Lecture 16- Fall 2023

Dr. DeCoster

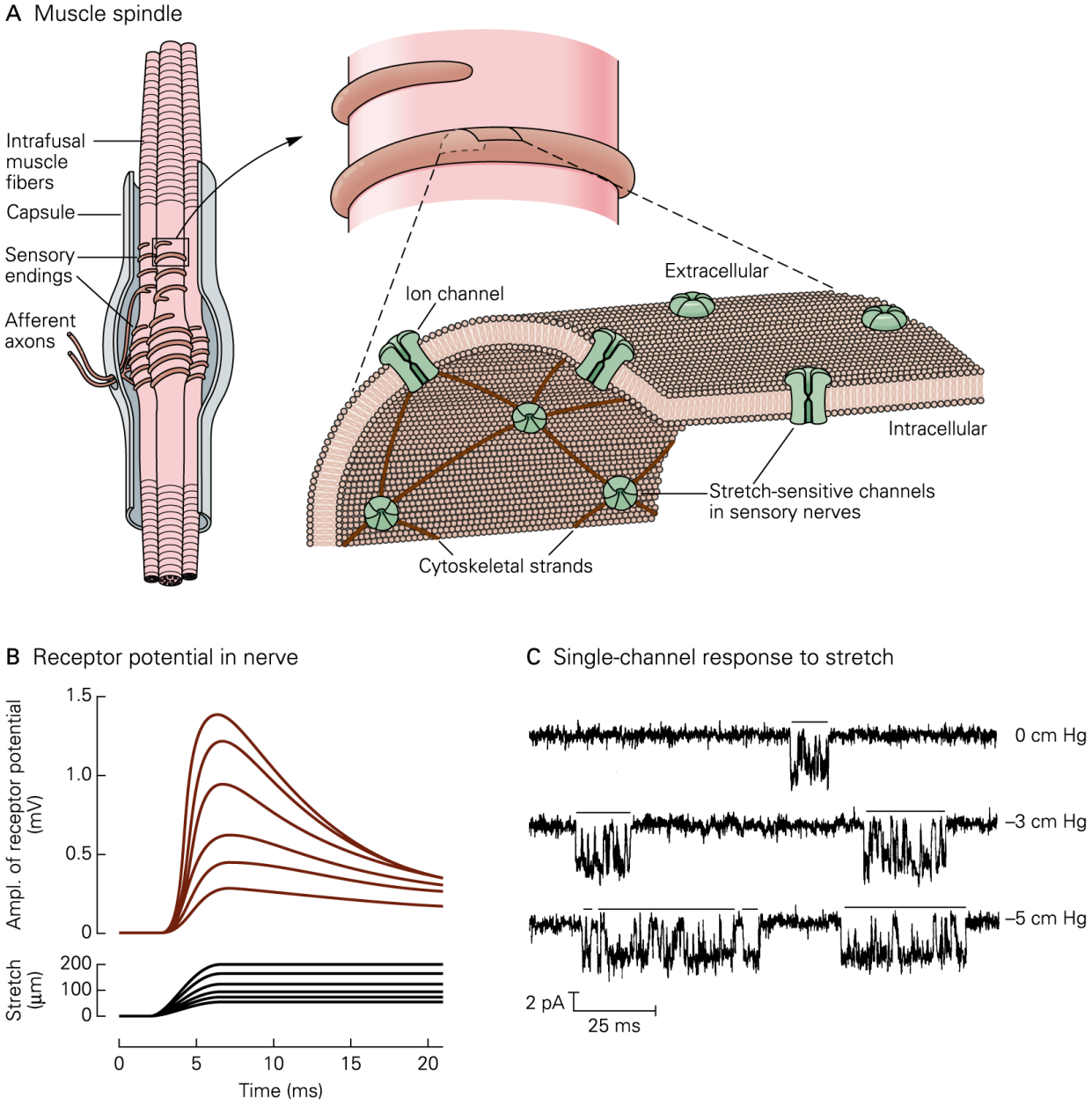
Sensory Integration including Pain

& thermal sensation

Incl. chap. 49 in Guyton and Hall

Receptors transduce specific types of energy into an electrical signal

- Mechanisms for transducing stimulus energy into the receptor potential vary with the types of physical stimuli
- Mechanoreceptors, for example sense physical deformation of the tissue in which they reside.
- Mechanical pressure, such as pressure on the skin or stretch of muscles, is transduced into electrical energy by the physical impact of the stimulus on cation channels in the membrane that are linked to the cytoskeleton. (Fig. 21-2A)
- Mechanical stimulation deforms the receptor membrane, thus opening the stretch-sensitive channels, and increasing ion conductances that depolarize the receptor (Fig. 21-2B).


A Muscle spindle
Intrafusal muscle fibers
Capsule
Sensory endings
Afferent axons
Ion channel
Extracellular
Intracellular
Stretch-sensitive channels in sensory nerves
Cytoskeletal strands
B Receptor potential in nerve
Ampl. of receptor potential (mV)
1.5
1.0
0.5
0
Stretch (μm)
200
100
0
0
5
10
15
20
Time (ms)
C Single-channel response to stretch
0 cm Hg
–3 cm Hg
–5 cm Hg
2 pA
25 ms

Sensory receptors transduce energy

- The depolarizing receptor potential for stretch-sensitive channels is therefore similar in mechanism to the excitatory postsynaptic potential.
- The amplitude of the receptor potential is proportional to the stimulus intensity: by opening more ion channels for a longer time, strong pressure produces a greater depolarization than does weak pressure.
- Removal of the stimulus relieves mechanical stress on the receptor membrane and causes stretch-sensitive channels to close

Each receptor responds to a narrow range of stimulus energy

- The receptor behaves as a filter for a narrow range or *bandwidth* of energy.
- Under normal circumstances each sensory neuron is sensitive primarily to one type of stimulus; however, this is not absolute.
- If a stimulus is strong enough, it can activate several kinds of fibers.

The spatial distribution of sensory neurons activated by a stimulus conveys information about the stimulus location

- In somatic sensation the spatial distribution of receptors conveys information about the location of the stimulus on the body. Spatial awareness involves 3 distinct perceptual abilities:
- 1) locating the site of stimulation on the body
- 2) discriminating the size and shape of objects
- 3) resolving the fine detail of the stimulus.
- These spatial abilities are linked to the structure of the *receptive field* of each sensory neuron- that area within the receptive sheet where stimulation excites the cell.

The receptive fields of sensory neurons in the somatosensory system define the spatial resolution of a stimulus

- Each receptor responds only to stimulation within its receptive field. A stimulus that affects an area larger than the receptive field of one receptor will activate adjacent receptors.
- The size of the stimulus thus influences the total number of receptors that are stimulated.
- A large object such as a basketball held between both hands will contact and activate more touch receptors than a pencil grasped between the thumb and index finger

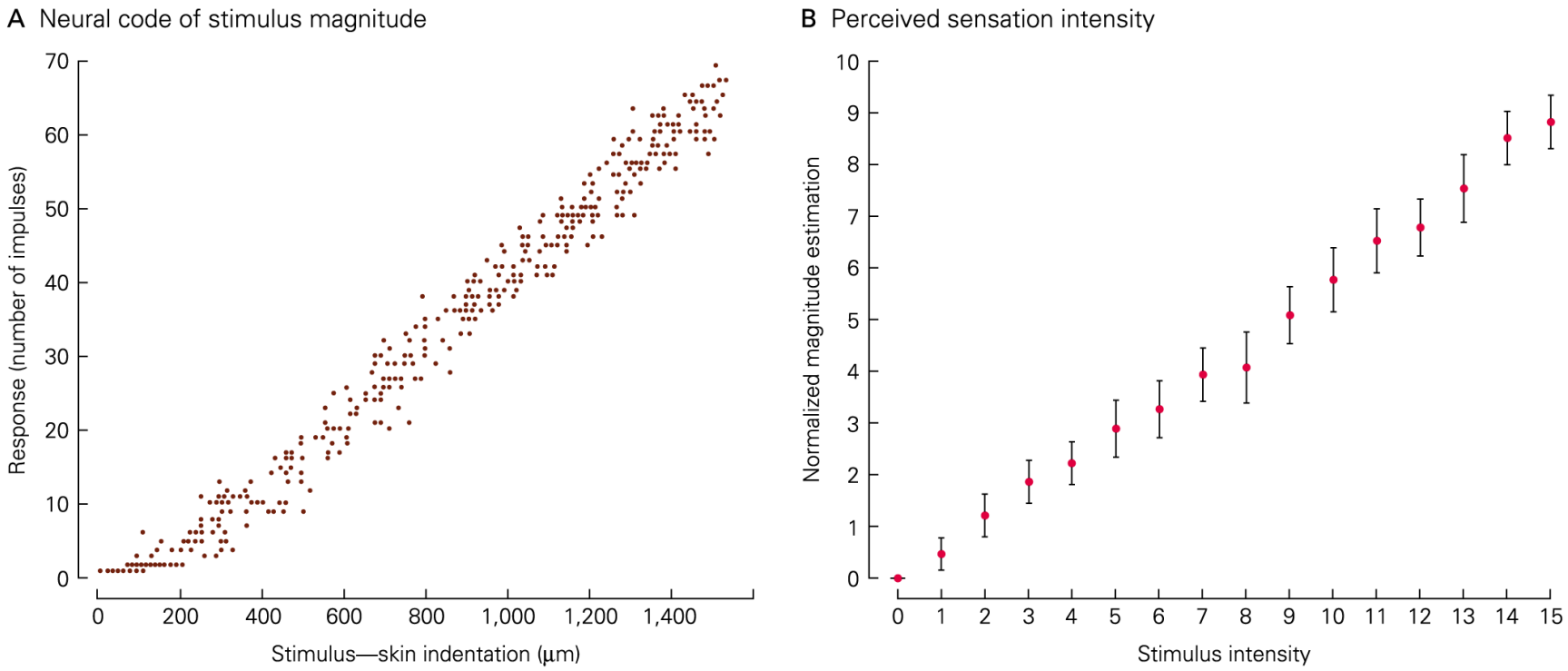
Intensity of sensation is determined by the stimulus amplitude

- Natural stimuli vary greatly in intensity
- Psychophysical laws govern the perception of stimulus intensity
- For example, in 1834 Weber demonstrated that the sensitivity of the sensory system to differences depends on the absolute strength of the stimuli:
- We can easily perceive that 1 kg is different from 2 kg, but it is difficult to distinguish 50 kg from 51 kg, yet both sets differ by 1 kg!
- This relationship is expressed in the equation now known as Weber's law:

- $\Delta S = K(S)$ where ΔS is the minimal difference in strength between a reference stimulus S and a second stimulus that can be discriminated, and K is a constant. This is termed the just noticeable difference or difference limit.
- It follows that the difference in magnitude necessary to discriminate between a reference stimulus and a second stimulus increases with the strength of the reference stimulus.

Intensity of stimulus

- The lowest stimulus strength a subject can detect is termed the sensory threshold.
- Stimulus intensity is encoded by the frequency of action potentials in sensory nerves.
- The details of neuronal activity- how long a neuron fires, how fast, and how many neurons are firing, encode the intensity and time course of sensory experience.
- Thus, strong stimuli evoke larger receptor potentials, which generate a greater number and a higher frequency of action potentials Fig. 21-8



The firing rates of sensory nerves encode the stimulus magnitude. A: The number of action potentials per second in a slowly adapting mechanoreceptor due to the amount of skin indentation. This receptor required a minimum indentation of 80 um to respond. The relationship between increases in frequency of firing and pressure on the skin is linear.

B: Estimates made by a human subject of the magnitude of sensation produced by pressure on the hand increase linearly as a function of skin indentation. These data suggest that the neural coding of stimulus intensity is faithfully transmitted from the peripheral receptors to the cortical centers that mediate sensation.

The duration of a sensation is determined in part by the adaptation rates of receptors

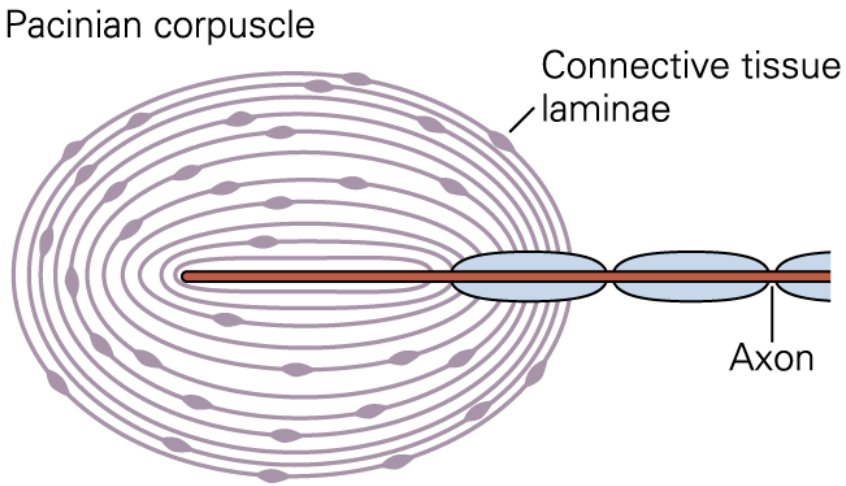
- The temporal properties of a stimulus are encoded as changes in the frequency of sensory neuron activity.
- Stimuli appear, rise in intensity, fluctuate or remain steady, and eventually disappear.
- Many receptors signal the rate at which the stimulus increase or decreases in intensity by rapidly changing their firing rate.
- For example, when a probe touches the skin, the initial spike discharge is proportional to both the speed at which the skin is indented and the total amount of pressure.

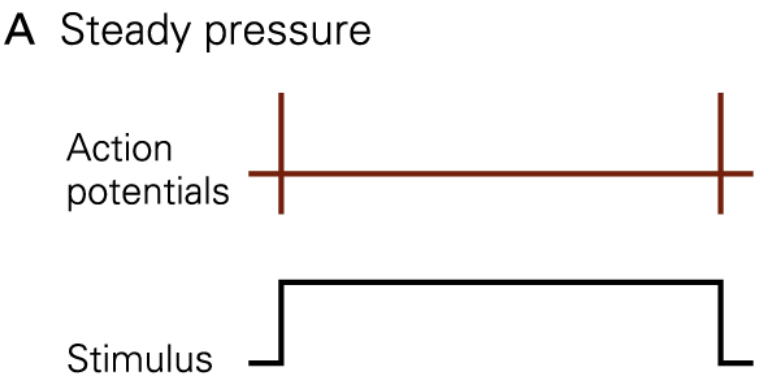
Adaptation

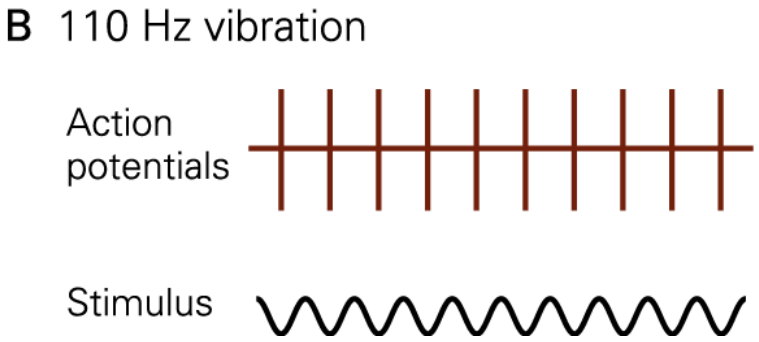
- Although the continuous firing of a sensory neuron encodes the intensity of the stimulus, if the stimulus persists for several minutes without a change in position, its intensity diminishes and sensation is lost. This decrease is called *adaptation*.
- All sensory receptors adapt to constant stimulation
- Receptor adaptation is thought to be an important neural basis of perceptual adaptation in which constant stimulus fades from consciousness.

rapidly adapting receptors

- Adaptation of rapidly adapting receptors depends on two factors:
- 1) in many of these receptors the prolonged depolarization of the receptor potential inactivates the spike generation mechanism in the axon.
- 2) the receptor structure filters the steady components of the stimulus by changing shape, thus decreasing the electrical signal generated by the receptor (Fig. 21-10).







Receptor morphology influences adaptation in rapidly adapting mechanoreceptors. The Pacinian corpuscle is a rapidly adapting mechanoreceptor located in the skin. The receptor consists of concentrically arranged, fluid-filled lamellae of connective tissue that form a capsule surrounding the sensory nerve terminal. Because of this capsule, the sensory endings specialize in the detection of motion.

A. The capsule of the Pacinian corpuscle deflects steady pressure. The receptor responds with one or two action potentials at the beginning and end of a pressure stimulus but is silent when the stimulus is constant in intensity. During steady pressure the capsule changes shape, reducing stretch of the nerve membrane.

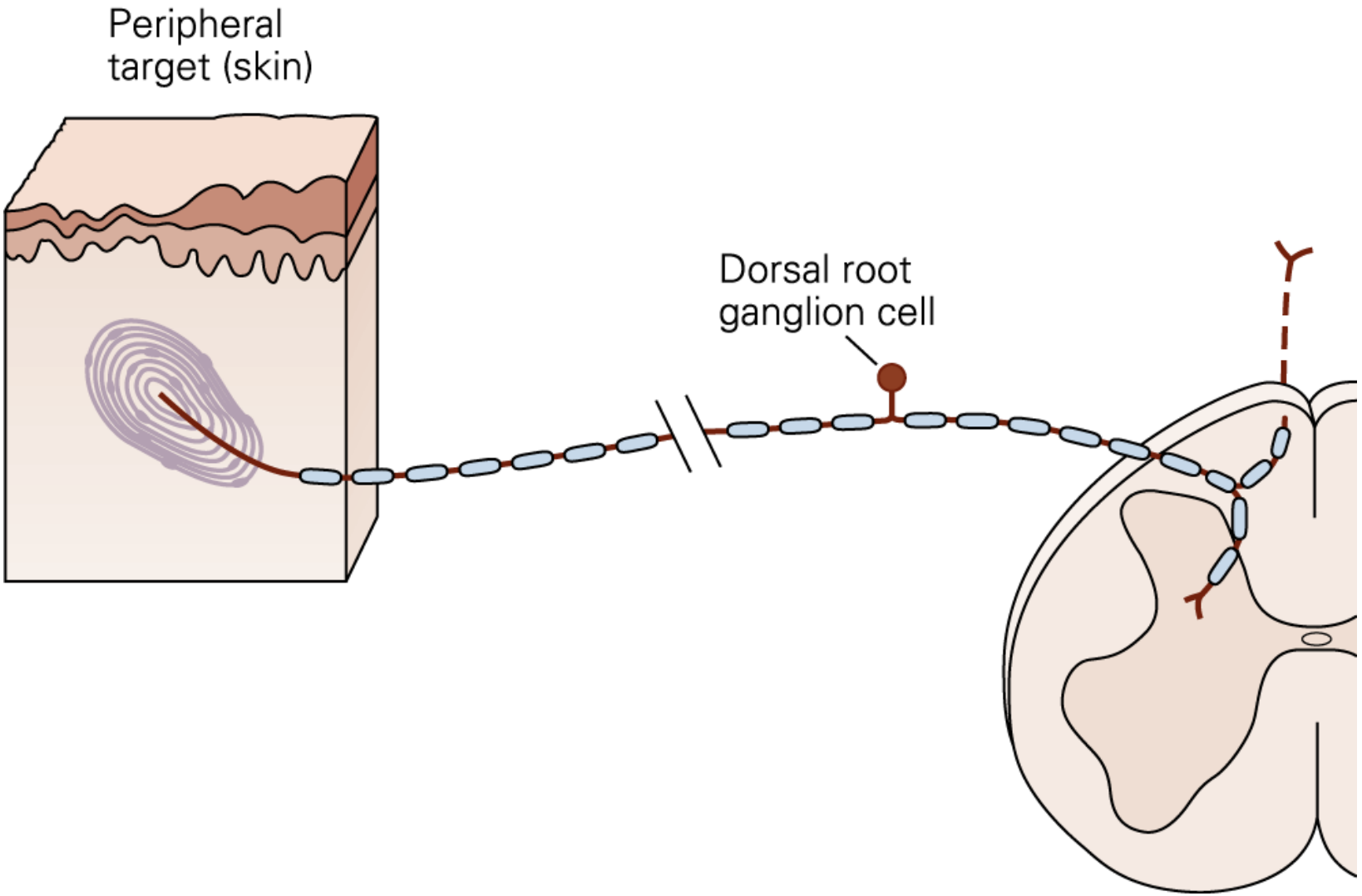
B. Pacinian corpuscles are sensitive to vibration. Rapid movements are transmitted through the lamellae to the nerve terminal, generating signals for each cycle of the vibration.

Somatic sensation

- Somatic sensation has four major modalities:
- 1) discriminative touch- required to recognize the size, shape and texture of objects and their movement across the skin
- 2) proprioception- the sense of static position and movement of the limbs and body
- 3) nociception- the signaling of tissue damage or chemical irritation, typically perceived as pain or itch
- 4) temperature sense- warmth and cold

The DRG neuron is the sensory receptor in the somatic sensory system

- Irrespective of modality, all somatosensory information from the limbs and trunk is conveyed by dorsal root ganglion neurons.
- The DRG neuron is well-suited to its two principal functions: 1) stimulus transduction and 2) transmission of encoded stimulus information to the central nervous system.
- The cell body lies in a ganglion on the dorsal root of a spinal nerve.
- The axon has two branches, one projecting to the periphery and one projecting to the CNS


Peripheral
target (skin)
Dorsal root
ganglion cell

DRG neuron

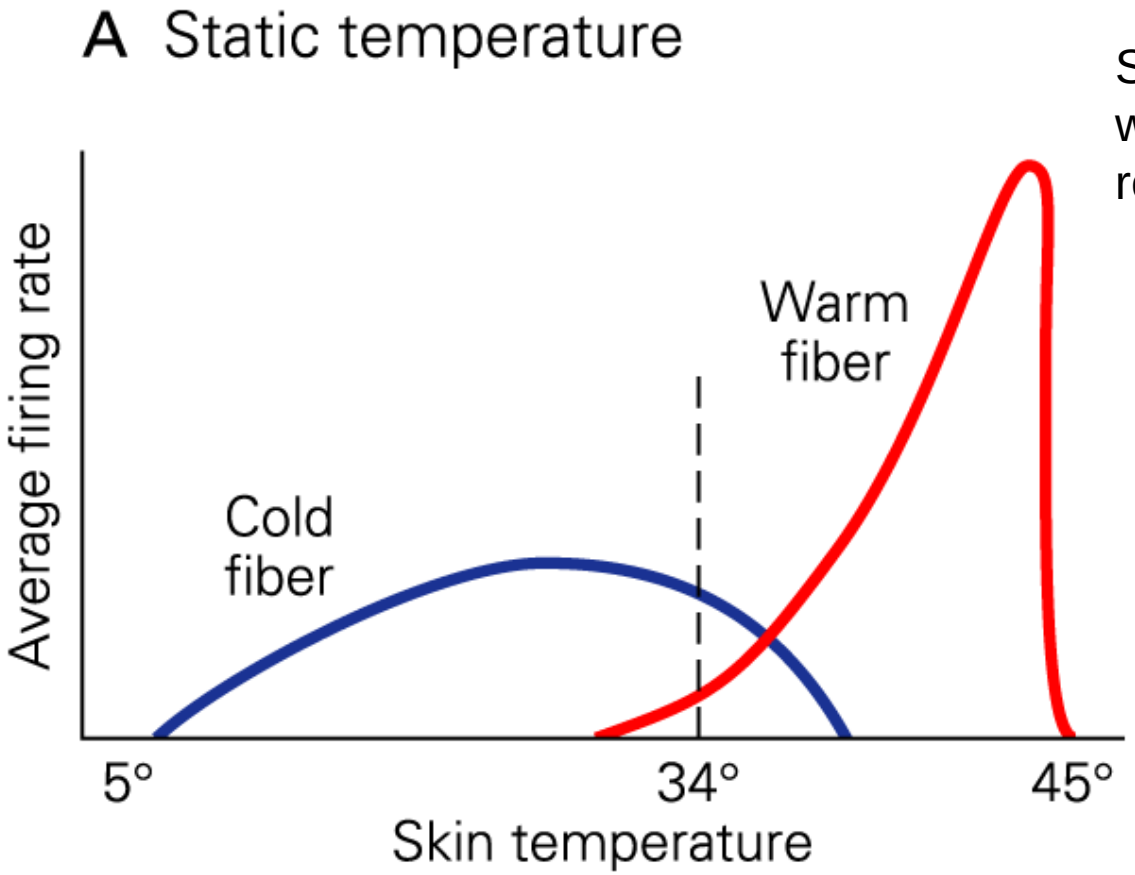
- The terminal of the peripheral branch of the axon is the only portion of the DRG cell that is sensitive to natural stimuli.
- The properties of the nerve terminal determine the sensory function of each DRG neuron.
- The remainder of the peripheral branch, together with the central branch, is called the *primary afferent fiber*; it transmits the encoded stimulus information to the spinal cord or brain stem.

DRG neuron-2

- The peripheral terminals of DRG neurons are of two types:
- the terminal may be a bare nerve ending or the nerve ending may be encapsulated by a nonneural structure.
- DRG neurons with encapsulated terminals mediate the somatic modalities of touch and proprioception; they sense stimuli that indent or otherwise physically deform the receptive surface.
- In contrast, DRG neurons with bare nerve endings mediate painful or thermal sensations.
- Mechanoreceptors and proprioceptors are innervated by DRG neurons with large-diameter, myelinated axons that conduct action potentials rapidly.
- Thermal receptors and nociceptors have small-diameter axons that are either unmyelinated or thinly myelinated; these nerves conduct impulses more slowly.

Other somatic sensations are mediated by a variety of specialized receptors

- Warmth and cold are mediated by thermal receptors.
- Humans recognize four distinct types of thermal sensation: cold, cool, warm, and hot. These thermal sensations result from differences between the external temperature of the air or of objects contacting the body and the normal ***skin*** temperature of 34 deg. C.
- Thermal receptors modulate their firing as a function of temperature. At constant temperature they have tonic discharges, firing action potentials at a steady rate governed by the actual temperature sensed.
- Unlike mechanoreceptors, which are silent in the absence of tactile stimuli, cold and warm receptors fire action potentials continuously at low rates (2-5 spikes per second) when the skin temperature is set at its normal value of 34 deg. C. Fig. 22-9A



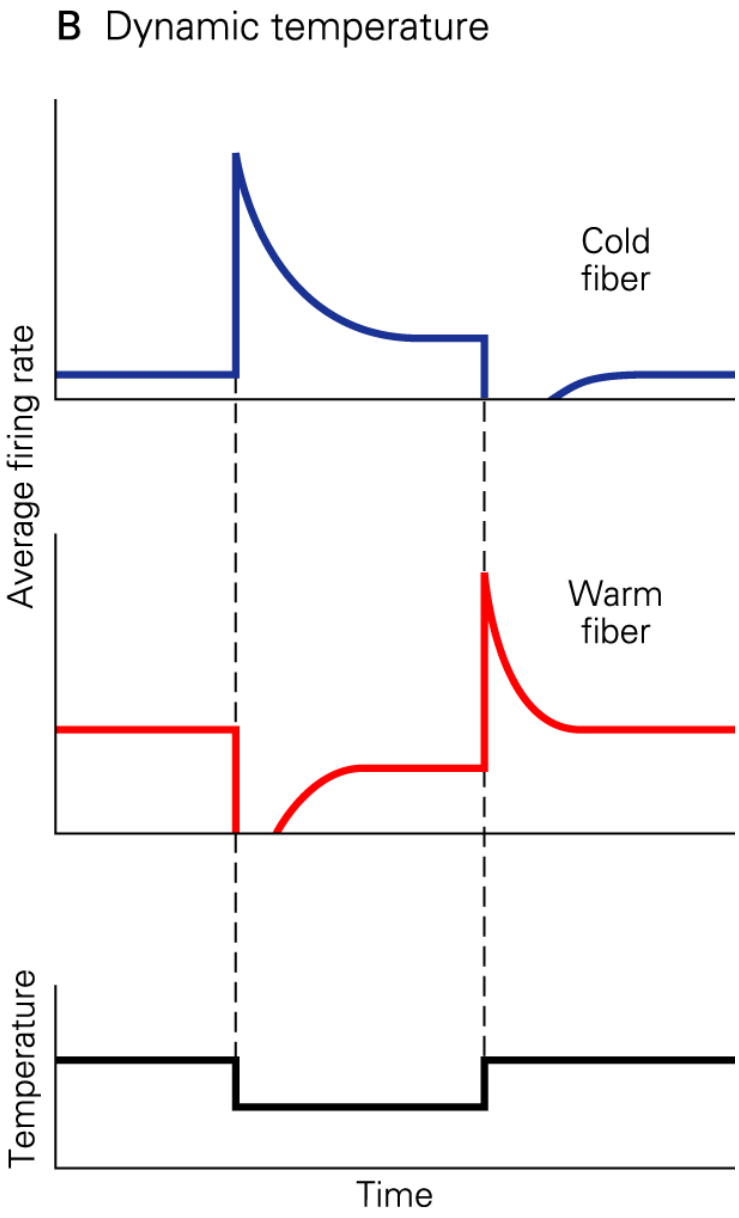
Skin temperature is coded by warmth receptors and cold receptors.

A. Static temperatures. Cold receptors and warm receptors differ in the range of steady-state temperatures to which they respond and in their peak temperature sensitivities. Cold receptors respond to steady-state temperatures of 5-40 deg. C., while warm receptors are tonically active at steady temperatures of 29-45 deg.C.

At the normal skin temperature of 34 deg. C., cold receptors are more active than warmth receptors.

Thermal receptors-2

- The steady-state firing rate does not increase or decrease monotonically if the skin is slowly warmed or cooled. Instead, each class of thermal receptor shows peak firing at a preferred skin temperature (25 deg. C. and 45 deg. C. for cold and warm receptors, respectively)
- Temperatures above or below these optimal firing temperatures evoke progressively weaker responses.
- Therefore, individual cold and warmth receptors do not give precise reading of skin temperature, rather the code for skin temperature involves comparing the relative activity of the different populations of thermal receptors and nociceptors.
- The coding of object temperature is analogous to the representation of color in the visual system.
- In each of these modalities there are populations of receptors sensitive to limited ranges of the energy bandwidth.
- Each population has a peak sensitivity in a specific position of the energy band. The perceived temperature (or color) is determined by the relative activity of each of the responding populations of receptors.
- Thermal receptors are very sensitive to differences between the temperature of the skin and the temperature of objects that are touched. Rapid changes in skin temperature evoke dynamic responses (Fig. 22-9B).



Both receptors are more sensitive to changes in skin temperature than to constant temperatures.

Cooling the skin below the resting level evokes a sharp rise in the firing rate of cold receptors and silences warmth receptors. If the cold temperature is maintained, the firing rates of the cold receptors ***adapt***.

When the skin temperature is rewarmed to the resting level, cold receptors are briefly silenced, whereas warmth receptors fire a burst of impulses. Warming the skin produces the opposite firing patterns in warmth and cold receptors.

Thermal receptors-3

- Warmth receptors respond proportionally to increases in skin temperature above the resting value of 34 deg. C. However, if the stimulus temperature exceeds 45 deg. C., warmth fibers fire an intense burst of impulses and then cease firing even if the heat stimulus is maintained.
- Warmth receptors are unresponsive to hot temperatures, as stimuli above 50 deg. C. fail to excite them– at these high temperatures humans perceive heat pain rather than sensations of warmth.

Pain is mediated by Nociceptors

- The receptors that respond selectively to stimuli that can damage tissue are called nociceptors (Latin *nocere*, to injure).
- Nociceptors respond directly to some noxious stimuli and indirectly to others by means of one or more chemicals released from cells in the traumatized tissue.
- A variety of substances have been proposed to act as the chemical intermediary for pain in humans: histamine, K+ released from injured cells, bradykinin, substance P, and acidity, for example.
- Humans experience burning pain when these substances stimulate nociceptors. Therefore, it is likely that most nociceptors are really chemoreceptors sensitive to the concentration of irritant chemicals released in the surrounding tissue by noxious thermal or mechanical stimuli, or to exogenous chemicals that may penetrate the skin and bind to their sensory endings.
- Some nociceptors respond to chemicals such as histamine, yielding itching sensations. These fibers become tonically active in inflamed tissue owing to the release of histamine, peptides, or certain exogenous chemicals such as allergens.

Nociceptors-2

- Three classes of nociceptors can be distinguished on the basis of type of stimulus: mechanical, thermal, and polymodal nociceptors.
- Mechanical and thermal nociceptors are activated by particular forms of noxious stimuli, whereas polymodal nociceptors are sensitive to the destructive effects of a stimulus rather than to its physical properties.

Nociceptors-3

- Mechanical nociceptors require strong, often painful tactile stimuli, such as a pinch, in order to respond.
- They are also excited by sharp objects that penetrate, squeeze, or pinch the skin (Fig. 22-11), and therefore mediate sensations of sharp or pricking pain.
- Their firing rates increase with the destructiveness of mechanical stimuli, from near-damaging to overtly destructive.
- The afferent fibers for mechanical nociceptors have bare nerve endings and, because they are myelinated, are the fastest-conducting nociceptive afferents.

Thermal Nociceptors

- Thermal nociceptors are excited by extremes of temperature as well as by strong mechanical stimuli.
- One group of thermal nociceptors is excited by noxious heat (temp. above 45 deg. C) and a second group by noxious cold (cooling the skin below 5 deg. C)

Polymodal Nociceptors

- Polymodal nociceptors respond to a variety of destructive mechanical, thermal, and chemical stimuli, such as pinch or puncture, noxious heat and cold, and irritant chemicals applied to the skin.
- These receptors are insensitive to gentle mechanical stimuli, such as stroking the skin or light pressure.
- Stimulation of these receptors in humans evokes sensations of slow, burning pain. Polymodal nociceptors provide the major sensory innervation of the tooth pulp (think root canal!)

Proprioception is mediated by mechanoreceptors in skeletal muscle and joint capsules

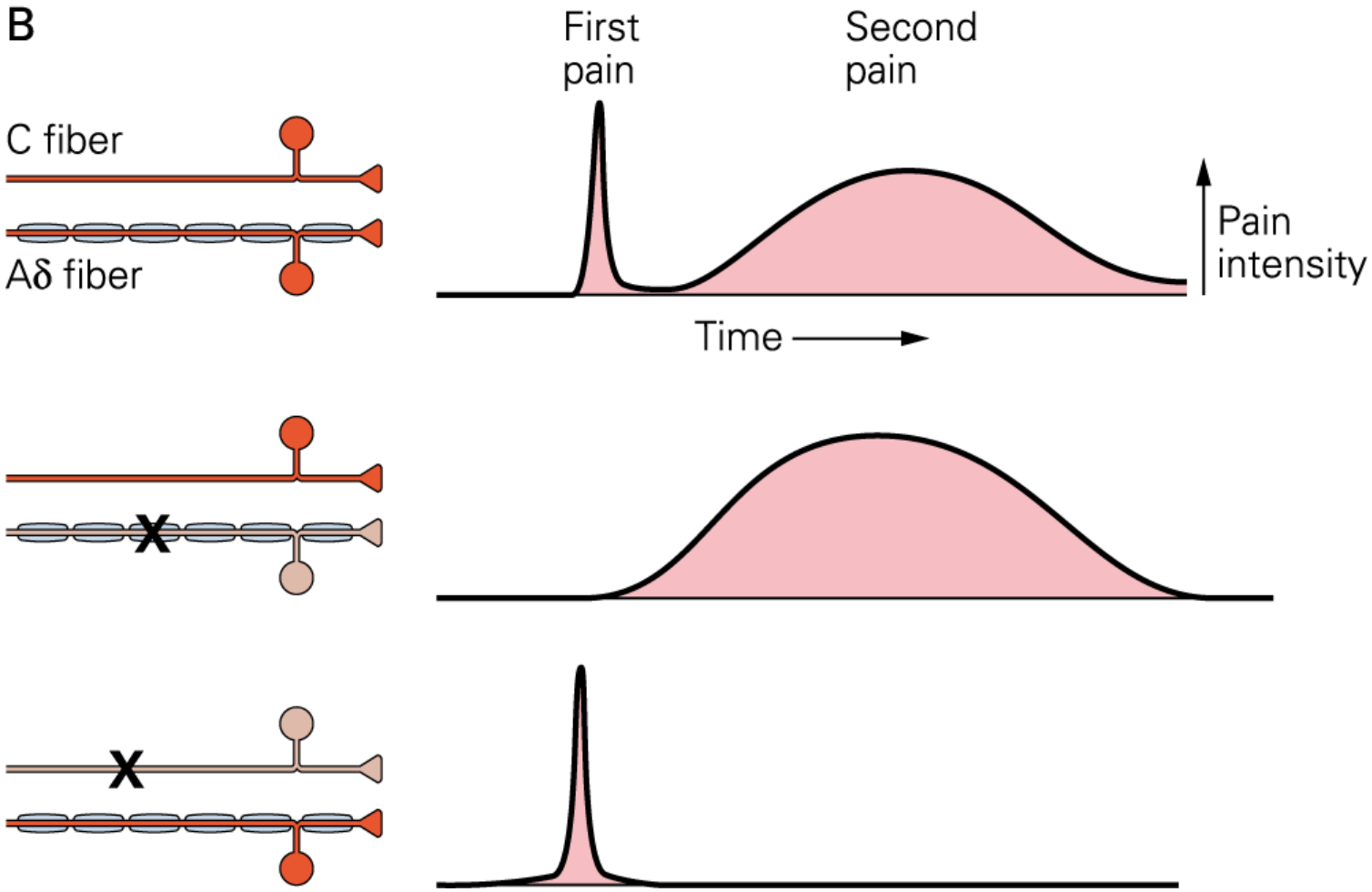
- Proprioception is the sense of position and movement of one's own limbs and body without the use of vision.
- There are two submodalities of proprioception: the sense of stationary position of the limbs (limb-position sense) and the sense of limb movement (kinesthesia).
- These sensations are important for controlling limb movements, manipulating objects that differ in shape and mass, and maintaining an upright posture.
- In addition, stretch-sensitive receptors in the skin (Ruffini endings, Merkel cells in hairy skin, and field receptors) also signal postural information. Cutaneous proprioception is particularly important for control of lip movements in speech and facial expression (think of what often happens to someone after a stroke--)

The perception of Pain

- Pain is a submodality of somatic sensation like touch, pressure, and position sense and serves an important protective function by warning of injury that should be avoided or treated.
- Although pain is mediated by the nervous system, a distinction between pain and the neural mechanisms of nociception- the response to perceived or actual tissue damage- is important both clinically and experimentally.
- Nociception does not necessarily lead to the experience of pain; thus the relationship between nociception and the perception of pain provides an example of the principle that *perception is a product of the brain's* ***abstraction*** *and* ***elaboration*** *of sensory input*.

Noxious insults activate nociceptors

- The three classes of nociceptors (mechanical, thermal, and polymodal) are widely distributed in skin and deep tissues and often work together.
- For example, when you hit your thumb with a hammer, a sharp first pain is felt immediately, followed later by a more prolonged aching, sometimes burning second pain.
- The fast sharp pain is transmitted by Aδ fibers that carry information from thermal and mechanical nociceptors; the slow dull pain is transmitted by C fibers activated by polymodal nociceptors. (Fig. 24-1).



First and second pain are carried by two different primary afferent axons. First pain is abolished by selective blockade of Aδ myelinated axons (middle) and second pain by blocking C fibers (bottom)

Noxious insults activate nociceptors

- Unlike the specialized somatosensory receptors for touch and pressure, most nociceptors are *free nerve endings*.
- The mechanism by which noxious stimuli depolarize free sensory endings and generate action potentials is not known. The membrane of the nociceptor is thought to contain proteins that convert the thermal, mechanical, or chemical energy of noxious stimuli into a depolarizing electrical potential.
- One such protein is the *receptor for capsaicin*, the active ingredient in hot peppers.
- The capsaicin, or vanilloid, receptor is found exclusively in primary afferent nociceptors and mediates the pain-producing actions of capsaicin.
- This receptor also responds to noxious heat stimuli, which suggests that it also is a transducer of painful heat stimuli.

Nociceptive afferent fibers use glutamate and neuropeptides as neurotransmitters

- Synaptic transmission between nociceptors and dorsal horn neurons is mediated by chemical neurotransmitter released from central sensory nerve endings.
- The major excitatory neurotransmitter released by Aδ and C fibers as well as by nociceptive afferents is the amino acid glutamate.
- The release of glutamate from sensory terminals evokes fast synaptic potentials in dorsal horn neurons by activating the AMPA-type glutamate receptors.

Nociceptive afferent fibers- release of neuropeptides as neurotransmitters

- Of the many neuropeptides present in nociceptive sensory neurons, substance P has been studied in most detail.

- Substance P is released from C fibers in response to tissue injury or to intense stimulation of peripheral nerves.

- Glutamate and neuropeptides are released together from primary afferent terminals, and have distinct physiological actions on postsynaptic neurons; neuropeptides such as substance P appear to enhance and prolong the actions of glutamate.

Nociceptive afferent fibers- release of neuropeptides as neurotransmitters-2

- The range of action of two classes of transmitters co-released may also differ.
- For example, the actions of glutamate released from sensory terminals are confined to postsynaptic neurons in the immediate vicinity of the synaptic terminal as a result of the efficient reuptake of amino acids into glial cells or nerve terminals.
- In contrast, neuropeptides released from sensory terminals can diffuse considerable distances from their site of release because there is no specific reuptake mechanism.
- Thus, the release of neuropeptides from a single afferent fiber is likely to influence many postsynaptic dorsal horn neurons.
- This feature, together with the fact that peptide levels significantly increase in persistent pain conditions, suggest that peptide action contribute both to the excitability of dorsal horn neurons and to the unlocalized character of many pain conditions.

Chemical factors in pain

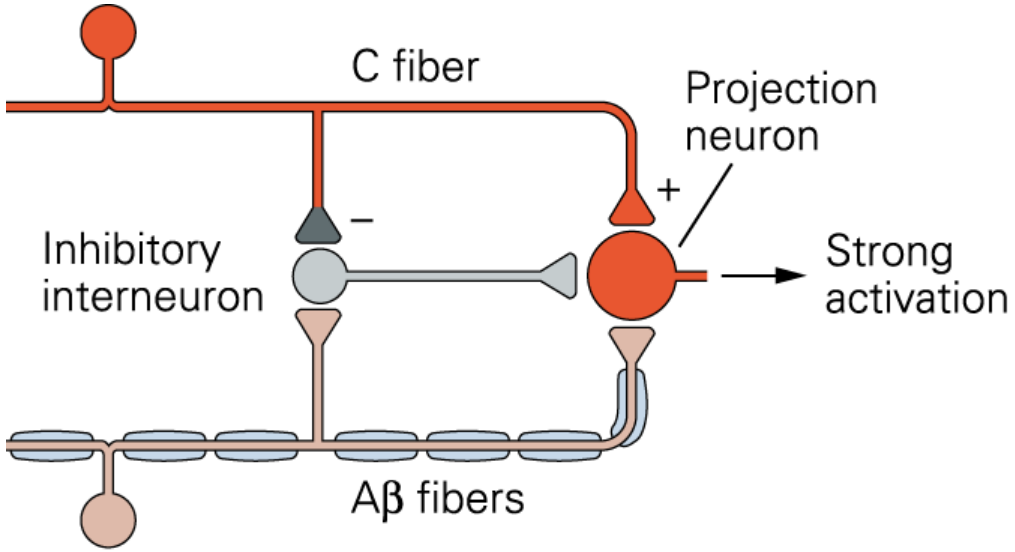
- Prostaglandin E_2 is a metabolite of arachidonic acid and is generated by the enzyme cyclooxygenase (COX) released from damaged cells.
- Aspirin and other non-steroidal anti-inflammatory analgesics are effective in controlling pain because they block COX, thereby preventing the synthesis of prostaglandins.

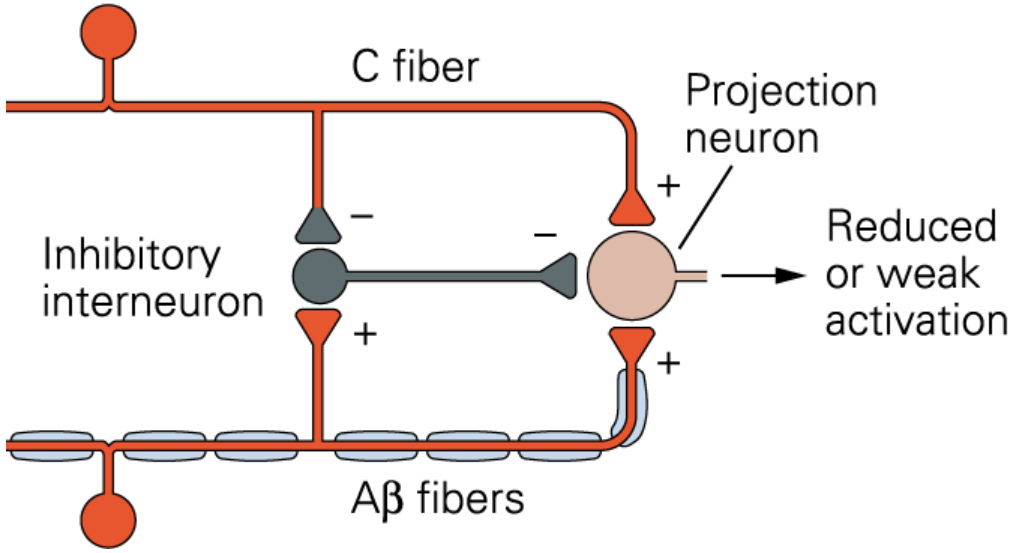
Pain can be controlled by central mechanisms

- One of the most remarkable discoveries in pain research is that the brain has modulatory circuits whose main function is to regulate the perception of pain.
- Several modulatory systems within the CNS affect responses to noxious stimuli. The initial site of modulation is in the spinal cord, where interconnections between nociceptive and nonnociceptive afferent pathways can control the transmission of nociceptive information to higher centers in the brain

Balance of activity in nociceptive and nonnociceptive primary afferent fibers can modulate pain: ***the gate control theory***

- Pain is not simply a direct product of the activity of nociceptive afferent fibers but is regulated by activity in other myelinated afferents that are not directly concerned with the transmission of nociceptive information.
- The idea that pain results from the balance of activity in nociceptive and nonnociceptive afferents was formulated in the 1960s and was called the gate control theory (Fig. 24-10).





The gate control hypothesis of pain

This hypothesis focuses on the interaction of four classes of neurons in the dorsal horn of the spinal cord: 1) nonmyelinated nociceptive afferents (C fibers), 2) myelinated nonnociceptive afferents (Aβ fibers), 3) projection neurons, and 4) inhibitory interneurons.

The projection neuron is excited by both nociceptive and nonnociceptive neurons, and the balance of this input translates into the intensity of pain. The inhibitory interneuron is spontaneously active and normally inhibits the projection neuron, thus reducing the intensity of pain. It is excited by the myelinated nonnociceptive afferent, but inhibited albeit not directly by the nonmyelinated nociceptor. The nociceptor thus has both direct and indirect effects on the projection neuron.

End!—