Pathophysiology of Pain: A Practical Primer

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Summary: The experience of pain is a subjective one and more than a simple sensation. Pain is commonly defined as an unpleasant sensory and emotional experience due to actual or potential tissue damage or described in such terms. Pain may be broadly classified into physiological and pathological pain. Nociceptive and inflammatory pains are physiological pain states, as they are protective and adaptive, whereas pathological pain is nonprotective and maladaptive. Nociception is the result of suprathreshold stimulation of peripheral nociceptors. Inflammatory pain follows release of various chemical mediators after tissue injury including surgery leading to peripheral sensitization. Nociceptive input is then transmitted to the spinal cord via primary afferents. Modulation of the nociceptive input occurs in the dorsal horn of the spinal cord, influenced by descending inhibitory systems. Central sensitization is a neuromodulatory change that results in the development of secondary hyperalgesia. The modulated nociceptive input then travels up the ascending tracts, mainly via the spinothalamic tract to the thalamus and subsequently to the higher centers of the brain. Pathological pain such as neuropathic pain and central nervous system dysfunctional pain are the result of neuroplasticity of the peripheral and central nervous system. Abnormal ectopic firing of neurons in the absence of a stimulus, increased neuronal hypersensitivity, changes within ion channels, and even alteration in gene expression and changes in the cortical representation are involved in the pathogenesis of these pain states. The development of persistent postsurgical pain is an example for this complex process. (Plast. Reconstr. Surg. 134: 8S, 2014.)

The perception of pain is a complex process, as pain is not just a sensation, but has a significant emotional dimension, which is influenced by one’s beliefs, expectations, culture, and past experience. According to the International Association for the Study of Pain, pain is defined as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.” Acute pain occurs for a short period of time after injury, has a warning function, and promotes healing and therefore is physiologically useful. In contrast, chronic pain persists beyond the period of healing of an injury. It is increasingly recognized that acute and chronic pain may represent a continuum rather than 2 separate entities. Global statistics show that approximately 1 in 5 adults (20%) suffers from pain, which may be acute, chronic, intermittent, or a combination, and 1 in 10 adults (10%) is newly diagnosed with chronic pain each year.

Pain is a subjective experience, which is self-reported. In the acute pain setting, pain is assessed by taking a focused pain history and using various pain measurement tools, such as the numerical rating scale, visual analogue scale, and verbal rating scale. Observer assessment of pain includes observing the patient for facial expression and level of activity, as well as vital signs such as blood pressure, heart rate, and respiratory rate. Patients with chronic pain are assessed under the concept of a biopsychosocial model to include evaluation of physiological, psychological, and socio-environmental factors that influence the pain experience. Assessment of pain is limited in subgroups of patients who have difficulty communicating, such as in pediatrics (age < 2 years) with dementia.

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and intellectual impairment, or due to language barriers.

A common and useful classification of pain separates physiological pain (nociceptive and/or inflammatory pain) and pathological pain [neuropathic and central nervous system (CNS) dysfunctional pain] (Table 1). Understanding the neurobiology of pain, the changes that occur at the cellular, molecular, and genetic level are essential. It allows targeted management of pain using a combination of pharmacological, interventional, and nonpharmacological approaches.

**PHYSIOLOGICAL PAIN: NOCICEPTIVE AND INFLAMMATORY**

Nociceptive pain is caused by actual or threatened damage to nonneural tissue and is due to activation of pain receptors (nociceptors) by intense noxious stimuli. Nociceptive pain has an important protective role because it evokes a painful sensation that draws immediate attention. The withdrawal reflex protects the organism from further injury.

Inflammatory pain involves activation of the immune system as a result of tissue injury. It also has an adaptive and protective role. When tissue injury occurs following trauma (including surgery), infection, or ischemia, there is an increase in pain sensitivity due to peripheral sensitization. This results in behavioral changes, such as reduced movement and minimal physical contact, which promotes healing of the injured body part.

**Peripheral Nociceptors**

Painful stimuli, such as intense heat, cold, mechanical force, or chemical irritants, are detected by nociceptors, free nerve endings widely distributed in the body (skin, musculoskeletal system, viscera). Nociceptors have a high threshold and their activation leads to generation of action potentials transmitted from the peripheral to CNS. The organization of the pain pathway is similar to that for other sensory modalities, including a receptor, primary afferent neuron, second-order neuron, and third-order neuron (Fig. 1). The dorsal root ganglia contain the cell bodies of the primary afferents that innervate the body with the exception of those innervating the head and neck.

Two distinct types of nociceptors are described. Thermomechanoreceptors responding to pinprick and sudden heat transmit via small myelinated fast conducting Aδ fibers. Polymodal receptors responding to thermal and chemical stimuli, such as hydrogen ions, potassium ions, bradykinin, serotonin, adenosine triphosphate, and prostaglandins, transmit via small unmyelinated slow conducting C fibers. Heat, for example, is detected by transient receptor potential channels; the most studied is the vanilloid-type transient receptor potential 1, which is sensitive to heat (>42°C), capsaicin, and hydrogen ions. Other receptors postulated to signal noxious mechanical stimuli include acid-sensing ion channels and potassium channels. Nerve growth factor binds to the tyrosine kinase receptor TrkA and induces pain states, particularly due to inflammation.

There are 2 types of voltage-gated sodium channels, which mediate conduction along primary sensory afferents to the CNS. They are differentiated depending on their sensitivity to tetrodotoxin, the poison of the puffer fish. The rapidly inactivating fast sodium channels blocked by tetrodotoxin are present in all sensory neurons;

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**Table 1. Classification of Pain**

<table>
<thead>
<tr>
<th>Physiological Pain</th>
<th>Pathological Pain</th>
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<tr>
<td><strong>Nociceptive pain</strong></td>
<td><strong>Pathological Pain</strong></td>
</tr>
<tr>
<td>Physiological protective system</td>
<td>Neuropathic pain due to a lesion or disease of the somatosensory nervous system (eg, painful peripheral neuropathy, poststroke, and multiple sclerosis)</td>
</tr>
<tr>
<td>To minimize and avoid damage from intense noxious stimuli (eg, heat, cold, mechanical force, and chemical irritants)</td>
<td>CNS dysfunctional pain in conditions where there is no such damage or inflammation (eg, fibromyalgia, irritable bowel syndrome, and interstitial cystitis)</td>
</tr>
<tr>
<td>High threshold pain</td>
<td>Common features:</td>
</tr>
<tr>
<td>Pain results in immediate attention and withdrawal reflex</td>
<td>Low-threshold pain</td>
</tr>
<tr>
<td><strong>Inflammatory pain</strong></td>
<td>Spontaneous pain</td>
</tr>
<tr>
<td>Heightened sensitivity after tissue injury or infection</td>
<td>Imbalance between excitatory/inhibitory mechanisms</td>
</tr>
<tr>
<td>Immune system is activated involving macrophages, mast cells, neutrophils, and granulocytes (inflammatory soup)</td>
<td>Central sensitization</td>
</tr>
<tr>
<td>Low threshold pain</td>
<td></td>
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<tr>
<td>Tenderness discourages physical contact and movement, thus reducing further risk of injury and promoting healing</td>
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these are the principal sites of action for local anesthetics. The tetrodotoxin-resistant sodium channels are present selectively on nociceptive fibers and are offering thereby interesting new targets for pain medications. Nerve injury may lead to changes in the expression of these sodium channels explaining spontaneous depolarization in neuropathic pain states. The SCN9A gene is encoding one of these, the Na(1.7) channel; a loss of function mutation results in congenital insensitivity to pain, whereas a gain of function mutation leads to a severe painful state, erythromelalgia.

Pain Transmission in the Spinal Cord

Small myelinated Aδ fibers, which respond to an initial stimulus, are faster conducting and terminate in lamina I and V of the dorsal horn. The main neurotransmitter here is the excitatory amino acid glutamate. Aδ fibers synapse directly with second-order neurons, which make up the ascending tracts. Small unmyelinated slow conducting C fibers, which transmit more a persistent ache, terminate in lamina II of the dorsal horn. The neurotransmitters involved in C fiber transmission include not only glutamate but also neuropeptides, such as substance P, calcitonin gene-related peptide, cholecystokinin, and brain-derived neurotrophic factor. C fibers often synapse indirectly with second-order neurons via interneurons. Aβ fibers conduct low-intensity mechanical stimuli like touch; they terminate in laminae III–VI of the dorsal horn and may also be involved in transmission of chronic pain.

Various receptors are involved in the synaptic transmission in the dorsal horn. Most important are the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid and N-methyl-D-aspartate (NMDA) receptors binding glutamate and
the neurokinin-1 receptors binding substance P. Noxious stimuli are initially mediated by glutamate acting on the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor. With increasing intensity of stimuli, the NMDA receptor becomes activated, too, and other neuropeptides like substance P are released which bind to neurokinin-1 receptors; these processes lead to hyperexcitability of the second-order neuron.

Ascending Pathways

Nociception is conveyed from the dorsal horn to the brain via ascending tracts in the white matter of the spinal cord. The second-order neurons cross over at the spinal cord before ascending to integrative centers in the thalamus. The 2 most important ascending tracts are the spinothalamic and the spinoreticular tracts. The lateral spinothalamic tract ascends directly to the ventral posterior lateral nucleus of the thalamus, serving the sensory discriminative aspect of pain perception. The medial spinothalamic tract sends collaterals to the periaqueductal grey matter, hypothalamus, and reticular system in the midbrain before reaching the medial thalamus; it is thought to be involved in mediating the autonomic and emotional component of pain. The spinoreticular tract arises from laminae VII and VIII of the dorsal horn, terminating in the reticular formation of the medulla and pons; it is believed to mediate the aversive component of pain. From the ventral posterior lateral and medial nuclei, third-order neurons project to higher cortical (somatosensory cortex) and to midbrain centers (limbic system). There are also important projections to the limbic system (hippocampus and amygdala) associated with memory, emotion, and behavior.

MODULATION OF PAIN

Gate Control Theory of Pain

The revolutionary gate control theory of pain was proposed by Melzack and Wall in 1965. Their “gate” in the spinal cord is located in the substantia gelatinosa (lamina II on Rexed’s laminae) of the dorsal horn, and the opening and closure of the gate is influenced by several neural pathways. The gate is opened by small ascending C fibers and closed by descending and large ascending Aβ fibers. Pain occurs when the impulse flow exceeds a certain threshold that exceeds the inhibition elicited, thus “opens the gate” and activates the pain pathways. This theory led to concepts that pain could be controlled by modulation, by reducing excitation and increasing inhibition. An example is use of transcutaneous electrical nerve stimulation for analgesia where stimulating Aβ fibers attenuates nociceptive impulses. However, although the theory revolutionized the thinking about pain, details are flawed, such as the oversimplification of the neural architecture of the spinal cord, the idea of how large afferent fiber stimulation produces modulation of C fibers, and the hypothesized modulatory system, which we are now aware includes descending small fiber projections from the brainstem.

Descending Inhibitory Pathways

The spinal cord also carries descending pathways that modulate the transmission of pain signals at the dorsal horn. Both inhibitory and facilitatory signals come mainly from areas in the brainstem, namely the periaqueductal grey matter, rostroventral medulla, and pontine tegmentum. The neurotransmitters involved are primarily noradrenaline and serotonin. Noradrenaline acts via postsynaptic α2-receptors, but the action of serotonin is less specific. Endogenous opioids, such as endorphins, dynorphins, and enkephalins, are also involved in descending inhibition at spinal and supraspinal level.

Peripheral and Central Sensitization

Peripheral sensitization is due to the local action of inflammatory mediators, such as prostaglandins, histamine, bradykinin, potassium and hydrogen ions, 5-hydroxytryptamine, adenosine triphosphate, and nitric oxide, released from damaged and immune cells. The effect of the inflammatory mediators on the peripheral terminals of high threshold nociceptors of sensory neurons leads to activation of intracellular signaling pathways. This triggers phosphorylation of ion channels and nociceptors on the terminal membrane, decreasing the threshold and increasing neuronal excitability. The hypersensitivity is known as primary hyperalgesia, as it reduces the intensity of the peripheral stimulus required to activate nociceptors at the site of inflammation. Primary hyperalgesia is reversible, as healing occurs, the amount of active mediator subsides and so does the local hyperexcitability.

In central sensitization, there is an increase in the excitability of the dorsal horn of the spinal cord leading to pain amplification. Intense noxious peripheral stimuli such as surgery evoke large amounts of action potentials. Consequently, there is increased synaptic activity in the dorsal
horn neurons compounded by humoral signals released from inflamed tissue. Activation of intracellular kinases produces alterations in proteins in dorsal horn neurons, and this increases the trafficking of ion channels and receptors to the membrane and change of their function by phosphorylation. Finally, there is even altered gene transcription in the sensory neurons and in the spinal cord. Central sensitization results in an abnormal response to a normal sensory input, and there is spread of sensitivity well beyond the peripheral site of injury, known as secondary hyperalgesia.14

PATHOLOGICAL PAIN

Pathological pain is called so as it has no biological function, is nonprotective and maladaptive, and is due to damage and/or abnormal functioning of the nervous system. Pathological pain has been recently subdivided into neuropathic pain following damage to or disease of the nervous system and CNS dysfunctional pain when there is no such damages but dysfunction of the CNS. Both conditions are largely the result of increased excitatory and decreased inhibitory activity in the CNS (Table 1).

Examples of peripheral neuropathic pain include painful peripheral neuropathy, trigeminal neuralgia, and postherpetic neuralgia, whereas central neuropathic pain includes poststroke and spinal cord injury pain.

Examples of dysfunctional pain include fibromyalgia, tension headache, and many visceral pain states such as irritable bowel syndrome. A detailed discussion is beyond the scope of this review.15

Neuropathic Pain

Neuropathic pain is defined as pain caused by a lesion or disease of the somatosensory nervous system.16 The etiology includes trauma, ischemia, infection, or metabolic disturbances. This type of pain is qualitatively different from other types of pain; the diagnosis is often clinical based on characteristic pain symptoms (positive signs such as hyperalgesia and allodynia) (Table 2), which coexist with signs of altered sensory function (negative signs such as hypoesthesia or sensory deficits).17 Characteristic descriptors of neuropathic pain include burning, electric shocks, shooting, numbness, itching, pins and needles. Neuropathic pain may be spontaneous or triggered by a stimulus. The pathophysiology of neuropathic pain is complex and involves peripheral and central mechanisms.

Neuroplastic Changes and Pain Modulation in Neuropathic Pain

When there is a lesion to the primary sensory neurons, they and their immediate noninjured neighbors start to fire action potentials spontaneously (ectopic discharge), following increased expression and altered trafficking of sodium channels.17 This ectopic activity contributes to spontaneous pain and by inducing central sensitization will augment pain sensitivity and cause allodynia. In addition, there are changes in expression of synaptic transmitters and receptors and gene alteration that modify transmission and responsiveness. For example, upregulation of the α2δ subunit of voltage-gated calcium channels causes increased neurotransmission in abnormally active sensory neurons.18 The α2δ subunit is the binding site for its modulators gabapentin and pregabalin, used to treat neuropathic pain and central sensitization. There are also neuromodular changes that occur following peripheral nerve injury. If an axon is severed, its distal end degenerates and is engulfed by inflammatory cells. Tumor necrosis factor-α, a pain-producing signal molecule, then acts on these axons to increase ectopic activity. Finally, glial cells are activated in the spinal cord and interact with dorsal horn neurons to produce pain hypersensitivity. The important role of glial cells such as microglia and astrocytes in neuropathic pain has only recently been identified. The release of pro-inflammatory neuromodulators such as cytokines and chemokines from these glial cells plays a previously underestimated role in neuropathic pain and may provide new options for treatment.

If reconnection of the injured axon with its target does not occur after a peripheral nerve injury, small nociceptor sensory neurons with unmyelinated axons start to die after many weeks. Sensory inflow to the CNS is permanently disrupted. The synaptic circuitry in the spinal cord is also modified and death by apoptosis of neurons in the dorsal horn occurs, and this seems to be related to excessive glutamate release. The neurons that die include inhibitory interneurons; hence, there is an irreversible reduction in local segmental inhibitory transmission in the dorsal horn. The changes are not limited to the spinal cord; they extend to alterations in the cortex and cortical grey matter.

Some patients may demonstrate neuropathic pain that is dependent on the activity of the sympathetic nervous system.19 Following a peripheral nerve
injury, axons develop increased α-adrenoreceptors and therefore have an exaggerated response to circulating catecholamines. Structural changes to the nerve also occur with sympathetic axons sprouting into the dorsal root ganglion surrounding the cell bodies of sensory neurons. These changes lead to sympathetically maintained pain, often as unilateral limb pain with associated features of vasomotor and sudomotor changes.

Central mechanisms involved in the generation of neuropathic pain occur primarily in the dorsal horn and are thought to result in neuroplastic changes in the CNS. Windup occurs when there is repetitive C fiber inputs that act mainly on NMDA receptors. Windup is short lived (lasting seconds to minutes). Further central sensitization changes differ from windup in that the changes remain long after the C fiber input has ceased. Other described central mechanisms of neuropathic pain include central disinhibition, where there is loss of modulatory control mechanisms due to downregulation of inhibitory neurotransmitters, recruitment,

<table>
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<th>Table 2. Typical Features of Neuropathic Pain[^1][^17]</th>
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<tr>
<td>Hyperalgesia</td>
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<tr>
<td>Alldynia</td>
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<tr>
<td>Dysesthesia</td>
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<tr>
<td>Hyperpathia</td>
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<td>Hypoalgesia</td>
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Fig. 2. Risk factors for persistent postsurgical pain.[^14][^20][^21]
gene expression, role of glial cells, and anatomical reorganization of the spinal cord. Finally, changes in the representation of the affected area in the somatosensory cortex occur.

**Persistent Postsurgical Pain**

A specific example of neuropathic pain relevant to surgeons is persistent postsurgical pain (PPSP). Chronic pain is common after surgery. The reported incidences of PPSP vary widely, for example, mastectomy 20–50%, amputation 50–85%, hysterectomy 5–30%, cardiac surgery 30–55%, hernia repair 5–35%, and thoracotomy 5–65%14,20; severe disabling pain (greater than 5 on a 10-point scale) occurs in 2–10% of cases. It has been suggested that PPSP should be defined as pain that persists for 2 months after surgery that is unexplained by other causes.20 The mechanism for development of PPSP is complex; it is often neuropathic pain and maladaptive neuronal plasticity has occurred.14 PPSP can be crippling resulting in disability and reduced quality of life and is a significant economic burden. Important risk factors include intraoperative nerve injury, preoperative pain, poorly controlled postoperative pain, and psychosocial factors. Figure 2 depicts factors contributing to PPSP.

**CONCLUSIONS**

The pain matrix is complex. Having gathered information on receptors, ion channels, and neurotransmitters over the last 20–30 years, we now have a better understanding on nociceptive and inflammatory pain transmission and pathological pain states. This allows future development of potential new targets for analgesic therapy.

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