Part 4, Sensory and Motor Systems

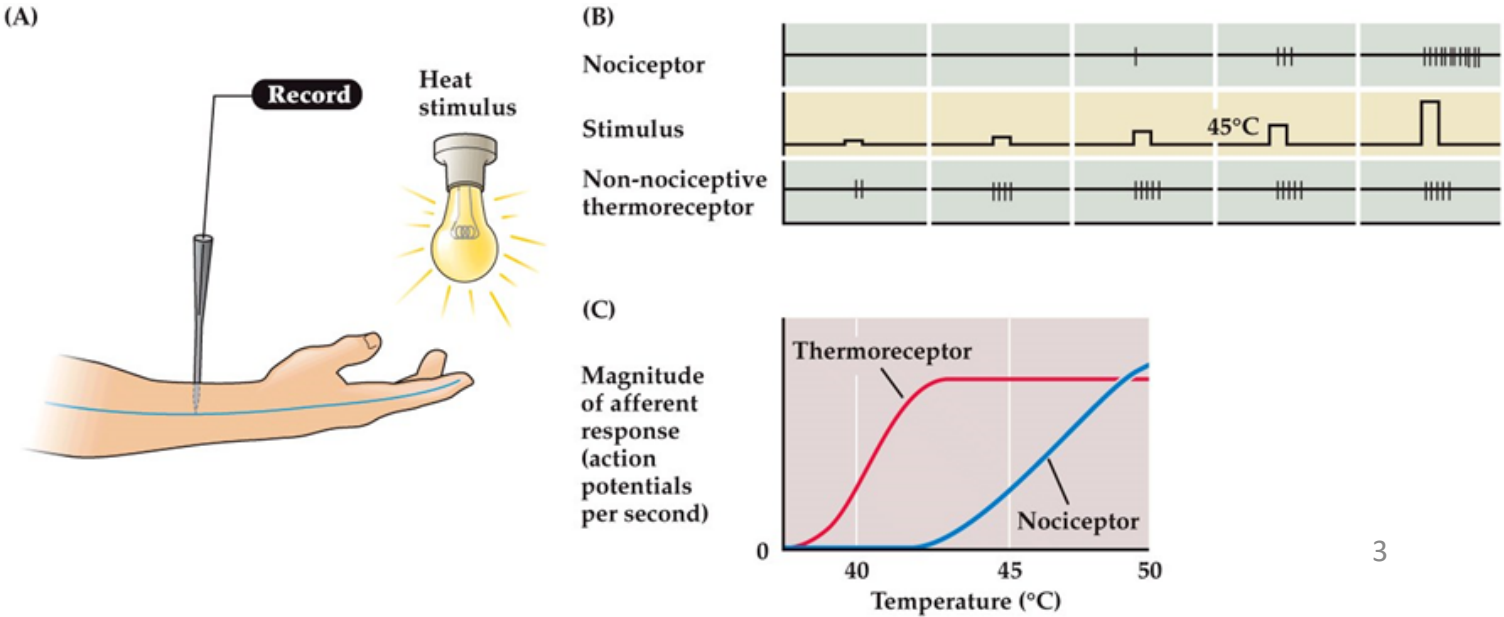
4.2. Pain

Nociceptors

- The perception of injurious stimuli, called nociception, depends on specifically dedicated receptors and pathways.
- The relatively unspecialized nerve cell endings that initiate the sensation of pain are called **nociceptors** (Latin *nocere*, "to hurt").
- Nociceptors, like other somatic sensory receptors, arise from cell bodies in dorsal root ganglia (or in the trigeminal ganglion) that send one axonal process to the periphery and the other into the spinal cord or brainstem.
- Because peripheral nociceptive axons terminate in morphologically unspecialized "free endings," it is conventional to categorize nociceptors according to the properties of the axons associated with them.
- The somatic sensory receptors responsible for the perception of innocuous mechanical stimuli are associated with myelinated axons that have relatively rapid conduction velocities.
- The axons associated with nociceptors, in contrast, conduct relatively slowly, being only lightly myelinated or, more commonly, unmyelinated.
- Accordingly, axons conveying information about pain fall into either the **Aδ group** of myelinated axons, which conduct at 5-30 m/s, or into the **C fiber group** of unmyelinated axons, which conduct at velocities generally less than 2 m/s.

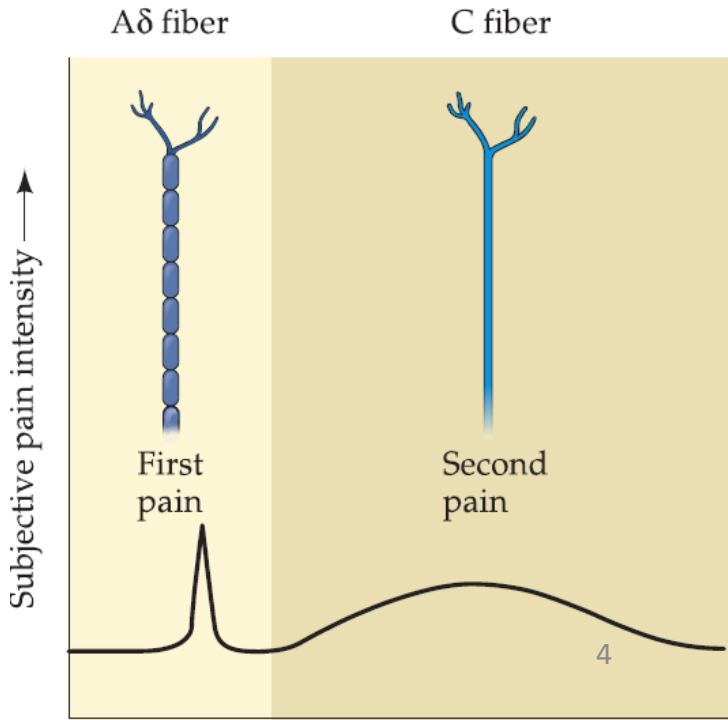
Neuronal basis of pain

- Studies carried out in both humans and experimental animals demonstrated some time ago that the rapidly conducting axons that subserve somatic sensation are not involved in the transmission of pain.
- The peripheral axons responsive to nonpainful mechanical or thermal stimuli do not discharge at a greater rate when painful stimuli are delivered to the same region of the skin surface.
- The nociceptive axons, on the other hand, begin to discharge only when the strength of the stimulus reaches high levels.
- This indicates the presence of both nociceptive and non-nociceptive thermoreceptors.



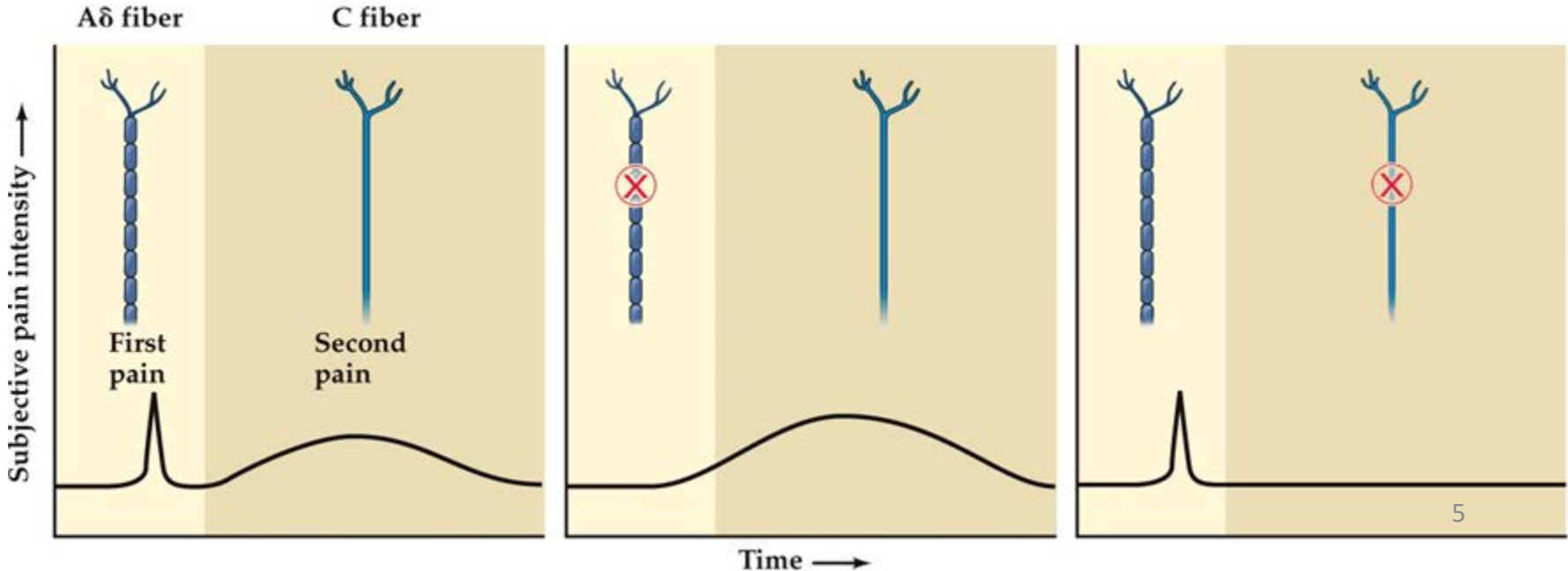
First and second pain

- In general, two categories of pain perception have been described: a sharp **first pain** and a more delayed, diffuse, and longer-lasting sensation that is generally called **second pain**.
- Stimulation of the large, rapidly conducting Aα and Aβ axons in peripheral nerves does not elicit the sensation of pain.
- When investigators raise the stimulus intensity to a level that activates a subset of Aδ fibers, however, a tingling sensation or, if the stimulation is intense enough, a feeling of sharp pain is reported.
- If the stimulus intensity is increased still further, so that the small-diameter, slowly conducting C-fiber axons are brought into play, then subjects report a duller, longer lasting sensation of pain.



Nociceptive axon subtypes

- Researchers can selectively anesthetize C fibers and Aδ fibers.
- These selective blocking experiments confirm that Aδ fibers are responsible for first pain and C fibers are responsible for the duller, longer-lasting second pain.
- The faster-conducting Aδ nociceptors fall into two main classes:
  - Type I Aδ fibers respond to dangerously intense mechanical and chemical stimulation but have relatively high heat thresholds.
  - Type II Aδ fibers have complementary sensitivities--i.e., much lower thresholds for heat, but very high thresholds for mechanical stimulation..

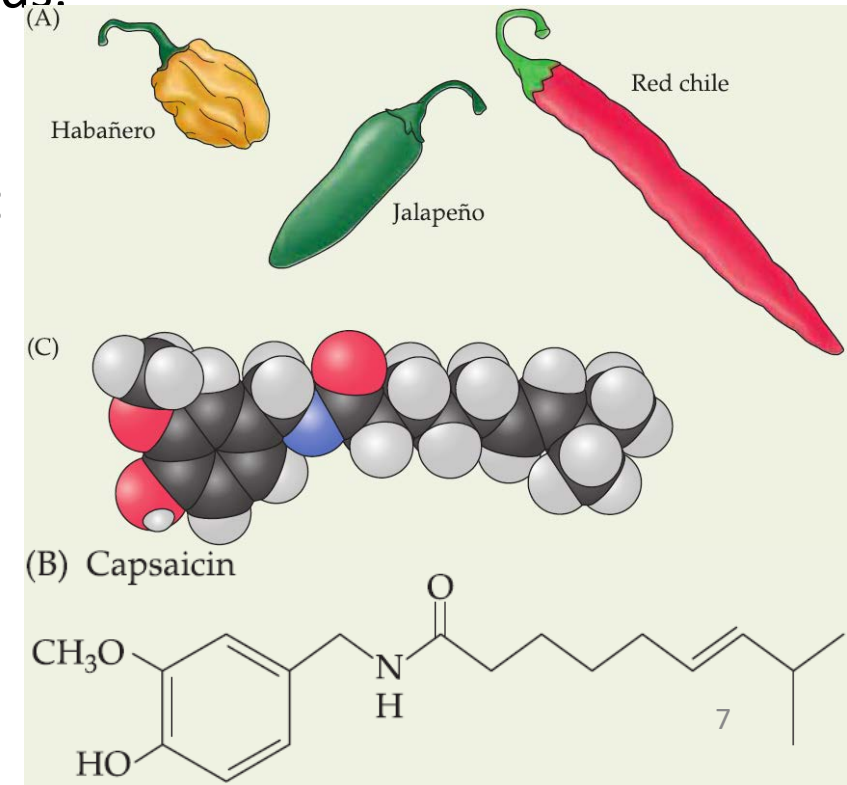


Nociceptive axon subtypes

- Most of the slower-conducting, unmyelinated C fiber nociceptors respond to all forms of nociceptive stimuli--thermal, mechanical, and chemical--and are therefore said to be polymodal.
- However, C-fiber nociceptors are also heterogeneous:
  - Subsets respond preferentially to heat or chemical stimulation rather than mechanical stimulation.
  - Further subtypes of C-fiber nociceptors are especially responsive to chemical irritants, acidic substances, or cold.
- Each of the major classes of nociceptive afferents is composed of multiple subtypes with distinct sensitivity profiles.

Transduction and transmission of nociceptive signals

- Significant insights have come from the identification of a specific receptor associated with the sensation of noxious heat.
- The threshold for perceiving a thermal stimulus as noxious is around 43°C (110°F), and this pain threshold corresponds with the sensitivity of subtypes of Aδ- and C-fiber nociceptive endings.
- The receptor that confers this sensitivity to heat also confers sensitivity to capsaicin, the ingredient in chili peppers responsible for the tingling or burning sensation produced by spicy foods.
- The so-called vanilloid receptor (TRPV1), found in both C and Aδ fibers, is a member of the larger family of **transient receptor potential** (**TRP**) channels, first identified in studies of the phototransduction pathway in fruit flies and now known to comprise a large number of receptors sensitive to different ranges of heat and cold.



Nociceptive receptors

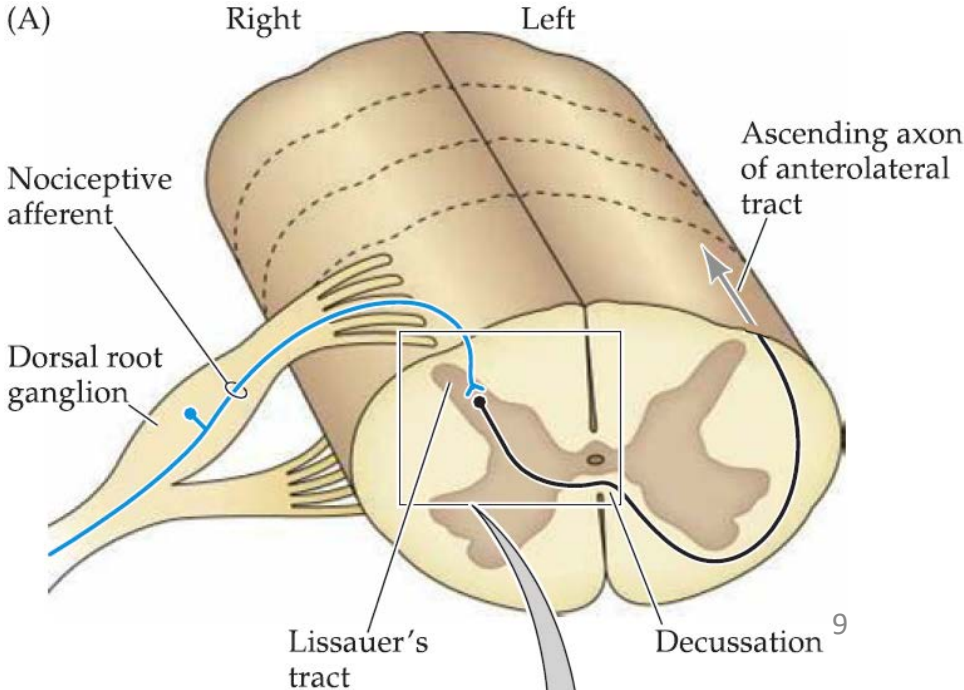
- Structurally, TRP channels resemble voltage-gated potassium or cyclic nucleotide-gated channels, having six transmembrane domains with a pore between domains 5 and 6.
  - Under resting conditions, the pore of the channel is closed.
  - In the open, activated state, these receptors allow an influx of sodium and calcium that initiates the generation of action potentials in the nociceptive fibers.

- Since the same receptor is responsive to heat as well as capsaicin, it is not surprising that many people experience the taste of chili peppers as “hot”.

- The receptors responsible for the transduction of mechanical and chemical forms of nociceptive stimulation are less well understood.

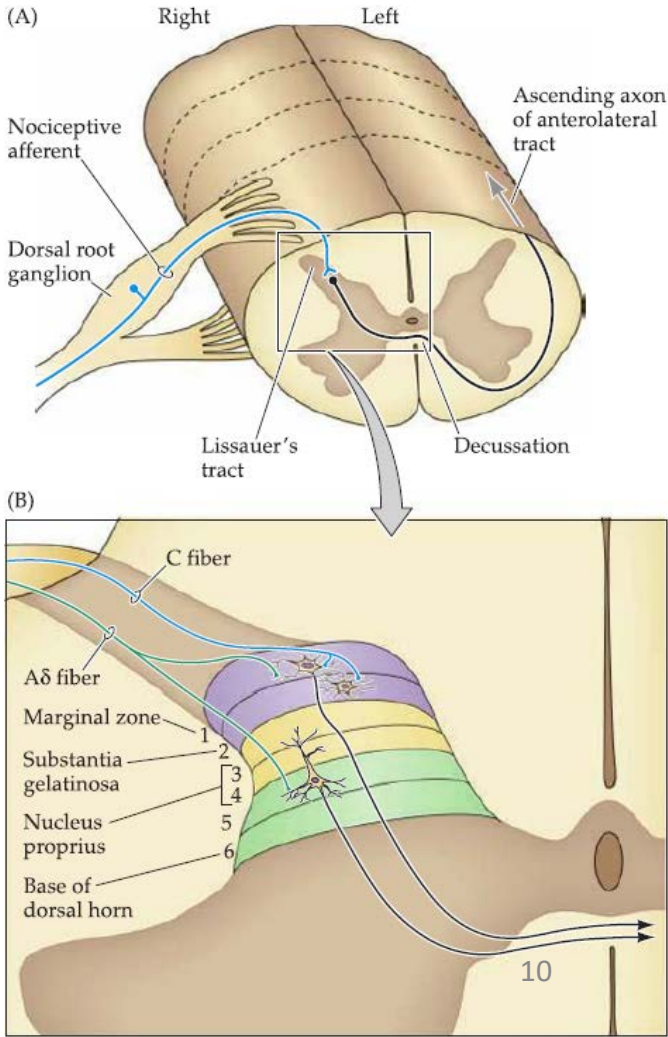
Central pain pathways

- Pathways responsible for pain originate with other sensory neurons in dorsal root ganglia and, like other sensory nerve cells, the central axons of nociceptive nerve cells enter the spinal cord via the dorsal roots.
- When these centrally projecting axons reach the dorsal horn of the spinal cord, they branch into ascending and descending collaterals, forming the **dorsolateral tract of Lissauer** (named after the German neurologist who first described this pathway in the late nineteenth century).
- Axons in Lissauer's tract typically run up and down for one or two spinal cord segments before they penetrate the gray matter of the dorsal horn.



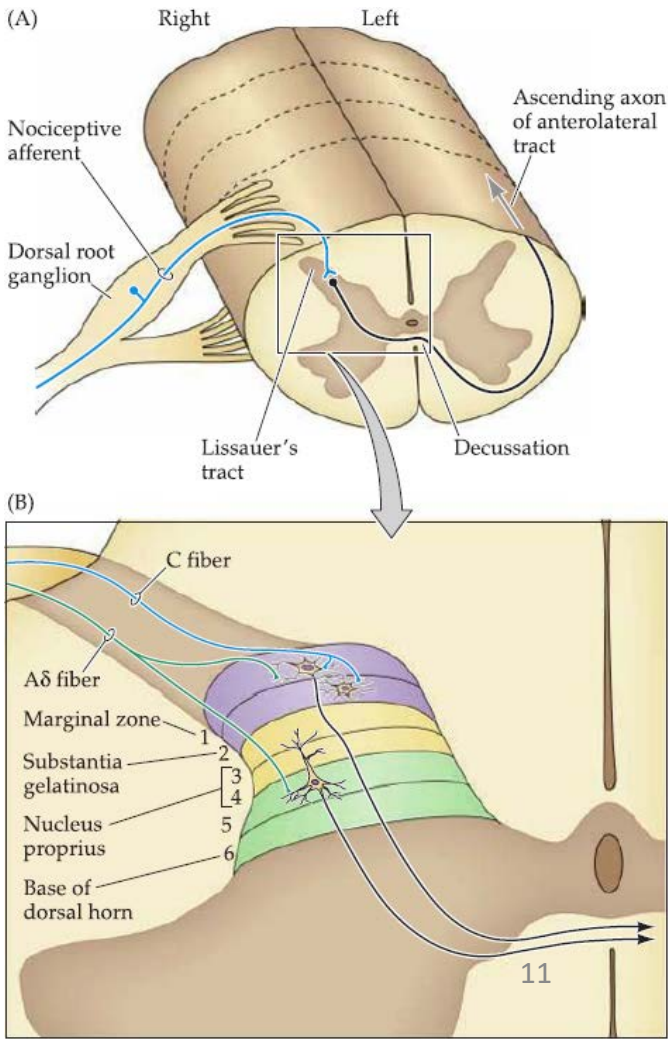
Central pain pathways

- Once within the dorsal horn, the axons give off branches at contact second-order neurons located in Rexed's laminae 1, 2, and 5.
- Rexed's laminae are the descriptive divisions of the spinal gray matter in cross section, named after the neuroanatomist who described these details in the 1950s.
  - Laminae 1 and 5 contain projection neurons whose axons travel to brainstem and thalamic targets.
  - Lamina 2 contains spinal cord interneurons.
- These afferent terminations are organized in a lamina-specific fashion:
  - C fibers terminate exclusively in Rexed's laminae 1 and 2.
  - Aδ fibers terminate in laminae 1 and 2.
  - Non-nociceptive (Aβ) afferents terminate primarily in laminae 5, and a subset of the lamina 5 neurons receive converging inputs from nociceptive and non-nociceptive afferents
  - These multimodal lamina 5 neurons are called **wide-dynamic-range neurons**.



Central pain pathways

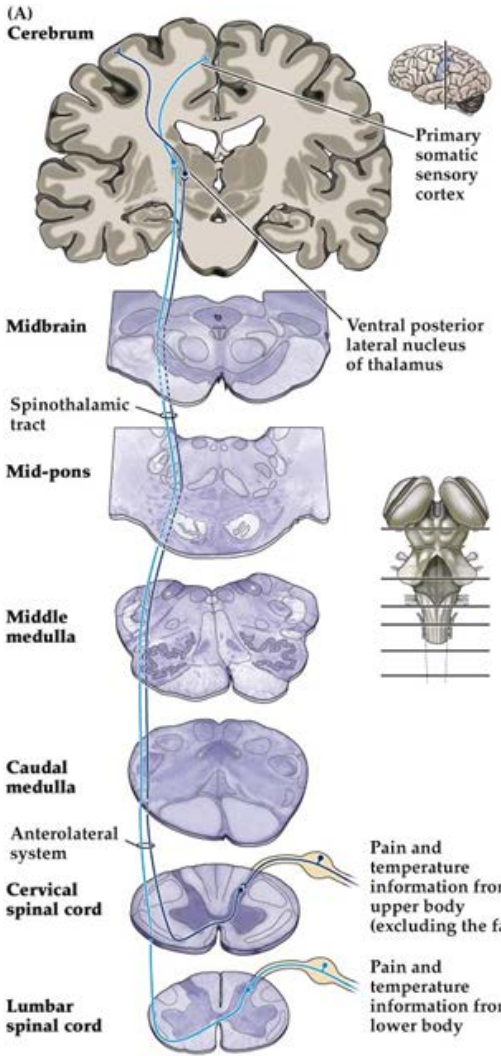
- The axons of the second-order neurons in laminae 1 and 5 of the dorsal horn of the spinal cord cross the midline and ascend to the brainstem and thalamus in the anterolateral (also called ventrolateral) quadrant of the contralateral half of the spinal cord.
- The neural pathway that conveys pain and temperature information to higher centers is often referred to as the **anterolateral system**, to distinguish it from the dorsal column-medial lemniscal system that conveys mechanosensory information.
- Axons conveying information for the anterolateral system and the dorsal column-medial lemniscal system travel in different parts of the spinal cord white matter.
- This difference provides a clinically relevant sign that is useful for defining the locus of a spinal cord lesion.

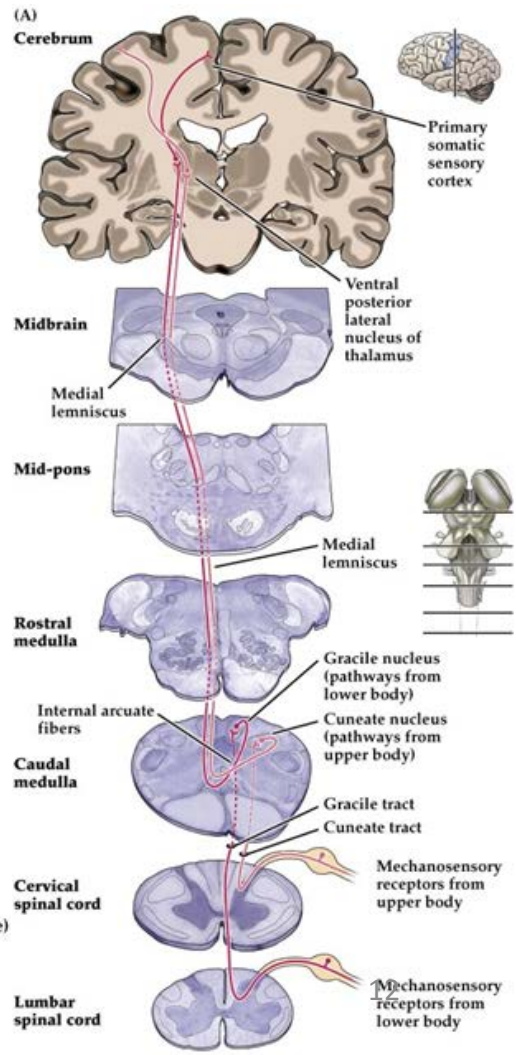


Nociceptive and mechanosensory pathways

- Dorsal column-medial lemniscal system:
  - Axons of the first-order neurons for the dorsal column-medial lemniscal system enter the spinal cord, turn, and ascend in the ipsilateral dorsal columns all the way to the medulla, where they synapse on neurons in the dorsal column nuclei.
  - The axons of neurons in the dorsal column nuclei then cross the midline and ascend to the contralateral thalamus.

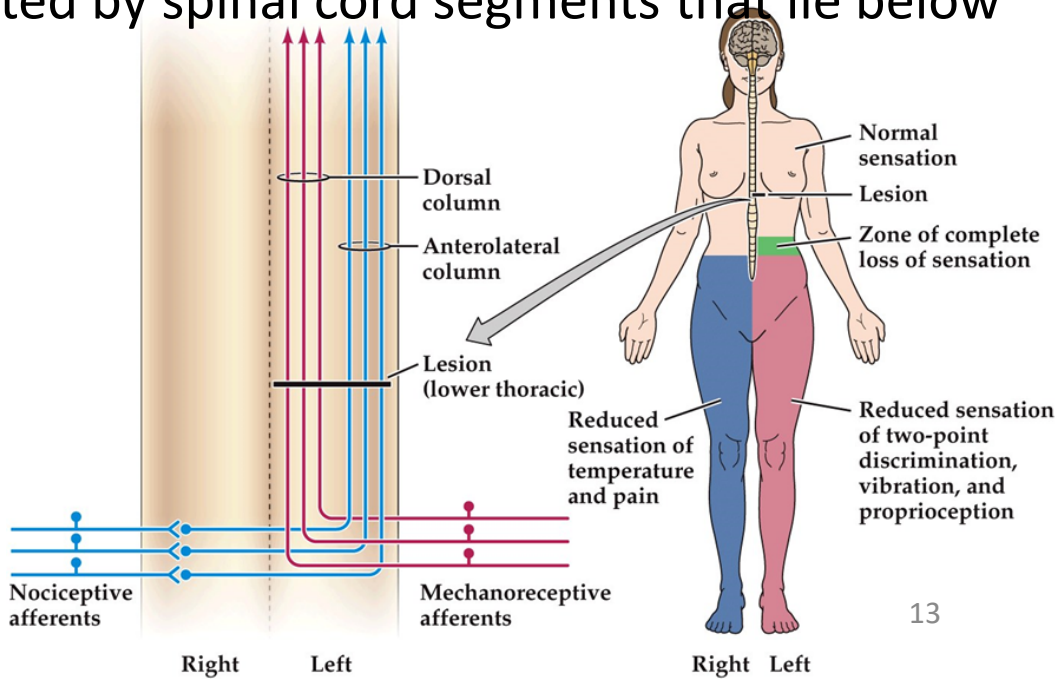
- Anterolateral system:
  - First-order neurons contributing to the anterolateral system terminate in the dorsal horn.
  - Second-order neurons in the dorsal horn send their axons across the midline and ascend on the contralateral side of the cord (in the anterolateral column) to their targets in the thalamus and brainstem.





Nociceptive and mechanosensory pathways

- Because of this anatomical difference in the site of decussation, a unilateral spinal cord lesion results in:
  - Dorsal column-medial lemniscal symptoms: loss of sensation of touch, pressure, vibration, and proprioception on the side of the body *ipsilateral* to the lesion.
  - Anterolateral symptoms: deficits of pain and temperature perception on the *contralateral* side of the body.
- The deficits are due to the interruption of fibers ascending from lower levels of the cord.
- They include all regions of the body (on either the contralateral or ipsilateral side) that are innervated by spinal cord segments that lie below the level of the lesion.
- This pattern of **dissociated sensory loss** (contralateral pain and temperature, ipsilateral touch and pressure) is a signature of spinal cord lesions and can be used to define the level of the lesion.

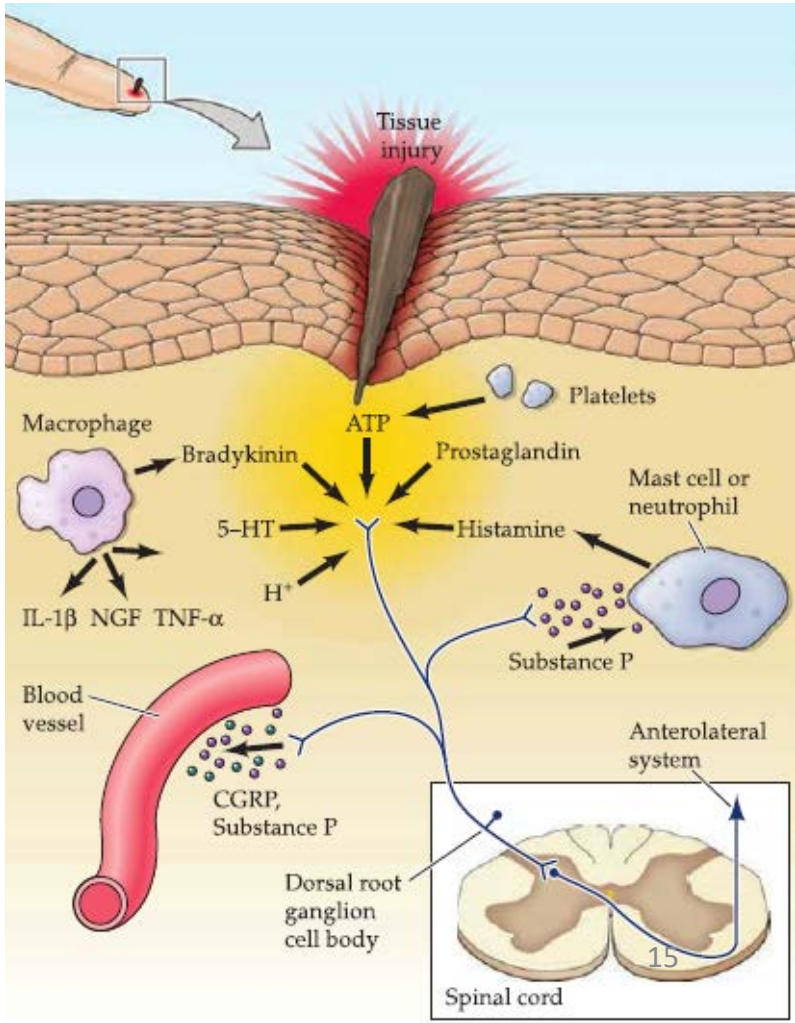


Sensitization

- Following a painful stimulus associated with tissue damage (e.g., cuts, scrapes, and bruises), stimuli in the area of the injury and the surrounding region that would ordinarily be perceived as slightly painful are perceived as significantly more so, a phenomenon referred to as **hyperalgesia**.
  - Examples?
- **Peripheral sensitization** results from the interaction of nociceptors with the "inflammatory soup" of substances released when tissue is damaged.
- These substances arise from activated nociceptors or from non-neuronal cells that reside within, or migrate to, the injured area.
- Nociceptors release peptides and neurotransmitters such as substance P, calcitonin gene-related peptide (CGRP), and ATP, all of which further contribute to the inflammatory response (vasodilation, swelling, and the release of histamine from mast cells).
- The list of non-neuronal cells that contribute to this "inflammatory soup" includes mast cells, platelets, basophils, macrophages, neutrophils, endothelial cells, keratinocytes, and fibroblasts.

Peripheral sensitization

- These cells are responsible for releasing extracellular protons, arachidonic acid and other lipid metabolites, bradykinin, histamine, serotonin, prostaglandins, nucleotides, nerve growth factor (NGF), and numerous cytokines such as interleukin-1β and tumor necrosis factor α (TNF-α).
- Most of these substances interact directly with receptors or ion channels of nociceptive fibers, augmenting their response.
- The presumed purpose of the complex chemical signaling cascade arising from local damage:
  - to protect the injured area (as a result of the painful perceptions produced by ordinary stimuli close to the site of damage)
  - to promote healing and guard against infection by means of local effects such as increased blood flow and the migration of white blood cells to the site.



Peripheral sensitization

- Identifying the components of the inflammatory soup and their mechanisms of action is a fertile area of exploration in the search for potential analgesics (compounds that reduce pain's intensity).

- For example, so-called NSAIDs (*n*on*s*teroidal *a*nti-*i*nflammatory *d*rugs), which include aspirin and ibuprofen, act by inhibiting cyclooxygenase (COX), an enzyme important in the biosynthesis of prostaglandins.

Central sensitization

- **Central sensitization** refers to an immediate-onset, activity-dependent increase in the excitability of neurons in the dorsal horn of the spinal cord following high levels of activity in the nociceptive afferents.
- As a result, activity levels in nociceptive afferents that were subthreshold prior to the sensitizing event become sufficient to generate action potentials in dorsal horn neurons, contributing to an increase in pain sensitivity.
- The induction of pain by a normally innocuous stimulus is referred to as **allodynia**.
- One form of central sensitization, called “windup”, involves a progressive increase in the discharge rate of dorsal horn neurons in response to repeated low-frequency activation of nociceptive afferents.
- The sustained depolarization of the dorsal horn neurons results in part from the activation of voltage-dependent L-type calcium channels, and in part from the removal of the Mg block of NMDA receptors.
- Removing the Mg block increases the sensitivity of the dorsal horn neuron to glutamate, the neurotransmitter in nociceptive afferents.

Neuropathic pain

- As injured tissue heals, the sensitization induced by peripheral and central mechanisms typically declines and the threshold for pain returns to pre-injury levels.
- However, when the afferent fibers or central pathways themselves are damaged--a frequent complication in pathological conditions including diabetes, shingles, AIDS, multiple sclerosis, and stroke--these processes can persist.
- The resulting condition is referred to as **neuropathic pain**: a chronic, intensely painful experience that is difficult to treat with conventional analgesic medications.
- Neuropathic pain can arise spontaneously (i.e., without any stimulus), or it can be produced by mild stimuli that are common to everyday experience, such as the gentle touch and pressure of clothing, or warm and cool temperatures.

The placebo effect

- The word *placebo* means "I will please", and the **placebo effect** is defined as a physiological response following the administration of a pharmacologically inert "remedy".
- In one classic study, medical students were given one of two different pills, one said to be a sedative and the other a stimulant.
  - In fact, both pills contained only inert ingredients
- Of the students who received the "sedative", more than two-thirds reported feeling drowsy.
  - Students who took two such pills felt sleepier than those who took only one.
- Conversely, a large fraction of the students who took the "stimulant" reported that they felt less tired.
- Moreover, about one-third of the entire group reported side effects ranging from headaches and dizziness to tingling extremities and a staggering gait!
- Only 3 of the 56 students in the group reported that the pills they took had no appreciable effect.