Basic Anatomy and Physiology of Pain Pathways

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• Hyperalgesia • Alloynia • Peripheral sensitization • Spino-thalamic tract • Gait control theory • Descending systems

INTRODUCTION
The pain pathways form a complex, dynamic, sensory, cognitive, and behavioral system that evolved to detect, integrate, and coordinate a protective response to incoming noxious stimuli that threatens tissue injury or organism survival.1 This defense system includes both the primitive spinal reflexes that are the only protection for simple organisms all the way up to the complex emotional responses humans consciously and subconsciously experience as pain. The mental representation of pain is stored as both short-term and long-term memory and serves as an early warning avoidance system for future threats.1 When severe, mental anguish may be projected with a physical complaint or symptom. Although many of the basic structures of the pain pathways have been defined, a more complete understanding of the interactions that would enable the development of targeted therapies remains elusive.

PERIPHERAL SENSORY SYSTEM AND MECHANISMS OF SENSITIZATION
The location, intensity, and temporal pattern of noxious stimuli are transduced into a recognizable signal through unmyelinated nociceptors at the...
terminal end of sensory neurons. Through physical deformation or molecular binding, membrane permeability and, consequently, the membrane potential fluctuate.\(^2\) If depolarization reaches a critical threshold, an action potential is propagated along the length of a sensory nerve toward the spinal cord.

Most sensory receptors respond to a single stimulus modality. Nociceptors, designed to detect tissue injury, are excited by three noxious stimuli: mechanical, thermal, and chemical. Mechanical stimuli deform the receptor to augment receptor ion permeability,\(^3\) whereas chemicals such as bradykinin, serotonin, histamine, potassium ions, acids, acetylcholine, and proteolytic enzymes\(^2\) bind directly to receptors to influence membrane permeability. Prostaglandins and substance P (SP) do not directly activate pain receptors but indirectly influence membrane permeability.

Nociceptive receptors sit at the ends of pseudounipolar sensory neurons with cell bodies in the dorsal root, trigeminal, or nodose ganglia (Fig. 1).\(^3\) Pain receptors are unencapsulated free nerve endings. Sensory nerve fibers range from 0.5 to 20 μm in diameter and can conduct impulses at speeds ranging from 0.5 to 120 m/sec. Larger diameter neurons conduct information at a faster speed.\(^5\) Nerve fibers are divided up into two main categories: type A, which are medium to large diameter myelinated neurons, and type C, small diameter unmyelinated neurons.\(^2\) Pain transmission is divided into two categories, fast and slow. A-delta fibers detect and transmit pain quickly. These fibers are relatively small (1–6 μm), thinly myelinated neurons that can conduct at speeds of 6 to 30 m/sec.\(^3\) C fibers are small (<1.5 μm) and unmyelinated, conducting pain at 0.5 to 2 m/sec.\(^2\) A-beta are large (6–12 μm) myelinated fibers that are high speed (30–70 m/sec).\(^2\) They have encapsulated receptors and transmit information about touch, pressure, and vibration.\(^3\) Most A-delta fibers are associated with thermo or mechanoreceptors. C fibers can be associated with polymodal receptors, suggesting a role in monitoring the overall tissue condition.\(^3\)

Innocuous stimuli may elicit excitation of neurons in the peripheral nociceptive system following repeated injury or inflammation. These pathologic changes contribute to phenomena such as sensitization, allodynia, or hyperalgesia. In peripheral sensitization, neurons fire at a lower threshold and have greater response magnitude to a given stimuli,\(^5\) may fire spontaneously, or may even have altered receptive field areas.\(^6,7\) This occurs via inflammatory mediators, including bradykinin, prostaglandins, serotonin, tumor necrosis factor alpha, and histamine.\(^8\) After integration in the brainstem, descending pronociceptive and antinociceptive pathways contribute to peripheral sensitization. When the function of these pathways becomes abnormal, chronic pain may occur.

The expression of molecules, including GABA, histamine, serotonin, and opiate receptors in nociceptive neurons, may be modulated by inflammation or injury.\(^8\) Near the receptor there is a high concentration of sodium channels. Increased channel expression can alter sensitivity of nerve endings to noxious stimuli by modulating integration of stimuli and threshold potential for action potential generation.\(^3\) Increased sodium channel expression has been reported after nerve injury and may contribute to hyperexcitability and associated abnormal sensation.\(^9\) C fibers have long response times and are slow to adapt. Because of this, they show summation of response to noxious stimuli in the presence of tissue injury,\(^10\) perhaps contributing to sensitization and hyperalgesia.

Inflammation results in an upregulation of SP, including in A-beta fibers.\(^11\) In this setting, A fibers may play a role in central sensitivity, perhaps contributing to hypersensitivity.\(^11,12\) A-beta fibers terminate in lamina III of the spinal cord where SP receptors are present. They may contribute to ongoing activation of SP expressing nociceptive neurons in chronic pain states.\(^12\)

**DORSAL ROOT GANGLIA**

Sensory neuron cell bodies are located in the dorsal root ganglia (DRG). DRG neurons are classically pseudounipolar; one process extends into the peripheral nerve and the other process extends centrally, transmitting information through the dorsal root into the spinal cord. Each DRG contains thousands of unique sensory neuron cell bodies that are capable of encoding and then transmitting specific information gathered from external stimuli.\(^13\) Cells in the DRG are subclassified into peptidergic neurons and non-peptidergic neurons. Peptidergic neurons contain peptides such as SP, calcitonin gene–related peptide (CGRP), and somatostatin.\(^14\) Each DRG neuron is surrounded by glial cell cytoplasm. The surface of the DRG neuron cell bodies are covered with perikaryal projections that are invested in the surrounding glial cytoplasm, increasing the surface area.\(^15\)

The soma of DRG neurons synthesizes and transports the substances needed for neuron functioning to the far reaches of the axon terminals, including receptors, ion channels, as well as...
molecules essential for synaptic transmission. The most common neurotransmitter that is synthesized by DRG cells is glutamate; however, many DRG cells also express SP, which facilitates pain transmission. There are no direct synaptic connections between DRG neurons but their activity is indirectly modulated. After injury, DRG neurons may become innervated by postganglionic axons in a neurotrophin-mediated process. C fibers may also modulate DRG sensitivity by altering
intracellular calcium concentration affecting N-methyl-d-aspartate receptor configuration and sensitivity. Therefore, plastic reorganization of the DRG is one of the many mechanisms involved in pain sensitization and chronification.

**SPINAL CORD**

Most sensory fibers project from the DRG through the dorsal root and into the dorsal root entry zone (DREZ). There is evidence that the ventral roots also receive projections from unmyelinated fibers originating from DRG cells that are involved in sensation, including nociception, violating the Bell-Magendie law. At the DREZ, most unmyelinated and small myelinated axons project laterally to enter. Lissauer tract (see Fig. 1) fibers then extend vertically in this tract for several spinal segments before synapsing. Second-order neurons then cross to the opposite side, in the ventral segment before synapsing. Second-order neurons project to ventral posterolateral nuclei originating from DRG cells that are involved in visceral pain. It receives some direct input from A-delta fibers and may play a role in integration of nociception.

Dorsal horn (DH) nociceptive neurons form glutamatergic synapses that may also release neuropeptides, including SP, CGRP, enkephalin, and serotonin. WDRs dynamic range neurons transmit both noxious and nonnoxious information. WDR display graded responses, proportional to the input stimulus by firing at a higher frequency. WDR neurons have a large receptive field, including a center that responds to both noxious and nonnoxious stimuli and surrounding area responds to noxious stimuli only. The large receptive fields of WDR neurons reflect its proposed integrative function that may contribute to allodynia through increased and disproportionate responsiveness to nonnoxious stimuli.

Lamina II (substantia gelatinosa) may play a role modulating spinothalamic and spinobulbar projection neurons via its numerous inhibitory interneurons that primarily release GABA. C fibers and A-delta fibers are the primaryafferent inputs of lamina II. Lamina II inhibitory neurons then arborize locally to other lamina, including I, II, III, and IV. There are very few projection neurons in lamina II. It has been hypothesized that disinhibition related to the functional loss of lamina II inhibitory neurons facilitates chronic neuropathic pain.

A-beta fibers project to lamina III and IV. Layer III also receives A-delta fiber mechanoreceptive input and may have sprouting of A-category neurons to lamina I and II after injury, possibly contributing to chronic pain and allodynia. Some layer IV neurons project to layer I, which contributes to integration of sensation. Lamina V receives input from A-delta and C fibers and neurons project to the spinothalamic tract (STT). Lamina V also contains a large number of WDR neurons with projections to reticular formation, periaqueductal gray, and medial thalamic nuclei, forming part of the mesial pathways that mediate the emotional characteristics of pain. Lamina X surrounds the spinal cord central canal. The function of this region is less well defined but likely is involved in visceral pain. It receives some direct input from A-delta fibers and may play a role in integration of nociception.

**SPINOTHALAMIC PATHWAYS**

The STT is oriented vertically along the ventrolateral portion of the spinal cord (see Fig. 1). It serves as the main conduit from the peripheral nerves to the brain by transmitting pain, temperature and deep touch signals to the thalamus. It receives projections from contralateral lamina I and IV-VI and is composed of two tracts: one dorsolateral, carrying axons from the superficial lamina, and the other ventrolateral, carrying axons from deeper lamina. Most projections are contralateral, although there is also an ipsilateral contribution. There is somatotopic organization of the STT with the lower limbs dorsolaterally and upper body and limbs positioned ventromedially. Cells projecting to ventral posterolateral nuclei originate from laminae II and V. Lateral STT neurons have small contralateral receptive fields and are most likely involved in sensory-discriminative aspects of pain signaling. Cells projecting to the medial thalamic nuclei originate from the deep dorsal laminae (ie, layer V; see above discussion) and
ventral horn. The medial STT relays the motivational and affective components of noxious stimuli. These neurons have large receptive fields to support this purpose.

The paleospinothalamic tract projects to brainstem reticular formation, hypothalamus, and thalamic nuclei. Neurons in lamina VI, VII, and VIII have direct projections to reticular formation nuclei, some of which are bilateral. Neurons in the marginal zone, nucleus proprius, and lateral reticulated area project both to thalamus and hypothalamus. These neurons include both WDR neurons and nociceptive-specific neurons. They project to reticular formation, periaqueductal gray (PAG), and medial thalamic nuclei, and may also be involved in motivational-affective component of pain.

Most of the projections to the reticular formation arise from A fibers, although A and C fiber innervation has been described. Reticular formation response is proportional to noxious characteristics of the stimulus. The spinoreticular tract travels with STT in ventrolateral spinal cord. Fibers largely terminate in ventral medial portion of the medulla reticular formation, medullae oblongatae centralis, pars ventralis, and nucleus gigantocellularis. These cells have large receptive fields and exhibit heterotopic convergence. This tract functions to activate homeostatic mechanisms in brainstem autonomic centers as well as to provide input to antinociceptive systems and motivational-affective systems.

The spinomesencephalic tract originates in laminae I and IV-VI, with some contribution from lamina X and ventral horn. It projects to areas including periaqueductal gray, pretectal nuclei, red nucleus, Edinger-Westphal nucleus, and interstitial nucleus of Cajal. Neurons in this tract are nociceptive, and generally have large, complex receptive fields. They are involved in aversive behavior and orientation responses, and may activate descending antinociceptive systems.

The 1965 gate control theory of pain by Melzack and Wall proposed that there were three spinal cord systems involved in pain transmission: the substantia gelatinosa, dorsal column fibers, and central transmission cells in the DH (Fig. 2). The substantia gelatinosa functions as a gate that modulates signals before they reach the brain.

Fig. 2. Illustration of the gate control theory of pain. The substantia gelatinosa (SG) serves as a gate in the spinal cord that closes in response to large fiber (L) inputs, suppressing pain transmission. Alternatively, small fiber inputs open the gate or facilitate pain transmission. The summated pain signal then ascends in a projection neuron (P) via the spinothalamic (S) tract. This theory has since been revised to include the role of higher cortical processing to explain pain perception. (Courtesy of the Cleveland Clinic Foundation, Cleveland, Ohio.)
Large diameter fibers have inhibitory effects to “shut the gate” whereas small diameter fibers carrying noxious stimuli open the gate to pain transmission. In a simplistic view of this model, rubbing of the injured area promotes proprioceptive (ie, large diameter) fiber input and reduces pain perception. The gate-control theory has been criticized and revisited because it is inherently incomplete in its view of the nervous system. Nevertheless, it needs to be recognized for its key role in advancing the understanding of pain perception five decades ago and promoting the development of modern neurostimulation for pain management.

THALAMUS

The sensory thalamus is divided into nuclei that roughly maintain the segmentation of the noxious and innocuous divisions from the periphery. The ventral caudal (Hassler’s nomenclature) or ventro-posterior (VP) nucleus thalamic nuclei are the most direct subcortical relay site for the STT and the trigeminal thalami ctract (TTT) before relaying pain signals to the primary sensory cortex and other cortical regions. Glutaminergic projections from the dorsal column nuclei and from the DH via the STT synapse on neurons in the VP. The VP is somatotopically organized with neurons excited by face stimulation medially (VPM) and arm and leg laterally (VPL). Cutaneous sensation from the distal extremities is located ventrally and truncal representation dorsally in the VP. The VP can be further subdivided into a core that responds to mechanical, nonnoxious stimuli and a posterior inferior region that transmits nociceptive signals. Deep brain stimulation (DBS) of VP (Vc [Ventralis caudalis]) has been studied as a target to treat intractable, chronic pain.

VP also receives WDR nociceptive neurons with large receptive fields and responses proportional to stimulus intensity. Some of these neurons project to areas 3b and 1. The ventralis posterior inferior (VPI) nucleus, which lies inferior to VPL and lateral to VPM, has larger receptive fields than VPL but retains somatotopic organization. It projects to SI. The ventromedial posterior (VMpo) nucleus plays an important role in pain processing. It receives projections from lamina I STT neurons and is composed of nociceptive-specific neurons with small, contralateral, receptive fields. VMpo neurons project to the insula and area 3a.

The central nuclei of the thalamus are also involved in pain transmission. Neurons from the STT terminate in the intralaminar nuclei, including the central medial nuclei, parafascicularis, medial dorsal nucleus, and in the centralis laterals. These midline intralaminar thalamic nuclei also receive indirect projections important in pain processing from the parabrachial nucleus and brainstem reticular nuclei. Neurons in these thalamic nuclei have large and nonspecific receptive fields that integrate pain signals and initiate protective responses such as arousal in response to noxious stimuli.

The receptive fields of the specific nuclei of the thalamus have been shown to reorganize following injury. This thalamic reorganization subsequently influences downstream cortical reorganization. Thalamic neurons with receptive fields adjacent to the receptive fields of an injured area gain a larger representation in the homunculus. Decreased excitatory input or increased inhibitory input leads to neuronal hyperpolarization and aberrant bursting. For example, membrane hyperpolarization secondary to loss of excitatory STT input following spinal cord injury contributes to cell bursting interspersed with periods of low firing between bursts. This irregular firing is associated with development of central pain following spinal cord injury. Patients with neuropathic pain also demonstrate detrimental thalamic reorganization that may lead to innocuous thermal stimuli encoded as nociceptive signals.

In some patients with chronic pain, the surface encephalographic recordings demonstrate a recognizable shift from normal alpha rhythms to low-frequency theta rhythms. This cortical dysrhythmia is best observed between the medial thalamic nuclei and the insular, parietal opercular, and cingulate cortices. Simultaneous thalamic recordings in patients with chronic pain show an increase in low frequency, coherent thalamocortical activity.

CORTICAL AREAS

Painful stimuli activate distant cortical regions, including the primary somatosensory cortex (SI; Brodmann areas 3a/b, 2, 1, postcentral gyrus), secondary somatosensory cortex (SII), insula, orbitofrontal cortex, dorsal-lateral prefrontal cortex, extended amygdala, and cingulate cortex. The SI is arranged with somatotopic organization of nociceptive signals that follows Penfield’s homuncular pattern. Projections from the VPM and VPL nuclei synapse directly in the SI. These neurons in SI demonstrate a graded response according to intensity of noxious stimulus. This suggests that SI is involved in the discriminative quality of pain. The SII (parietal operculum) receives projections from ventrobasal thalamus, the VPM-VPL, and from the SI, as well as contralateral input.
Neurons in both the SII and Broadmann’s area 7 also show responses proportional to magnitude of noxious stimuli.27

C fibers stimulation is associated with activation of the contralateral SI, in particular area 3a, the SII, and ipsilateral SII.34 Similarly, activation of A-group fibers causes activation of the contralateral SI followed by SII.34 This nociceptive input mainly projects to cortical layers III and IV.3 The insula receives input from SI, SII, VPI, pulvinar, central median and parafascicular nuclei, medial dorsal nucleus, and Vmpo.27 It demonstrates a graded response proportional to intensity of noxious stimulus and is likely involved in the sensory-discriminative processing of pain.27 The insula projects to limbic structures such as amygdala and perirhinal cortex.27 These widespread connections of the insula are involved in higher order pain processing and require consciousness for activation with painful stimuli.3 Insula lesions have been associated with altered motivational-affective responses to pain.

The anterior cingulate cortex (ACC) and middle cingulate cortex receive projections from the medial and intralaminar thalamic nuclei and the VPI. These areas are activated with noxious stimuli that elicit an affective or motivational response to pain. Lesioning of the cingulate cortex attenuates these motivational-affective characteristics of pain, particularly in patients with chronic cancer pain.27 Increased ACC activity may be seen in those with chronic pain.39

In the late 1990s, Melzack1 revisited the original gate control theory and proposed the neuromatrix theory, adding higher cortical functions as key elements of pain transmission and interpretation. It postulates that individuals possess a genetically determined neural matrix that is shaped and modulated by sensory input. The neuromatrix contains parallel and interacting thalamocortical and limbic loops. Nodes in the sensory signaling circuitry are predetermined pattern generators and contribute to abnormal nociception. The structure and output of the neuromatrix is also controlled by cognitive and affective spheres. Thus, the final pain experience is determined not only by sensory input but also by behavioral and cognitive interpretation of pain, which includes prior experiences, injuries, and cultural background.

DESCENDING SYSTEMS

Descending pathways originating in the brain regulate incoming signals from noxious stimuli primarily through synapses on DH neurons (Fig. 3). Facilitative regulation amplifies the response as observed in sensitization. Alternatively, inhibitory regulation suppresses ascending pain signals during life-threatening events and other periods of extraordinary stress. These descending pathways include several relevant supraspinal structures: the rostral ventromedial medulla (RVM), the dorsolateral pontomesencephalic tegmentum, and the PAG region. The descending systems exert their effect predominantly in lamina I and II in the DH through the release of the monamine-serotonin, norepinephrine, and dopamine.40 The monoamine released and receptor subtype will dictate an antinoceptive or pronociceptive effect. Dysregulation of these descending systems are believed to play a major role in chronic pain states.

The PAG-RVM-DH pathway is a descending pain modulatory system that has been well characterized. Stimulation of the PAG, first reported in the 1960s, induces analgesia and blocks the response of lamina V interneurons to noxious stimuli.41,42 This net analgesic effect of PAG stimulation depends, in part, on the release of serotonin from neurons activated in the RVM.43 Functional depletion of 5-hydroxytryptamine (5-HT) from RVM neurons has been shown to inhibit persistent pain in a rat model.44 In addition to these serotoninergic neurons, three additional neuron subtypes found in the RVM regulate pain transmission. Unlike the 5-HT neurons, the bulk of these neurons are GABA-ergic. ON-cells are inhibited by opioids and excite DH neurons to facilitate nociceptive pain. OFF-cells are excited by opioids and inhibit DH neurons to attenuate nociceptive pain. The function of the third population of neurons, NEUTRAL-cells, is not known. These three neuron types project to the spine and branch locally within the RVM.

The PAG also has direct projections to the spinal cord and additional indirect projections via the reticular formation and the parabrachial nuclei. Furthermore, the PAG has widespread connections with structures in rostral midbrain, diencephalon, and telencephalon.26 The PAG projects to central nuclei of the thalamus, including centrolateral, paraventricular, parafascicular, and central medial areas, along with several dopaminergic areas, including ventral tegmental area and substantia nigra pars compacta. The PAG is likely also involved in the ascending modulation of nociception and integration of behavioral responses.28

Descending noradrenergic systems originating from the pontine A7 cell group (subcoeruleus) and A5, A6 (locus coeruleus) also show bidirectional pain control.45 This pontine noradrenergic system is at least partly influenced by direct projections from neurons that release SP located in the RVM.46 The regulation of pain signals transiting through the DH of the spinal cord is also under...
the control of dopaminergic descending neurons from the periventricular region of the hypothalamus (A11). The dopamine receptor subtype expressed by primary afferents or DH neurons in lamina I dictate an antinociceptive or pronociceptive effect. Dysfunction of this descending pain system may lead to chronic pain conditions; however, this descending dopaminergic system is another potential target for treatment.

The descending endogenous opioid pain modulation system also augments pain processing. Activation of opioid receptors in the brain, specifically the mu receptor, blocks pain transmission centrally in the brain but also will activate descending systems. Opioid receptor binding alters membrane conductance and protein phosphorylation states. Dynorphin is found in laminae I and V as well as PAG and midbrain reticular formation. It hypothesized that dynorphin contributes to pain centralization.

The interactions of the descending systems are still being defined although several hypothesis have been proposed to explain certain abnormal pain states. For example, central sensitization is believed to involve an increase in the activity of the ascending pain pathway coupled with a decrease in activity in the descending inhibitory pathway. Similarly, the release of tonic inhibition at the DH is associated with chronic pain.

SUMMARY

Although the details underpinning the pain systems are debatable, the evolutionary advantage to
having an integrative pain system culminating in the conscious recognition of pain is not. When studied using modern neuroimaging or electrophysiological studies, the nature of the perceptual experience of pain still remains fragmented. This has unfortunately delayed the development of novel neurosurgical approaches to treat chronic non-cancer pain. Nevertheless, the surgical treatments represented in this issue have taken advantage of what is known currently and represent an important step forward for those patients with chronic pain.

REFERENCES