Chapter 3
Physiology of Pain
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Pain is not only an unpleasant sensation, but a complex sensory modality essential for survival. There are rare cases of people with no pain sensation. An often-cited case is that of F.C., who did not exhibit a normal pain response to tissue damage. She repeatedly bit the tip of her tongue, burned herself, did not turn over in bed or shift her weight while standing, and showed a lack of autonomic response to painful stimuli. She died at the age of 29.

The nervous system mechanism for detection of stimuli that have the potential to cause tissue damage is very important for triggering behavioral processes that protect against current or further tissue damage. This is done by reflex reaction and also by preemptive actions against stimuli that can lead to tissue damage such as strong mechanical forces, temperature extremes, oxygen deprivation, and exposure to certain chemicals.

This chapter will cover the neuronal receptors that respond to various painful stimuli, substances that stimulate nociceptors, the nerve pathways, and the modulation of the perception of pain. The term nociception (Latin nocere, “to hurt”) refers to the sensory process that is triggered, and pain refers to the perception of a feeling or sensation which the person calls pain, and describes variably as irritating, sore, stinging, aching, throbbing, or unbearable. These two aspects, nociception and pain, are separate and, as will be described when discussing the modulation of pain, a person with tissue damage that should produce painful sensations may show no behavior indicating pain. Nociception can lead to pain, which can come and go, and a person can have pain sensation without obvious nociceptive activity. These aspects are covered in the IASP definition: “An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.”

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Nociceptors and the transduction of painful stimuli

The nervous system for nociception that alerts the brain to noxious sensory stimuli is separate from the nervous system that informs the brain of innocuous sensory stimuli.

Nociceptors are un specialized, free, unmyelinated nerve endings that convert (transduce) a variety of stimuli into nerve impulses, which the brain interprets to produce the sensation of pain. The nerve cell bodies are located in the dorsal root ganglia, or for the trigeminal nerve in the trigeminal ganglia, and they send one nerve fiber branch to the periphery and another into the spinal cord or brainstem.

The classification of the nociceptor is based on the classification of the nerve fiber of which it is the terminal end. There are two types of nerve fibers: (1) small-diameter, unmyelinated nerves that conduct the nerve impulse slowly (2 m/sec = 7.2 km/h), termed C fibers,
and (2) larger diameter, lightly myelinated nerves that conduct nerve impulses faster (20 m/sec = 72 km/h) termed Aδ fibers. The C-fiber nociceptors respond polymodally to thermal, mechanical, and chemical stimuli; and the Aδ-fiber nociceptors are of two types and respond to mechanical and mechanothermal stimuli. It is well known that the sensation of pain is made up of two categories—an initial fast, sharp (“epicritic”) pain and a later slow, dull, long lasting (“protopathic”) pain. This pattern is explained by the difference in the speed of propagation of nerve impulses in the two nerve fiber types described above. The neuronal impulses in fast-conducting Aδ-fiber nociceptors produce the sensation of the sharp, fast pain, while the slower C-fiber nociceptors produce the sensation of the delayed, dull pain.

Peripheral activation of the nociceptors (transduction) is modulated by a number of chemical substances, which are produced or released when there is cellular damage (Table 1). These mediators influence the degree of nerve activity and, hence, the intensity of the pain sensation. Repeated stimulation typically causes sensitization of peripheral nerve fibers, causing lowering of pain thresholds and spontaneous pain, a mechanism that can be experienced as cutaneous hypersensitivity, e.g., in skin areas with sunburn.

### Table 1

<table>
<thead>
<tr>
<th>Substance</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium</td>
<td>Damaged cells</td>
</tr>
<tr>
<td>Serotonin</td>
<td>Platelets</td>
</tr>
<tr>
<td>Bradykinin</td>
<td>Plasma</td>
</tr>
<tr>
<td>Histamine</td>
<td>Mast cells</td>
</tr>
<tr>
<td>Prostaglandins</td>
<td>Damaged cells</td>
</tr>
<tr>
<td>Leukotrienes</td>
<td>Damaged cells</td>
</tr>
<tr>
<td>Substance P</td>
<td>Primary nerve afferents</td>
</tr>
</tbody>
</table>

Hypersensitivity may be diagnosed by taking history and by careful examination. Certain conditions may be discriminated:

a) Allodynia: Pain due to a stimulus that does not normally provoke pain, e.g., pain caused by a T-shirt in patients with postherpetic neuralgia.

b) Dysesthesia: An unpleasant abnormal sensation, whether spontaneous or evoked. (Note: a dysesthesia should always be unpleasant, while paresthesia should not be unpleasant; e.g., in patients with diabetic polyneuropathy or vitamin B₁ deficiency.)

c) Hyperalgesia: An increased response to a stimulus that is normally painful. (Note: hyperalgesia reflects increased pain on suprathreshold stimulation; e.g., in patients with neuropathies as a consequence of perturbation of the nociceptive system with peripheral and/or central sensitization.)

d) Hyperesthesia: Increased sensitivity to stimulation, excluding the special senses, e.g., increased cutaneous sensibility to thermal sensation without pain.

With the knowledge of pain pathways and sensitization mechanisms, therapeutic strategies to interact specifically with the pain generation mechanisms can be developed.

### Central pain pathways

The spinothalamic pathway and the trigeminal pathway are the major nerve routes for the transmission of pain and normal temperature information from the body and face to the brain. Visceral organs have only C-fiber nociceptive nerves, and thus there is no reflex action due to visceral organ pain.

**The spinothalamic pathway**

The nerve fibers from the dorsal root ganglia enter the spinal cord through the dorsal root and send branches 1–2 segments up and down the spinal cord.
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(dorsolateral tract of Lissauer) before entering the spinal gray matter, where they make contacts with (innervate) the nerve cells in Rexed lamina I (marginal zone) and lamina II (substantia gelatinosa). The Aδ fibers innervate the cells in the marginal zone, and the C fibers innervate mainly the cells in the substantia gelatinosa layer of the spinal cord. These nerve cells, in turn, innervate the cells in the nucleus proprius, another area of the spinal cord gray matter (Rexed layers IV, V, and VI), which send nerve fibers across the spinal midline and ascend (in the anterolateral or ventrolateral part of the spinal white matter) through the medulla and pons and innervate nerve cells located in specific areas of the thalamus. This makes up the spinothalamic pathway for the transmission of information on pain and normal thermal stimuli (<45°C). Dysfunctions in the thalamic pathways may themselves be a source of pain, as is observed in patients after stroke with central pain (“thalamic pain”) in the area of paralysis.

The trigeminal pathway

Noxious stimuli from the face area are transmitted in the nerve fibers originating from the nerve cells in the trigeminal ganglion as well as cranial nuclei VII, IX, and X. The nerve fibers enter the brainstem and descend to the medulla, where they innervate a subdivision of the trigeminal nuclear complex. From here the nerve fibers from these cells cross the neural midline and ascend to innervate the thalamic nerve cells on the contralateral side. Spontaneous firing of the trigeminal nerve ganglion may be the etiology of “trigeminal neuralgia” (although most of the time, local trigeminal nerve damage by mechanical lesion through a cerebellar artery is found to be the cause, as seen by the positive results of Janetta’s trigeminal decompression surgery).

The area of the thalamus that receives the pain information from the spinal cord and trigeminal nuclei is also the area that receives information about normal sensory stimuli such as touch and pressure. From this area, nerve fibers are sent to the surface layer of the brain (cortical areas that deal with sensory information). Thus, by having both the nociceptive and the normal somatic sensory information converge on the same cortical area, information on the location and the intensity of the pain can be processed to become a “localized painful feeling.” This cortical representation of the body—as described in Penfield’s homunculus—may also be a source of pain. In certain situations, e.g., after limb amputations, cortical representation may change, caus-

Appreciating the complexity of the pain pathway can contribute to understanding the difficulty in assessing the origin of pain in a patient and in providing pain relief, especially in chronic pain.

Pathophysiology of pain

Pain sensations could arise due to:

1) Inflammation of the nerves, e.g., temporal neuritis.
2) Injury to the nerves and nerve endings with scar formation, e.g., surgical damage or disk prolapse.
3) Nerve invasion by cancer, e.g., brachial plexopathy.
4) Injury to the structures in the spinal cord, thalamus, or cortical areas that process pain information, which can lead to intractable pain; deafferentation, e.g., spinal trauma.
5) Abnormal activity in the nerve circuits that is perceived as pain, e.g., phantom pain with cortical reorganization.

Modulation of the perception of pain

It is well known that there is a difference between the objective reality of a painful stimulus and the subjective response to it. During World War II, Beecher, an anesthesiologist, and his colleagues carried out the first systematic study of this effect. They found that soldiers suffering from severe battle wounds often experienced little or no pain. This dissociation between injury and pain has also been noted in other circumstances such as sporting events and is attributed to the effect of the context within which the injury occurs. The existence of dissociation implies that there is a mechanism in the body that modulates pain perception. This endogenous mechanism of pain modulation is thought to provide the advantage of increased survival in all species (Überlebensvorteil).

Three important mechanisms have been described: segmental inhibition, the endogenous opioid system, and the descending inhibitory nerve system. Moreover, cognitive and other coping strategies may also play a major role in pain perception, as described in other chapters in this guide.

Segmental inhibition

In 1965, Melzack and Wall proposed the “gate theory of pain control,” which has been modified subsequently
but which in essence remains valid. The theory proposes that the transmission of information across the point of contact (synapse) between the Aδ and C nerve fibers (which bring noxious information from the periphery) and the cells in the dorsal horn of the spinal cord can be diminished or blocked. Hence, the perception of the painfulness of the stimulus either is diminished or is not felt at all. The development of transcutaneous electrical nerve stimulation (TENS) was the clinical consequence of this phenomenon.

The transmission of the nerve impulse across the synapse can be described as follows: The activation of the large myelinated nerve fibers (Aβ fibers) is associated with the low-threshold mechanoreceptors such as touch, which stimulate an inhibitory nerve in the spinal cord that inhibits the synaptic transmission. This is a possible explanation of why rubbing an injured area reduces the pain sensation (Fig. 2).

![Fig. 2. The gate control theory of Pain (Melzack and Wall). + excitatory synapse; – inhibitory synapse]

**Endogenous opioid system**

Besides the gating of transmission of noxious stimuli, another system modulates pain perception. Since 4000 BCE, it has been known that opium and its derivatives such as morphine, codeine, and heroin are powerful analgesics, and they remain the mainstay of pain relief therapy today. In the 1960s and 1970s, receptors for the opium derivatives were found, especially in the nerve cells of the periaqueductal gray matter and the ventral medulla, as well as in the spinal cord. This finding implied that chemicals must be produced by the nervous system that are the natural ligands of these receptors. Three groups of endogenous compounds (enkephalins, endorphins, and dynorphin) have been discovered that bind to the opioid receptors and are referred to as the endogenous opioid system. The presence of this system and the descending pain modulation system (adrenergic and serotonergic) provides an explanation for the system of internal pain modulation and the subjective variability of pain.

**Descending inhibitory nerve system**

Nerve activity in descending nerves from certain brainstem areas (periaqueductal gray matter, rostral medulla) can control the ascent of nociceptive information to the brain. Serotonin and norepinephrine are the main transmitters of this pathway, which can therefore be modulated pharmacologically. Selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (e.g., amitriptyline) may therefore have analgesic properties (Fig. 3).

![Fig. 3. Ascending (solid lines) and descending pain pathways. The raphe nucleus and locus ceruleus provide serotoninergic (5-HT) and adrenergic modulation. PAG = periaqueductal gray matter, part of the endogenous opioid system.]

**Referred pain**

Visceral organs do not have any Aδ nerve innervation, but the C fibers carrying the pain information from the visceral organs converge on the same area of the spinal cord (substantia gelatinosa) where somatic nerve fibers from the periphery converge, and the brain localizes the pain sensation as if it were originating from that somatic peripheral area instead of the visceral organ. Thus, pain from internal organs is perceived at a location that is not the source of the pain; such pain is referred pain.

**Spinal autonomic reflex**

Often the pain information from the visceral organs activates nerves that cause contraction of the skeletal muscles and vasodilation of cutaneous blood vessels, producing reddening of that area of the body surface.
Conclusion

Chemical or mechanical stimuli that activate the nociceptors result in nerve signals that are perceived as pain by the brain. Research and understanding of the basic mechanism of nociception and pain perceptions provides a rationale for therapeutic interventions and potential new targets for drug development.

References
