The Physiology and Processing of Pain

A Review

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Despite the many advances in our understanding of the mechanisms underlying pain processing, pain continues to be a major healthcare problem in the United States. Each day, millions of Americans are affected by both acute and chronic pain conditions, costing in excess of $100 billion for treatment-related costs and lost work productivity. Thus, it is imperative that better treatment strategies be developed. One step toward improving pain management is through increased knowledge of pain physiology. Within the nervous system, there are several pathways that transmit information about pain from the periphery to the brain. There is also a network of pathways that carry modulatory signals from the brain and brainstem that alter the incoming flow of pain information. This article provides a review to the physiology and processing of pain. (KEYWORDS: ascending pain pathways, descending modulation, pain, nociceptors)

Congress declared the years of 2000 to 2010 as the Decade of Pain Control and Research, yet pain continues to be a leading public health and nursing problem in the United States. Pain is the principal symptom causing patients to seek medical attention, affecting 1 in 5 Americans on any given day. It is estimated that pain accounts for 1 in 6 visits to a healthcare provider and the American Academy of Pain Management reports that uncontrolled pain is at epidemic proportions, with 50 million Americans suffering from some form of chronic pain and another 25 million experiencing acute pain caused by accident or surgical procedures each year. Studies estimate that 70 million visits to healthcare providers were motivated by pain and that 4.9 million people visited a healthcare provider for treatment of chronic pain, all at an estimated cost exceeding $100 billion. Further, pain patients and their families suffer from intangible costs related to the pain, such as decreased quality of life, depression, and interpersonal stresses.

Pain not only affects patients and their families, but also society and the economy as well. Beyond the cost of medical treatment, society bears the costs of increased healthcare utilization and lost productivity by patients in pain. More than two thirds of those living with chronic pain have had their pain for 5 or more years, often producing significant limitations on daily activity, and it is estimated that 36 million Americans missed nearly 4 billion work days due to pain, resulting in a substantial loss of work

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productivity and an estimated cost of $65 billion annually.\(^7\)

A critical step toward minimizing the physical, emotional, and financial drain on patients and caregivers is improving the clinical management of pain. When managing the care of a patient with pain, the advanced practice nurse must work together with the patient to establish a common treatment goal. In many cases, the goal of the treatment strategy may be to achieve maximal analgesia (the absence of a pain response to a noxious stimulus).\(^{10,11}\) However, when maximal analgesia is not possible, the treatment goal shifts to reducing the pain to a level that the patient finds tolerable and allows for the performance of normal activities of daily living. Upon establishment of the treatment goal, the next step is to develop a plan to meet that goal. A key factor that aids in the process of selecting the most appropriate treatment modalities, in addition to a thorough pain assessment, is an in-depth understanding of pain physiology. A thorough understanding of how pain is processed at each stage in the peripheral and the central nervous systems allows the treatment strategy to be tailored to meet the needs of the individual patient. This article provides a primer on major structures and processes involved in pain physiology.

□ What Is Pain?

When a region of the body is exposed to a tissue-damaging or potentially tissue-damaging insult, one experiences the unpleasant sensation of pain.\(^12\) Pain has been described as a multifaceted and highly subjective experience that is unique to each person. Pain is not only influenced by physiological processes, but also influenced by psychological and emotional processes as well. It has been reported that the intensity of pain can be influenced by contextual cues. For example, similar types of traumatic injury may be seemingly painless in certain situations and extremely painful in others.\(^{13,14}\) This phenomenon was first described by Beecher,\(^15\) who found that soldiers with severe wounds often reported little pain while civilians with similar injuries typically reported severe pain. The subjective nature of the pain experience led McCafferey\(^15\) to define pain as “whatever the experiencing person says it is, existing whenever the experiencing person says it does.”\(^7\) Pain has further been defined by the International Association for the Study of Pain (IASP)\(^10\) as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.”\(^6\)

Two broad categories of pain, acute and chronic, are seen in the clinical setting. Under these broad categories fall the subtypes of pain, which include inflammatory, neuropathic, cancer, etc. Acute pain tends to be of a short duration, typically has an identifiable cause, and is focal to the site of injury.\(^{10–15,16}\) Further, acute pain functions as an endogenous protective mechanism that signals the brain of the occurrence of real or potential tissue injury, thus prompting a protective response.\(^12\) Clinically, acute pain functions as a symptom, tends to be self-limited, and generally responds to a straightforward treatment plan with a good to excellent prognosis.\(^16\) However, pain can persist beyond the point of tissue healing and develop into a chronic and debilitating state. Chronic pain is unremitting, has no identifiable cause, spreads beyond the original site of injury, and serves no biological function.\(^{10–15,16}\) Clinically, chronic pain has the characteristics of a disease state, can produce psychological disturbances, requires complex treatment strategies, and typically has a poor prognosis.\(^16\)

□ Pain Transmission: The Ascending Pain Pathways

The ascending pain pathways transmit nociceptive information from peripheral tissues to the cerebral cortex for interpretation as pain. The ascending pathways are complex structures, involving both the peripheral (PNS) and central nervous systems (CNS).

Nociception

Nociception, the initial processing of pain, involves a system of mechanisms that encode and transmit the pain signal, along the ascending pathway, from the point of noxious stimulation in the periphery to higher
centers in the CNS, including the cerebral cortex where an awareness of the presence of pain occurs12 (see Figure 1). The first step in the complex pain process is the transduction of a noxious stimulus (nociception) by specialized nerves (nociceptors).17,18 Nociceptors are found in most organs and tissues in the body and are activated by either a noxious mechanical (touch or pressure), thermal (hot or cold), or chemical (endogenous or exogenous) stimulus12,17,18 (see Figure 2). The term noxious is applied to nociceptive stimuli because nociceptors are activated in response to strong stimuli that fall in the tissue-damaging range, whereas nonnociceptive mechanoreceptors, thermoreceptors, and chemoreceptors respond to milder stimuli that fall in a range below the tissue-damaging level.12,17,18 In addition to exogenous chemicals that stimulate nociceptors, a number of endogenous chemicals have been identified that can activate nociceptors, including potassium, bradykinin, serotonin, histamine, prostaglandins, and others.19–23

**Spinal Dorsal Horn**

When a noxious stimulus is transduced by a nociceptor, a signal is generated that is transmitted as an electrical action potential along small diameter A-delta (myelinated, fast transmission, sharp or pricking first pain)24,25 and C (unmyelinated, slow transmission, dull or burning second pain)25,26 primary afferent nerve fibers to the gray matter of the spinal cord (see Figure 2 inset). On cross-section, the spinal gray matter forms a butterfly shape and can be divided into 10 laminae, or layers, which are numbered I through
Figure 2. Pain transmission from peripheral tissues to the spinal cord. Noxious stimuli (thermal, chemical, or mechanical) that are applied to peripheral tissues activate nociceptors that are located within the tissues. The stimulus is transduced by the nociceptor to generate a nociceptive signal that is transmitted as an action potential along a primary afferent nerve to the dorsal horn of the spinal cord. Within the primary afferent nerve (inset), the signal can be transmitted rapidly by myelinated A-delta fibers or more slowly by unmyelinated C fibers. The dorsal root ganglion is part of the primary afferent nerve, located near the spinal cord, and contains the cell bodies of all fibers traveling within the nerve.

Figure 3. Structure of the spinal cord. The gray matter is a butterfly-shaped area in the center of the spinal cord. The gray matter contains unmyelinated nerve fibers and the cell bodies of the neurons. The spinal gray matter is surrounded by white matter, which is composed of myelinated nerve fibers. The central canal is a conduit for cerebral spinal fluid and runs the full length of the spinal cord. The spinal gray matter has two dorsal and two ventral horns. The dorsal horns, comprising the dorsal aspect of the gray matter bilaterally, are primarily responsible for receiving and transmitting sensory information. The ventral horns, comprising the ventral aspect of the gray matter bilaterally, are primarily responsible for sending motor information out to the periphery. Based on cellular organization, the gray matter can be divided into ten laminae (layers), which are numbered I-IX from dorsal to ventral. Lamina X surrounds the central canal.
transmitted to a discrete location within the area of pathology.

In the dorsal horn, the primary afferent fibers synapse (connect), either directly or indirectly (via interneurons), with second-order projection neurons and convey the nociceptive message through the release of a variety of neurotransmitters, such as the excitatory amino acid glutamate or the peptide substance P.12,31,32,33 After the nociceptive signal has been received in the dorsal horn, the information is transmitted to higher centers in the CNS by projection neurons.17,18,34,35

**Ascending Tracts**

The projection neurons transmit the nociceptive signal rostrally along the ascending pathways in the spinal cord to various supraspinal structures in the brainstem and diencephalon, including the medullary reticular formation, periaqueductal gray, parabrachial region, hypothalamus, thalamus, and various limbic structures.17,18,34,35

The function of the ascending pathways is simply the transmission of the nociceptive information. Within the supraspinal target structures of the ascending pathways, third-order neurons further process the nociceptive signal and transmit it to cortical and limbic structures, where the signal is interpreted as pain.12

The organization of and the neuroanatomy within the ascending pain pathways are quite complex.17,18,34,35 The most prominent and well-described of the ascending pathways is the spinothalamic tract (STT—spinal cord to thalamus), which is thought to transmit sensations of pain, temperature, and touch.12,17,18 The majority of the projection neurons that travel in the STT originate in the superficial laminae I and II and deeper laminae V of the spinal dorsal horn.36,37 Before ascending, the STT neurons decussate (cross midline) through the ventral white commissure (junction between two parts) to the opposite ventrolateral quadrant of the spinal cord white matter, where they ascend in the ventrolateral funiculus (VLF—bundle of nerve fibers) to the thalamus12,36,37 (see Figure 6a). A second prominent ascending pathway that is involved in pain transmission is the spinomesencephalic tract (SMT—spinal cord to mesencephalon), which originates in laminae I, II, and V of the spinal dorsal horn, decussates, and also travels in the VLF to the mesencephalon (also known as the midbrain)12,36,38,39 (see Figure 6b). Within the midbrain, the neurons in the SMT terminate in several areas, such as the periaqueductal gray (PAG) and nucleus cuneiformis, among others.18,39–41 A third tract that has also been shown to convey nociceptive information is the spinoreticular tract (SRT—spinal cord to reticular formation), which terminates in the reticular formation of the medulla12,17,18 (see Figure 6c). Though each ascending tract has a primary target structure, they also send collateral projections to other areas of the brainstem as they pass through.

When the projections from the spinal cord reach their targets, they synapse with third-order neurons that serve as relays and project to other regions within the brainstem, diencephalons, and forebrain.12,17 While the three pathways described above are thought to be the predominant pathways involved in pain transmission, they do not constitute a complete list of all ascending sensory pathways. A detailed description of the remaining pathways is beyond the scope of this review.
Figure 5. Synapse of the primary afferent fiber with a projection neuron in the dorsal horn. The primary afferent fiber (PAF) enters the spinal dorsal horn and synapses (A) directly with a projection neuron (PN; second-order neuron) or (B) with an interneuron (IN) that then synapses with a projection neuron. The pain signal is transmitted across the synapse by the release of neurotransmitters from the presynaptic neuron that cross the synaptic cleft and bind with receptors on the postsynaptic neuron.

Thalamus
The thalamus is thought of as the major supraspinal relay structure for the integration and transfer of ascending nociceptive information to the cerebral cortex. As such, the thalamus not only receives input from the

Figure 6. Ascending transmission tracts. (A) Spinothalamic tract (STT). The projection neurons that form the STT originate predominantly in laminae I, II, and V of the spinal dorsal horn. The STT neurons decussate (cross midline) through the ventral white commissure to the opposite ventrolateral quadrant of the spinal cord. In the ventrolateral quadrant, the STT neurons ascend from the spinal cord to the thalamus in the ventrolateral funiculus (VLF; bundle of fibers). (B) Spinomesencephalic tract (SMT). The neurons that form the SMT also originate predominantly in laminae I, II, and V of the dorsal horn. The SMT neurons decussate through the ventral white commissure to the VLF, where they ascend from the spinal cord to the mesencephalon and terminate in several structures such as the periaqueductal gray (PAG). (C) Spinoreticular tract (SRT). The SRT neurons originate predominantly in laminae I, II, and V of the dorsal horn, decussate through the ventral white commissure to the VLF and ascend from the spinal cord to the reticular formation of the medulla. Adapted with permission from Fields and Basbaum.
STT, but it also receives input from collateral projections sent out of the other ascending tracts that carry nociceptive information.\textsuperscript{18,42} Within the thalamus, nociceptive information regarding the type, temporal pattern intensity, and topographic localization of the pain is encoded prior to sending the information onward to limbic structures and cortical sites.\textsuperscript{12,18,42}

\textbf{Cerebral Cortex}

Ultimately, the nociceptive signal reaches the cerebral cortex where it is integrated and undergoes cognitive and emotional interpretation as stemming from a painful stimulus.\textsuperscript{12,43} The nociceptive signal is transmitted from the thalamus to a variety of cortical sites: the somatosensory S1 area and S2 area, the insular cortex, the anterior cingulate cortex, and the medial prefrontal cortex.\textsuperscript{44–48} Within these cortical regions, there is a complex network of interconnections that include the thalamus and limbic structures.\textsuperscript{49} This network of cortical structures is responsible for the sensory-discriminative (perception of the intensity, location, duration, temporal pattern, and quality of noxious stimuli) and motivational-affective (relationship between pain and mood, attention, coping, tolerance, and rationalization) components of the pain experience.\textsuperscript{12,50,51}

\section*{Descending Modulation of Nociception}

The idea that pain undergoes modulatory effects from higher areas of the CNS was first introduced by Head and Holmes.\textsuperscript{52} Over the past century, a large volume of information has been learned regarding pain perception and modulation. Thus, much effort has been put into understanding the mechanisms involved in the modulatory process.\textsuperscript{53–55} Several decades after Head and Holmes\textsuperscript{52} first theorized that pain is under the influence of higher areas in the CNS, studies confirmed their theory by providing evidence that a number of supraspinal sites contribute to the control of ascending sensory input by exerting tonic inhibitory control of neurons in the spinal dorsal horn.\textsuperscript{56–58} Further research into the contribution of supraspinal structures to nociceptive modulation showed that the mammalian CNS has several well-defined, supraspinally organized descending pathways. These pathways form a network of neural systems that modulate the ascending transmission of nociceptive information, with the most well-described being the circuitry mediating the brainstem control of nociceptive transmission at the level of the spinal dorsal horn.\textsuperscript{53–63}

The effects of descending modulation are exerted in the spinal dorsal horn on the synapse between the primary afferent and projection neurons or on interneurons that synapse with projection neurons (see Figure 7). This synapse in the dorsal horn is the point where nociceptive information is first integrated before being transmitted to higher centers in the CNS.\textsuperscript{12,18,54,64} The descending modulatory effect is applied either by inhibiting the release of neurotransmitter from the primary afferent fiber (see Figure 7A) or by inhibiting the function of neurotransmitter receptors on the postsynaptic neuron (see Figure 7B). Several supraspinal sites are known to contribute to the descending modulation of nociception, either directly (sending projection neurons to the spinal cord) or indirectly (sending projection neurons to other regions in the brainstem that send projections to the spinal cord). These include the PAG, locus coeruleus (LC), and the rostral ventromedial medulla (RVM) among others.\textsuperscript{12,54,63,65,66}

\textbf{Periaqueductal Gray}

The PAG is a midline structure, composed of densely packed heterogenous neurons, that surrounds the cerebral aqueduct throughout the mesencephalon\textsuperscript{67,68} (see Figure 8). It has been well established that the PAG is a major component of the pain modulatory circuitry, since Reynolds\textsuperscript{53} first reported the phenomenon of stimulation produced analgesia after performing abdominal surgery on an unanesthetized rat while electrically stimulating the PAG.\textsuperscript{59,69} Given that few PAG efferents project directly to the spinal dorsal horn,\textsuperscript{70–72} researchers have focused on discovering other pathways that mediate the
spinal effects of PAG stimulation. It was found that the modulatory effect of the PAG is exerted indirectly through efferent connections with a variety of brainstem structures, such as the RVM, parabrachial nucleus, locus coeruleus, and the A5 and A7 noradrenergic cell groups.\textsuperscript{73–78}

**LOCUS COERULEUS:** The LC is a bilateral structure, composed of noradrenergic neurons, that is located in the pons on the border of the fourth cerebral ventricle\textsuperscript{79} (see Figure 9). Bilateral projections from the LC and nearby A7 cell group descend primarily to the contralateral spinal dorsal horn laminae I, II, and V where they exert an antinociceptive effect.\textsuperscript{79–81} In addition to the intrinsic antinociceptive effects of the pontine noradrenergic cell groups, they also receive neuronal projections from the RVM and PAG, thus serving as relays for the modulatory effects from the RVM and PAG to the spinal dorsal horn.\textsuperscript{82,83}

**Rostral Ventromedial Medulla**

The RVM has been studied at length and is recognized as a major component of the
pain modulatory circuitry, exerting its own modulatory effects in addition to relaying the modulatory effects from higher brainstem sites. It is a large region of the medulla that includes the midline nucleus raphe magnus (NRM) and portions of the adjacent reticular formation; the nucleus reticularis gigantocellularis pars alpha (Gia) and the nucleus paragigantocellularis lateralis (LPGi) (Figure 10). Efferent projections from the RVM extend bilaterally, have been identified in all levels of the spinal cord, and comprise a major portion of the neurons projecting to the spinal dorsal horn. These neurons have widely collateralized yet lamina-specific projections, with dense bilateral terminations in laminae I, II, and V of the spinal cord dorsal horn. While all of the components of the descending modulatory network are important, the PAG and RVM have been shown to play key roles in the underlying mechanisms of pain modulation. The RVM exerts its modulatory effect on nociceptive transmission at the spinal level, producing antinociception to painful stimuli. During persistent noxious stimulation, such as during a prolonged inflammatory state, there is continued activation of the descending pain modulatory circuitry and increased neuronal activity in the RVM that results in a progressive enhancement of descending modulation of spinal nociceptive transmission.

**Biphasic Modulation**

The descending modulation of nociception is not wholly inhibitory. Several lines of evidence demonstrate time-dependent biphasic properties of the pain modulatory system that can both inhibit and facilitate nociceptive transmission. However, many aspects of the underlying mechanisms of nociceptive modulation and the shift from facilitation to inhibition remain unclear.

The RVM is one area in the pain modulatory system that puts forth opposing modulatory effects and is a crucial site for balancing descending modulation. When activating the descending pathways that originate in the RVM, the resulting effect (inhibitory or facilitatory) is dependent on the intensity and nature of the intra-RVM stimulus. Although the circuitry responsible for generating facilitatory and inhibitory modulation may be distinct, an anatomical and neurochemical differentiation of the bimodal modulatory structures has not been determined. However, several studies that used either electrical stimulation or lesions have shown opposing modulatory effects from the different subregions of the RVM. The effects of both descending inhibition and facilitation have been observed during multineuron recording in the dorsal horn, where it has been shown that neighboring neurons are simultaneously under facilitatory and inhibitory control from supraspinal structures. The balance between inhibition and facilitation determines the net effect of descending modulation on nociceptive transmission.

In summary, the processing of pain is a complex phenomenon, involving both the peripheral and central nervous systems. Nociceptive information regarding actual or potential tissue injury is transmitted from peripheral nerve endings (nociceptors), via a complex series of ascending pathways, to the brain. Within the brain, the nociceptive
signals are further processed in the somatosensory cortex and interpreted as pain. As the ascending nociceptive information passes through the brainstem and reaches the brain, it triggers the activation of a network of brainstem structures and pathways that exert a modulatory effect on nociceptive transmission. The structures involved in pain modulation send neuron projections from the brainstem to the spinal dorsal horn where their modulatory effect alters the transfer of nociceptive information from the primary afferent to the second-order neuron. Thus, the flow of further nociceptive information from the periphery is either inhibited (resulting in less pain) or facilitated (resulting in more pain).

**Clinical Significance**

New scientific discoveries that stem from research into the mechanisms that underlie pain can lead to the development of new treatment strategies for managing patients with pain, whether acute or chronic. For example, it is known that nonsteroidal anti-inflammatory drugs (NSAIDs) block the synthesis of prostaglandins, which play a role in the sensitization of nociceptors, thus decreasing pain from inflammation. However, prostaglandins do not act alone. There are many other endogenous substances (inflammatory mediators) that can sensitize nociceptors, such as bradykinin, serotonin, cytokines, and others. Therefore, pain research can lead to the development of new pharmacological agents that are directed against the actions of these sensitizing substances and provide new avenues of pain management.13

Our understanding of the mechanisms underlying pain and endogenous modulation is increasing, and many targets exist along the pain pathways for intervention in the treatment of pain. Pain transmission can be interrupted in the periphery by giving drugs that block sensitization of nociceptors (NSAIDs) or by blocking nerve transmission (lidocaine injection into a peripheral nerve). Pain perception can also be altered by giving drugs that work in the CNS (opioids). By gaining increased knowledge of the how the pain processing system works, the advanced practice nurse will be better able to design a treatment plan that is appropriate for each individual patient.

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