Learning Objectives:

By the end of the lecture, the student should be able to:

- Name the types of peripheral nerve fibers and receptor types that mediate nociception.
- Explain the difference between pain and nociception.
- Explain the differences between fast and slow pain and acute and chronic pain.
- Explain hyperalgesia and allodynia.
- Describe and explain referred pain.

Pain:

Definition:

A warning that something is wrong, pre-empts other signals, and is associated with an unpleasant affect.

- Central nociceptor pathways are sensitized and reorganized if pain is prolonged and tissue is damaged.

Nociceptor:

Definition:

A group of cells that acts as a receptor for painful stimuli. Impulses from nociceptors (pain) are transmitted via two fiber types.

- Thinly myelinated Aδ fibers: conduct at rates of 12–30 m/s.
- Unmyelinated c fibers: conduct at low rates of 0.5–2 m/s.
Classification of Pain:

Pain has been classified into two major types.

- **Fast pain** felt within about 0.1 second after a pain stimulus is applied.
- **Felt when a needle is stuck into the skin, when the skin is cut with a knife, or when the skin is acutely burned.**
- **Not felt** in most deeper tissues of the body.

- **Slow pain** begins only after 1 second or more and then increases slowly over many seconds and sometimes minutes.
- **Usually associated with tissue destruction.**

Pain is frequently classified as:

- **Physiologic or acute pain:**
  - Sudden onset and recedes during the healing process.
  - Considered as “good pain” as it serves an important protective mechanism.
  - Withdrawal reflex is an example of this protective role of pain.

- **Pathologic or chronic pain:**
  - Inflammatory pain and
  - Neuropathic pain: result from nerve injury.
  - Considered “bad pain” because it persists long after recovery from an injury.

**Hyperalgesia and allodynia:**

- Hyperalgesia is an exaggerated response to a noxious stimulus.
- Allodynia is a sensation of pain in response to an innocuous stimulus e.g. painful sensation from a warm shower when the skin is damaged by sunburn.
- Hyperalgesia and allodynia signify increased sensitivity of nociceptive afferent fibers.
In response to tissue injury, chemical mediators can sensitize and activate nociceptors. These factors contribute to hyperalgesia and allodynia. Tissue injury releases bradykinin and prostaglandins that sensitize or activate nociceptors, which in turn releases substances P and calcitonin gene-related peptide (CGRP). Substance P acts on mast cells to cause degranulation and release histamine, which sensitizes nociceptors. Substance P also excites primary afferent C-fibers and CGRP (a neuropeptide) that release substance P and activate nociceptors.

- **Chemicals released at site of injury can activate nociceptors leading to inflammatory pain.**
- **Injured cells release chemicals such as K+ that depolarize nerve terminals, making nociceptors more responsive.**
- **Injured cells also release bradykinin and Substance P, which can further sensitize nociceptive terminals.**
- **Histamine is released from mast cells, serotonin (5-HT) from platelets, and prostaglandins from cell membranes, all contributing to the inflammatory process and they activate or sensitize the nociceptors.**
- **Bradykinin activates both A and C fibers and increases synthesis and release of prostaglandins.**
- **Prostaglandin E2 (a cyclooxygenase metabolite of arachidonic acid) is released from damaged cells and produces hyperalgesia.**
- **This is why aspirin and other NSAIDs (inhibitors of cyclooxygenase) alleviate pain.**
Stimuli for Pain Receptors

Three Types of Stimuli Excite Pain Receptors:
• Mechanical,
• Thermal, and
• Chemical.
- fast pain is elicited by mechanical and thermal types of stimuli.
- slow pain can be elicited by all three types.

Pathways for Transmission of Pain

Dual Pathways for Transmission of Pain Signals into the Central Nervous System.

• Two pathways mainly correspond to two types of pain:
  – A fast-sharp pain pathway and
  – A slow-chronic pain pathway.

Peripheral Pain Fibers

Fast fibers:
• Fast sharp pain signals are elicited by either mechanical or thermal pain stimuli.
• Transmitted in peripheral nerves to spinal cord by small type A δ fibers at velocities between 6 and 30 m/sec.
**Slow Fibers:**

- Slow-chronic type of pain is elicited mostly by chemical types of pain stimuli but sometimes by persisting mechanical or thermal stimuli.
- Transmitted to the spinal cord by type C fibers at velocities between 0.5 and 2 m/sec.

**Dual Pain Pathways in the Cord and Brain Stem**

On entering spinal cord, pain signals take two pathways to brain, through

1. **neospinothalamic tract** and
2. **paleospinothalamic tract.**

**Neospinothalamic Tract for Fast Pain.**

- Fast type A δ pain fibers transmit mainly mechanical and acute thermal pain.
- Terminate mainly in lamina I (lamina marginalis) of the dorsal horns and
- Excite second-order neurons of the neospinothalamic tract.

**Termination of Neospinothalamic Tract in Brain Stem and Thalamus.**

- Few fibers of the neospinothalamic tract terminate in the reticular areas of the brain stem, but most pass all the way to the thalamus without interruption.

**Neurotransmitter of Type A δ Fibers:**

- *Glutamate* is the neurotransmitter substance secreted in the spinal cord at the type A δ pain nerve fiber endings.
Paleospinothalamic Pathway for Transmitting Slow-Chronic Pain.

- Peripheral fibers terminate in spinal cord almost entirely in laminae II and III of dorsal horns, which together are called *substantia gelatinosa*.
- Most signals then pass through one or more short fiber neurons within the dorsal horns themselves before entering mainly lamina V, also in the dorsal horn.
- Last neurons in series give rise to long axons that mostly join fibers from fast pain pathway.

**Slow-Chronic Neurotransmitter of Type C Nerve Endings**

- Type C pain fiber terminals entering spinal cord secrete both glutamate transmitter and substance P transmitter.
- Glutamate transmitter acts instantaneously and lasts for only a few milliseconds.
- Substance P is released much more slowly, building up in concentration over a period of seconds or even minutes.

**Referred Pain**

- Irritation of a visceral organ frequently produces pain that is felt not at that site but in some somatic structure that may be a considerable distance away. Such pain is said to be referred to the somatic structure.
- For instance, pain in one of the visceral organs often is referred to an area on the body surface.

Diagram of the way in which convergence of somatic and visceral nociceptive fibers in lamina VII of the dorsal horn may cause referred pain. When a visceral stimulus is prolonged, somatic fiber facilitation occurs. This leads to activation of spinothalamic tract neurons, and of course the brain cannot determine whether the stimulus came from the viscera or from the somatic area.
Mechanism of Referred Pain.

- Branches of visceral pain fibers are shown to synapse in the spinal cord on the same second-order neurons (1 and 2) that receive pain signals from the skin.
- When visceral pain fibers are stimulated, pain signals from viscera are conducted through at least some of the same neurons that conduct pain signals from skin, and person has feeling that sensations originate in skin itself.

Visceral Pain

- Afferent fibers from visceral structures reach the CNS via sympathetic and parasympathetic nerves. Their cell bodies are located in the dorsal roots and the homologous cranial nerve ganglia. Specifically, there are visceral afferents in the facial, glossopharyngeal, and vagus nerves; in the thoracic and upper lumbar dorsal roots; and in the sacral roots (Figure 10-2). There may also be visceral afferent fibers from the eye in the trigeminal nerve.
Lecture Resources

• Ganong’s Review Of Medical Physiology
  — 23\textsuperscript{RD} Edition.

• Text book of Medical Physiology.

THANKS