and was abolished by lidocaine microinjected into the RVM [76]. These results are consistent with the hypothesis that behavioral manifestations of chronic pain states is dependent on descending facilitation of spinal nociceptive input from the RVM since this region is a principal source of descending projections [61,66].

Considerable evidence now exists to show that the activation of descending facilitation from the RVM is essential to maintain the behavioral features of the neuropathic pain state [36,37,73,77,78]. Behavioral signs of neuropathic pain were blocked by lidocaine microinjected into the RVM [33,64,77,79,80]. The selective activation of on-cells with CCK microinjected into the RVM caused hypersensitivity to noxious and innocuous mechanical and thermal stimuli [81–83]. Electrophysiologic evidence strongly suggests that the population of RVM neurons that expresses the mu-opioid receptor is likely to drive descending facilitation [84–86]. The development and maintenance of neuropathic pain states may be linked to the increased expression or availability of CCK in the RVM.

Summary

The processing and interpretation of pain signals is a complex process that entails excitation of peripheral nerves, local interactions within the spinal dorsal horn, and the activation of ascending and descending circuits that comprise a loop from the spinal cord to supraspinal structures and finally exciting nociceptive inputs at the spinal level. Although the “circuits” described here appear to be part of normal pain processing, the system demonstrates a remarkable ability to undergo neuroplastic transformations when nociceptive inputs are extended over time, and such adaptations function as a pronociceptive positive feedback loop. Manipulations directed to
disrupt any of the nodes of this pain facilitatory loop may effectively disrupt the maintenance of the sensitized pain state and diminish or abolish neuropathic pain. Understanding the ascending and descending pain facilitatory circuits may provide for the design of rational therapies that do not interfere with normal sensory processing.

References


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