Pain and nociception

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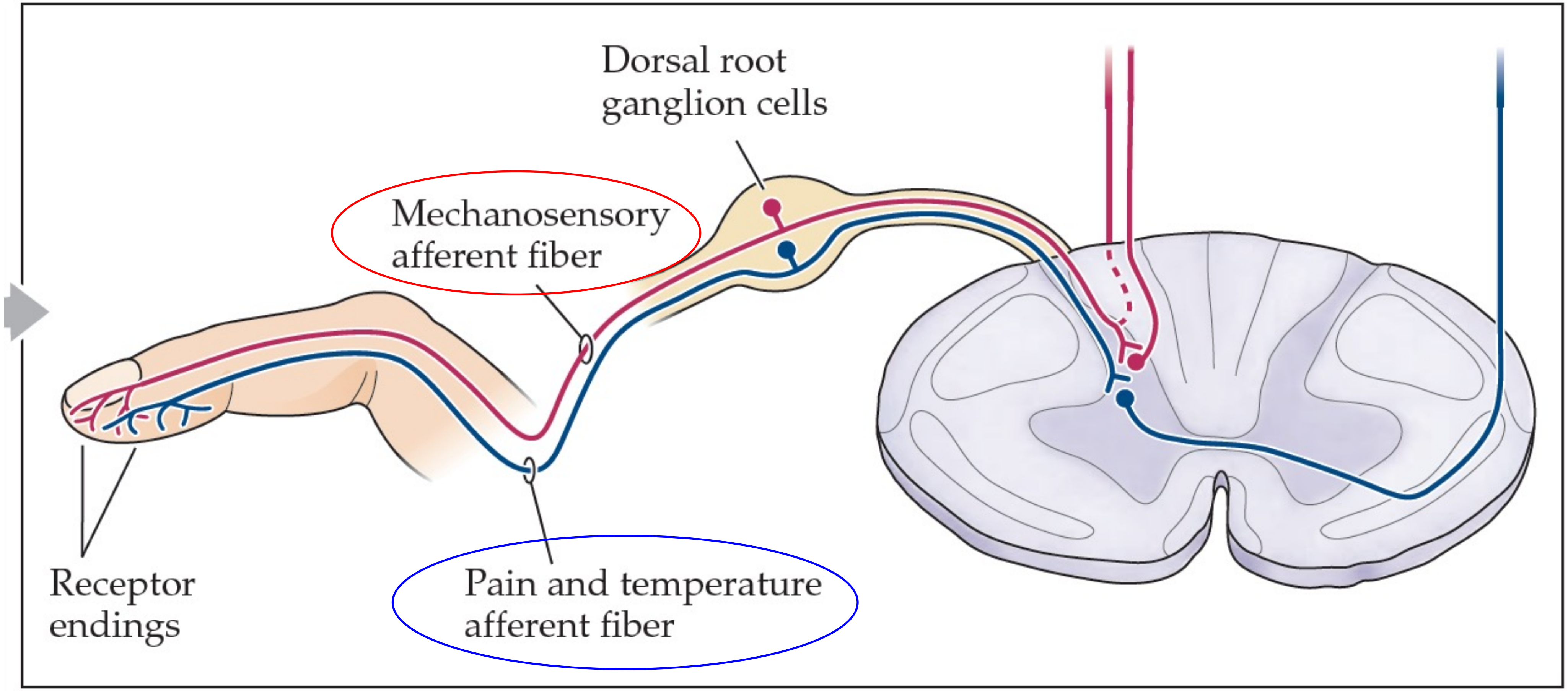
Read **Purves** Chapter 10, with an emphasis on pgs. 213 - 222 and 227 - 230

BIO-311

Image credit:
https://www.romatem.com/en/pain-treatment/

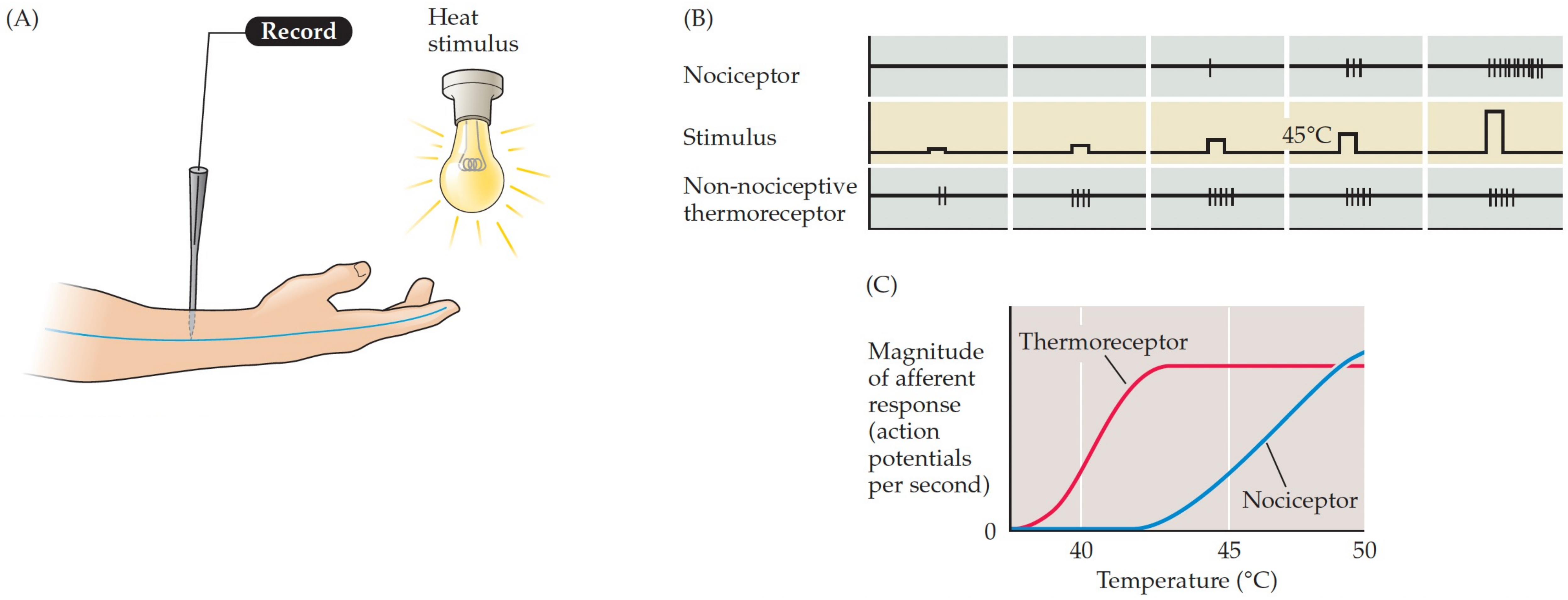
Relative organization of the somatosensory system for touch and the nociceptive system



Purves, Figure 9.1

The Nociceptive system conveys pain and temperature

Painful stimuli are transduced by the activation of special pain receptors ("nociceptors")



Purves, Figure 10.1

(1) **Nociceptive** system
"Painful" signals with a strong negative emotional component

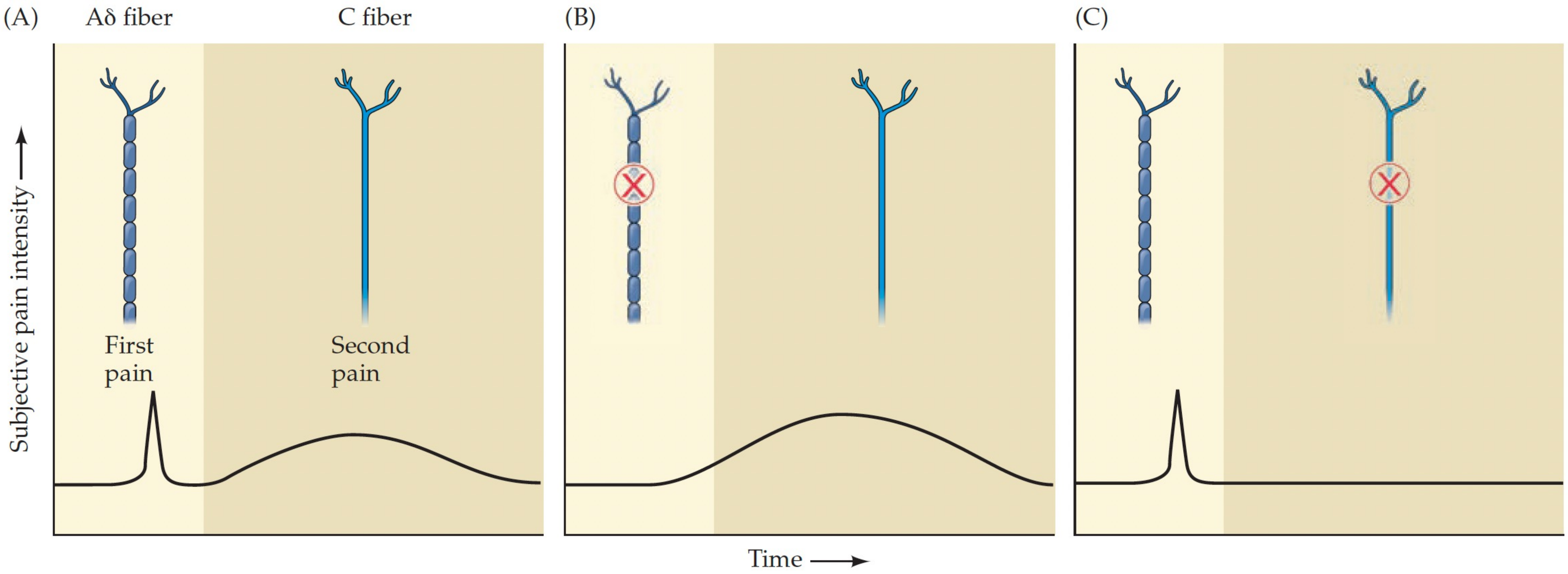
e.g.
- Temperature > 43°C ("pain threshold")
- Excessive mechanical stimuli close to / exceeding tissue damage
- Burning cold on the skin

(2) **Temperature-sensitive** system
- Sensation of warmth and cold
- Important for adaptive behavior to maintain body temperature

Similar anatomy:
antero-lateral system

Often grouped together in
”nociception"

Pain can be separated into early perception and a later sensation



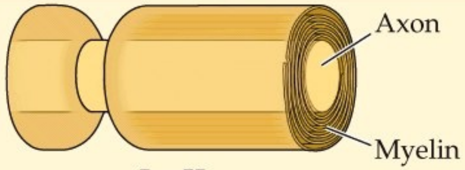
Duller, burning pain

Sharp pain

Purves, Figure 10.2

Classification of sensory axons according to axon diameter and conduction velocity

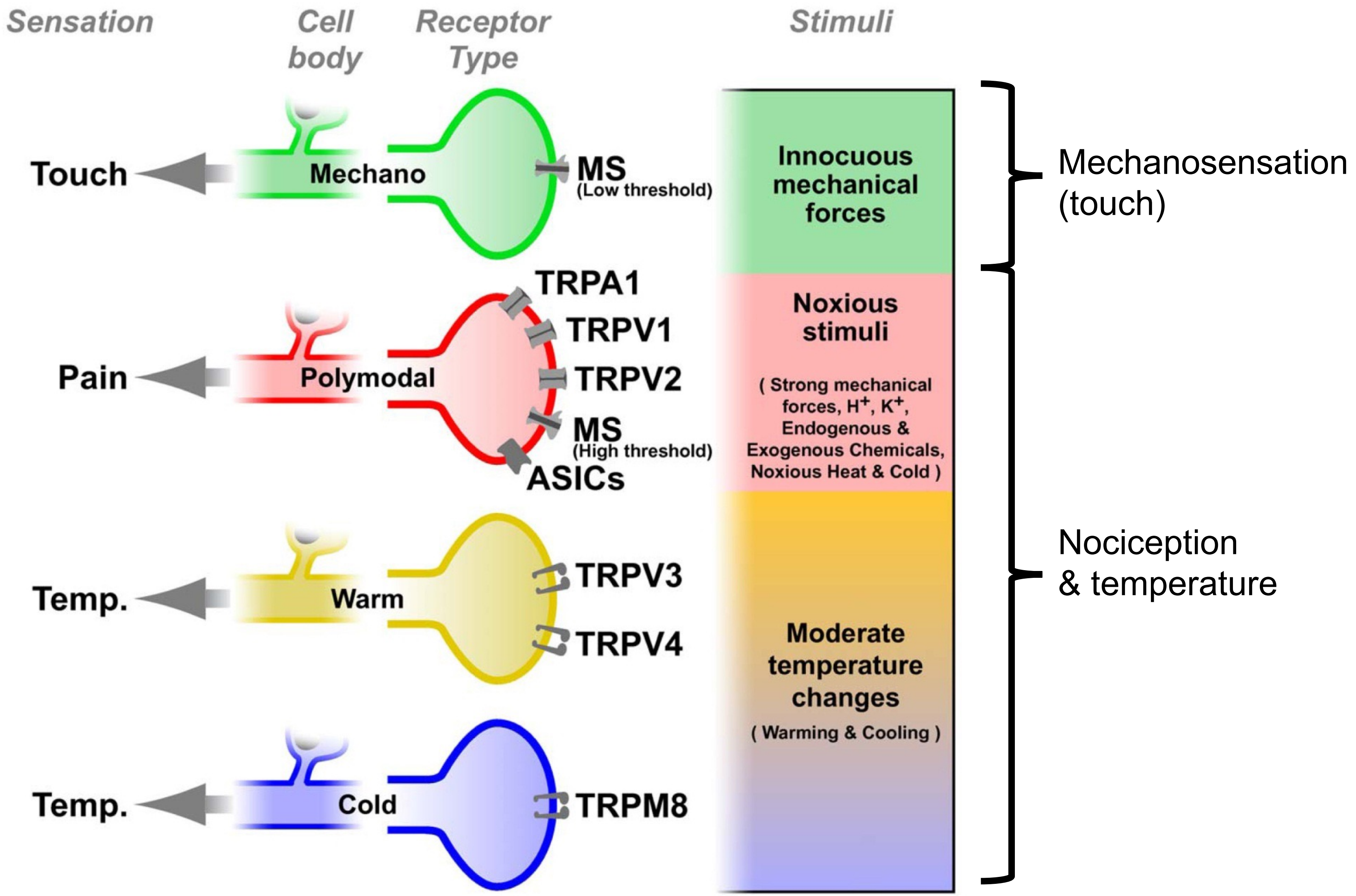
TABLE 9.1 Somatic Sensory Afferents that Link Receptors to the Central Nervous System

SENSORY FUNCTION	RECEPTOR TYPE	AFFERENT AXON TYPE[a]	AXON DIAMETER	CONDUCTION VELOCITY
Proprioception	Muscle spindle	 Ia, II	13–20 μm	80–120 m/s
Touch	Merkel, Meissner, Pacinian, and Ruffini cells	 Aβ	6–12 μm	35–75 m/s
Pain, temperature	Free nerve endings	 Aδ	1–5 μm	5–30 m/s
Pain, temperature, itch	Free nerve endings (unmyelinated)	 C	0.2–1.5 μm	0.5–2 m/s

Today

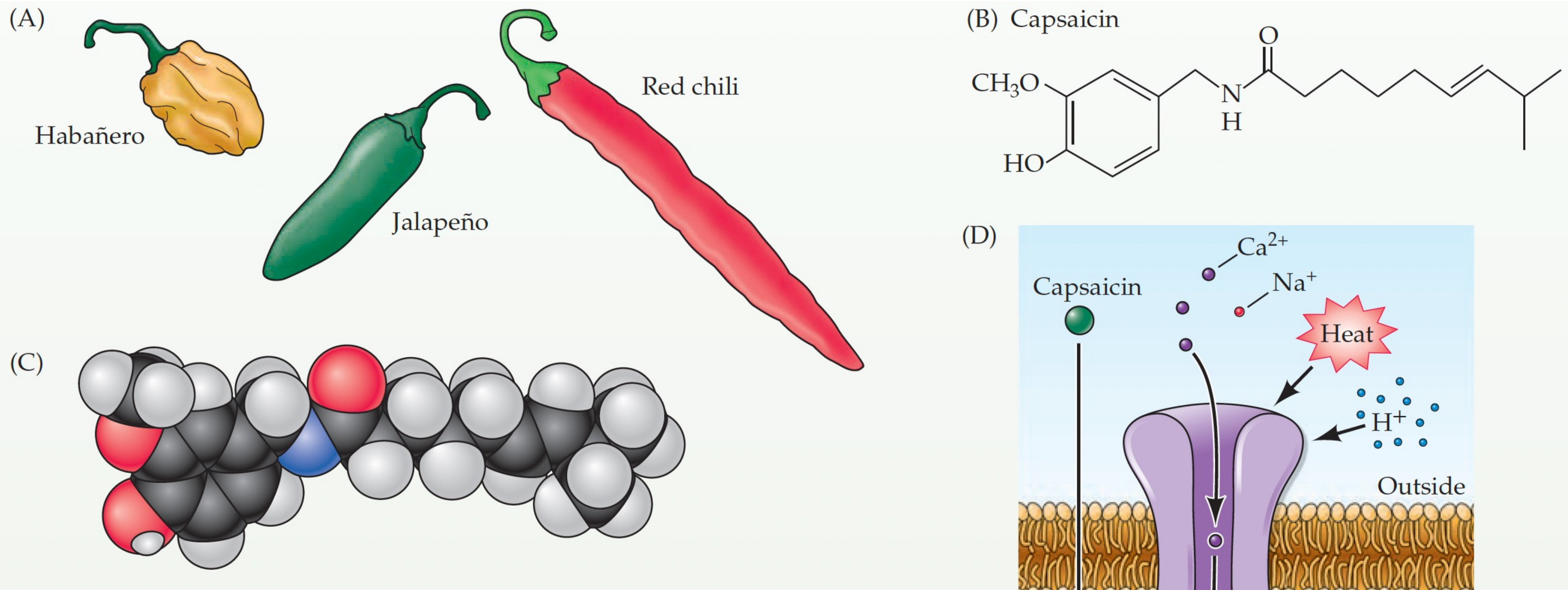
Purves (older version), Table 9.1

Various TRP channels transduce primary sensory stimuli in sensory nerve endings



Belmonte & Viana,
Mol. Pain 2008

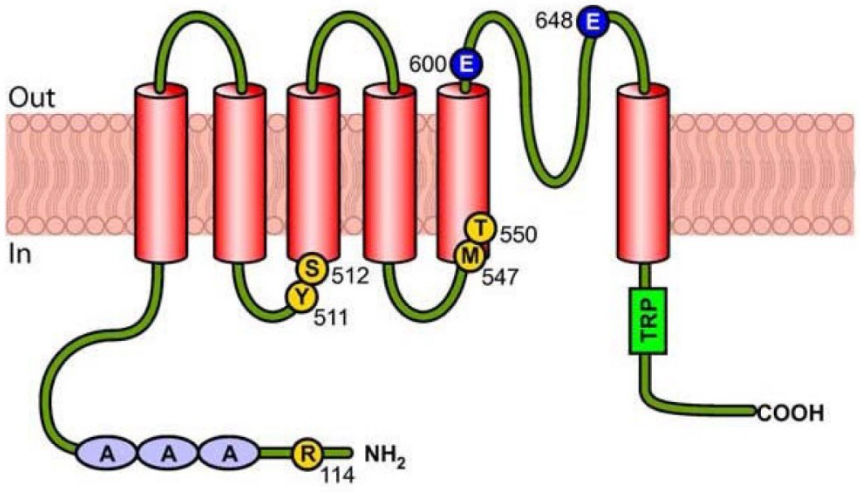
Heat-sensitive ion channels (TRPV1) important for heat and pain sensation are also activated by Capsaicin



(A) Some widely used peppers that contain capsaicin. (B) The chemical structure of capsaicin. (C) The capsaicin molecule. (D) Schematic of the VR-1/capsaicin receptor channel. This channel can be activated by capsaicin intracellularly, or by heat or protons (H^+) at the cell surface.

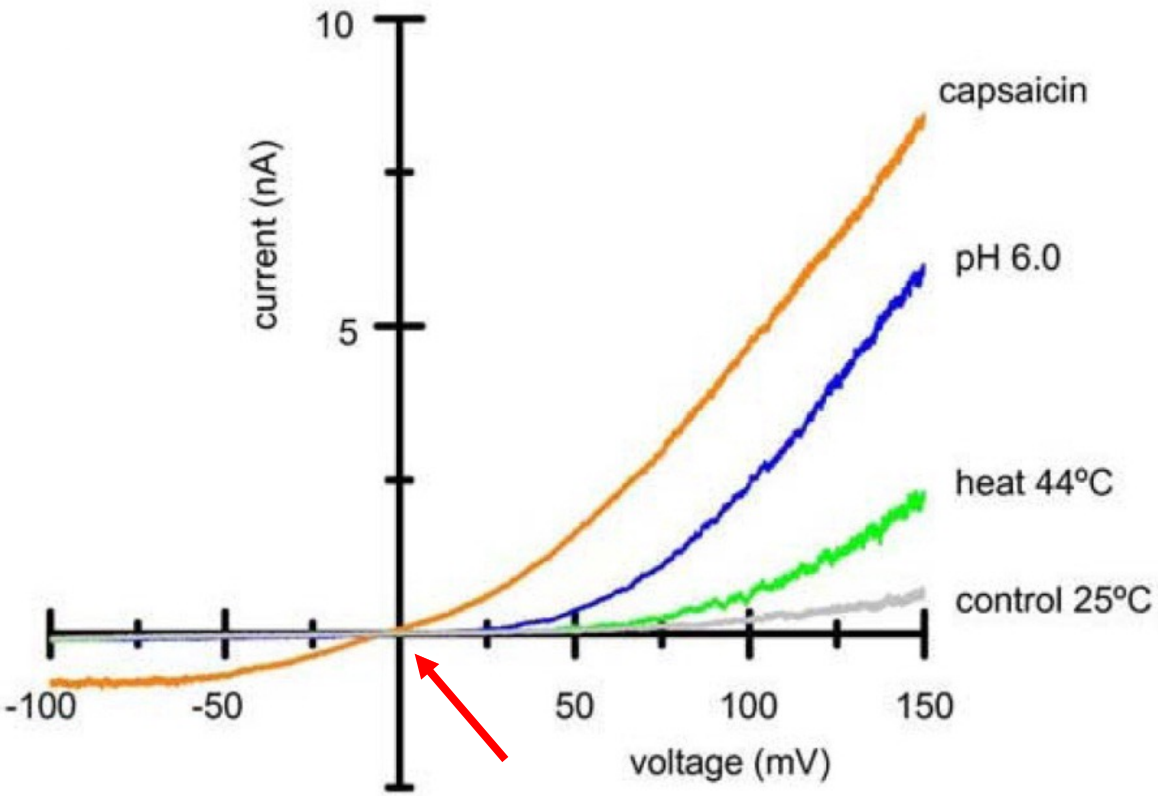
Purves, Box 10A

TRP channels: non-selective cation channels activated by different chemical and physical signals



Subfamilies:
TRP-C
TRP-V

TRP-M
TRP-A
TRP-N
...



Note: E_{rev} = 0 mV
So non-selective cation channels

Belmonte & Viana,
Mol. Pain 2008

For somatosensation:

Both a **mechanosensitive ion channel**

AND a **voltage-gated Na^+ channel**

… are in the nerve ending of "low threshold mechanosensitive" DRG sensory neurons

For pain & temperature sensation (i.e., different type of sensory neuron in the DRG)

~~mechanosensitive ion channel~~

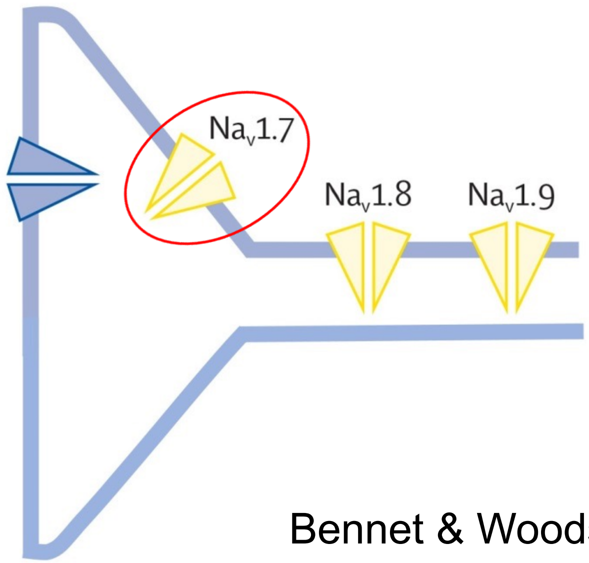
Both a **TRP channel** (broader spectrum of activators)

AND a **voltage-gated Na^+ channel,** α-subunit: NaV1.7

…are in the nerve endings

Mutations in the voltage-gated Na^+ channel $Na_V1.7$ cause congenital insensitivity to pain (a "channelopathy")

A nociceptor nerve ending:



Bennet & Woods 2014, Lancet

<u>Congenital insensitivity to pain</u>:
In patients:

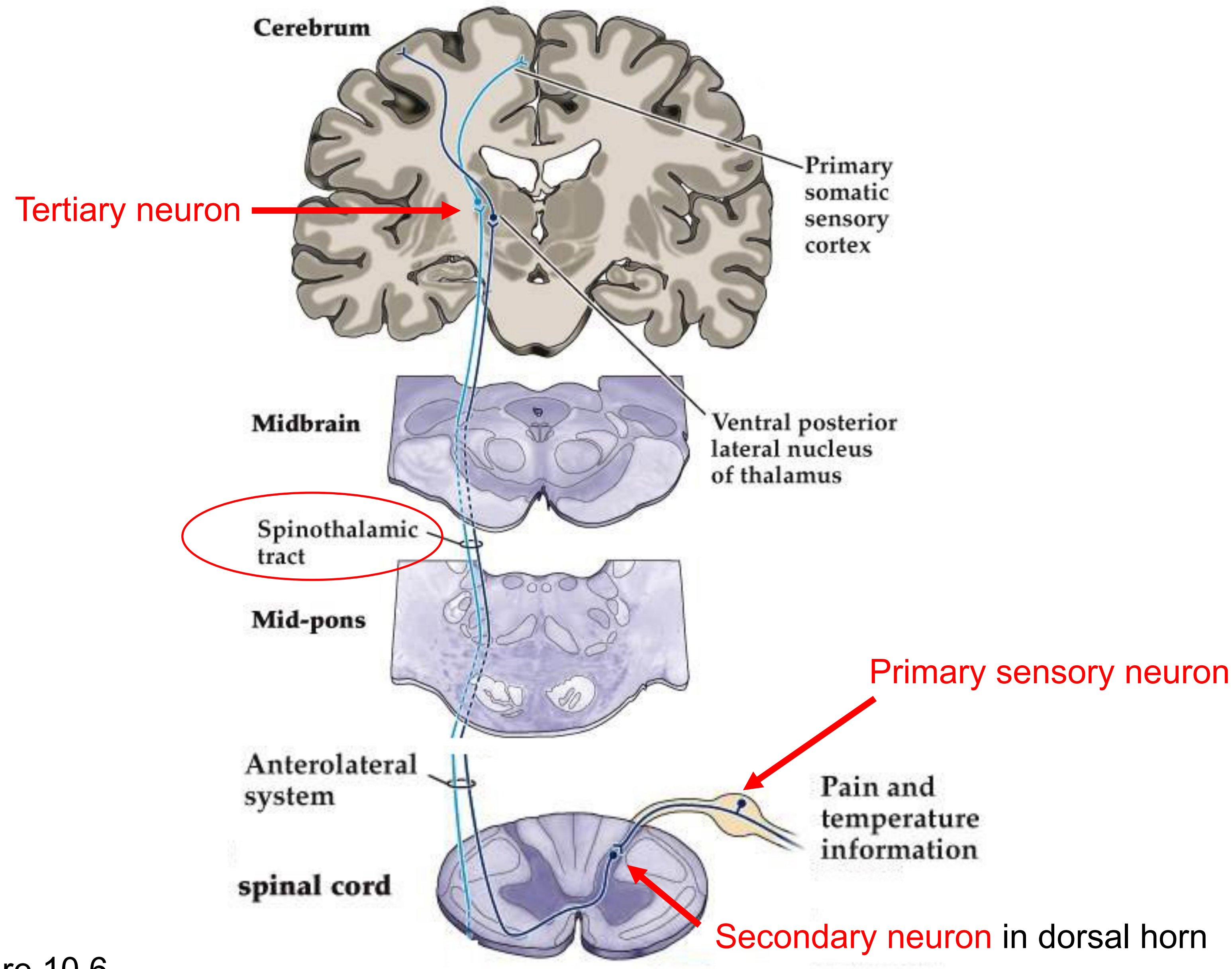
- No pain is felt anywhere in the body from birth onwards
- Skin bruises, cuts, and bone fractures. The tip of the tongue is often lost
- Excessive risk-taking behavior leads to early mortality (~20-30 yrs)

Shows that nociception/pain is needed to protect the body from tissue injury

Anatomy of the nociceptive (pain sensation) system

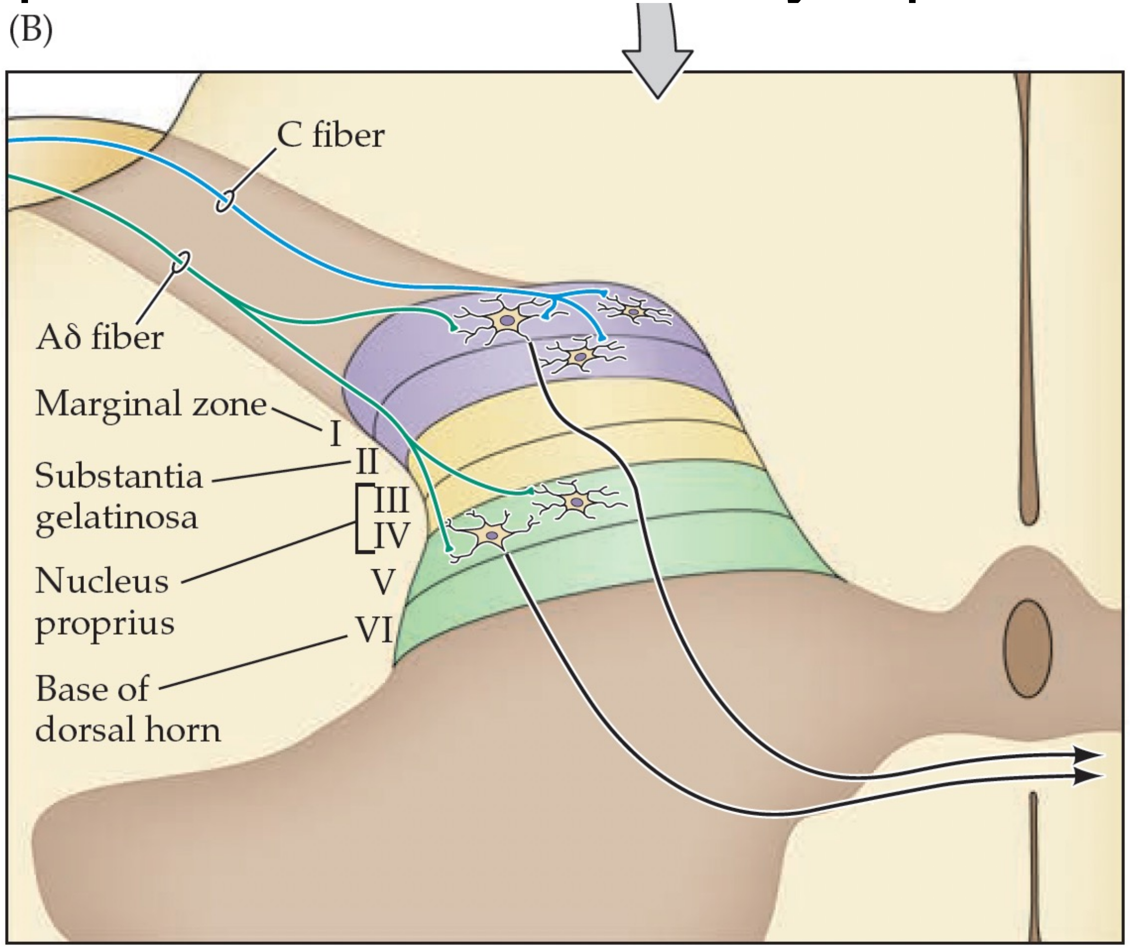
Spinothalamic tract

<u>The Anterolateral / Spinothalamic tract</u>: Major pathway for *discriminative* aspects of pain and temperature sensation



Purves, Figure 10.6

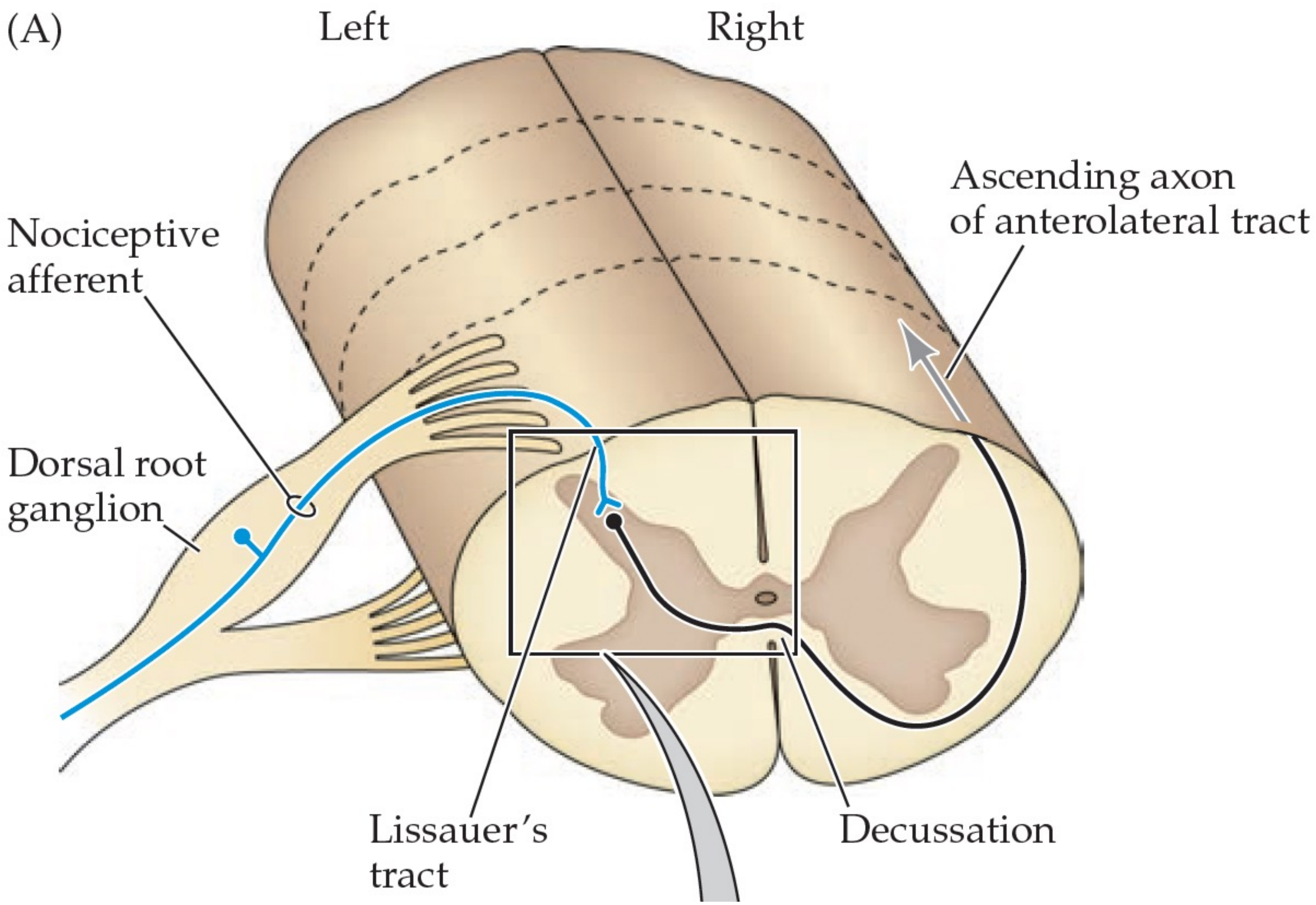
The Anterolateral/Spinothalamic tract:
Nociceptive afferents makes synapses in the dorsal horn



- Secondary sensory neurons of the nociceptive/pain pathway mainly in **Laminae I, II** (innervated by **C/ Aδ** fibers) and in **Lamina V** (innervated by **Aδ** fibers). Non-nociceptive primarily to III, IV, and V.

Purves, Figure 10.3

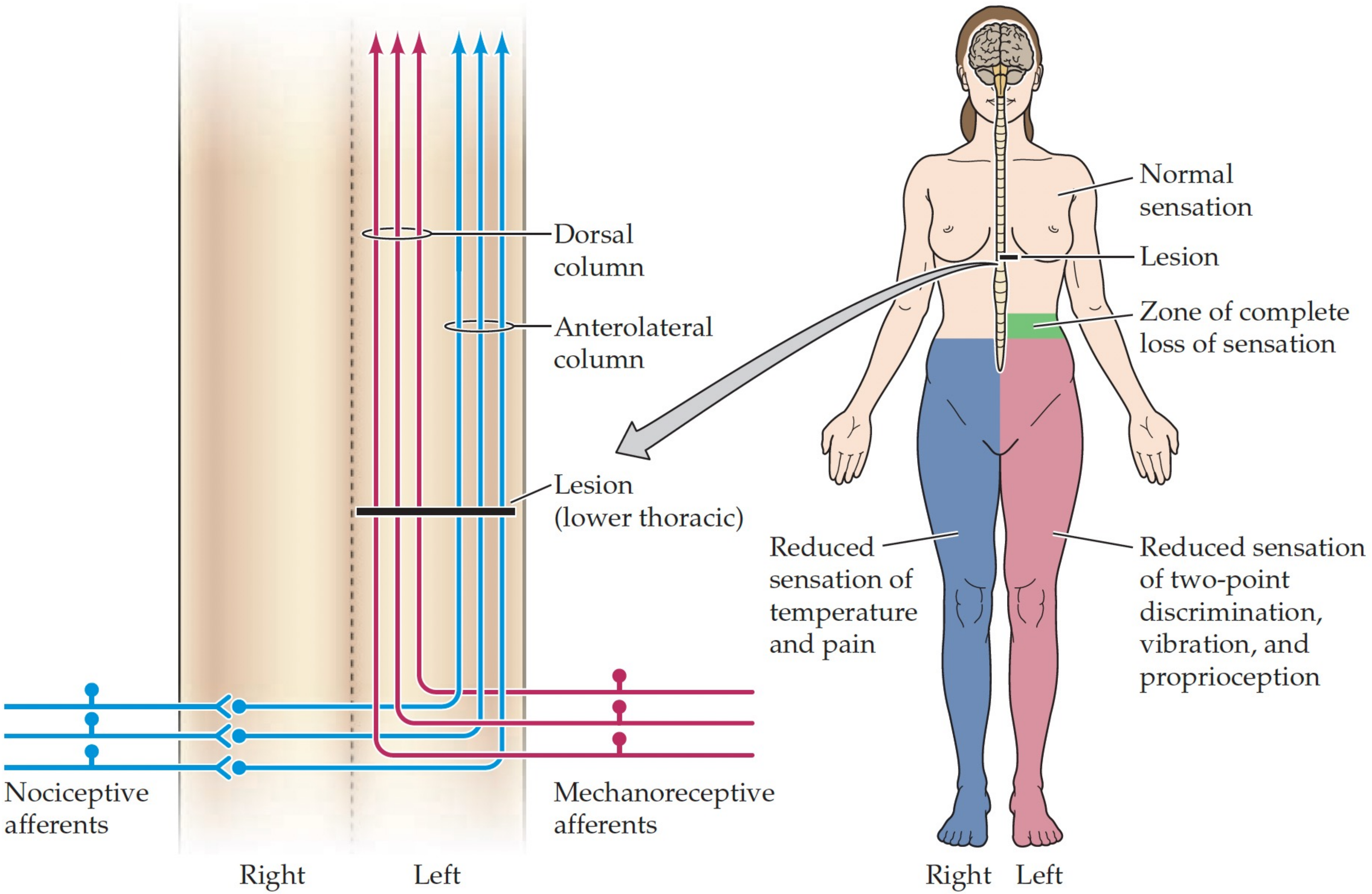
The Anterolateral tract



The secondary sensory neuron (in dorsal horn) sends axon over the midline, and ascends in anterolateral tract.

Purves, Figure 10.3

Pattern of “dissociated” sensory loss following a spinal cord *hemisection*

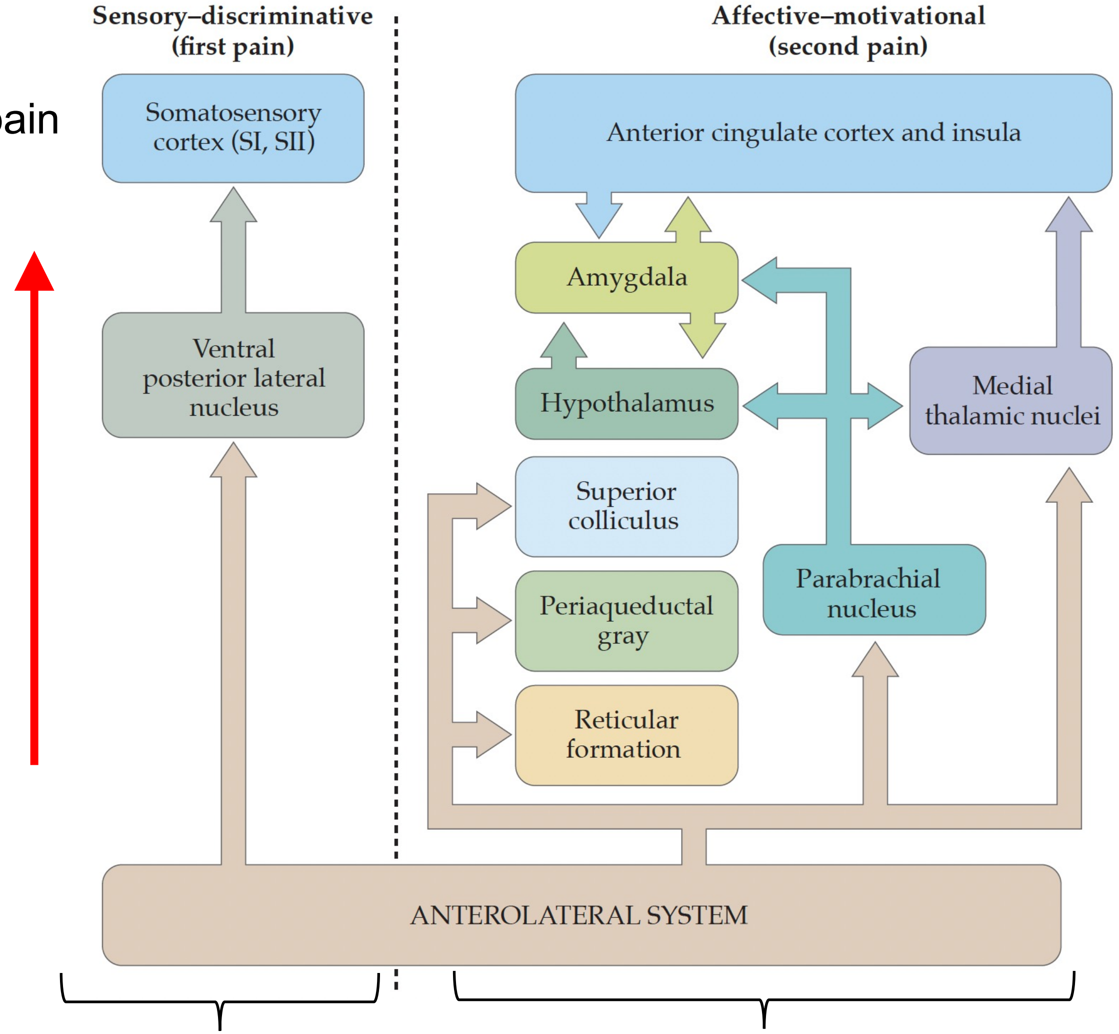


Purves, Figure 10.4

Central (brain) representations and modulation of pain

Ascending information from the Anterolateral system is distributed via two major pathways into the brain

Location, intensity, quality of pain



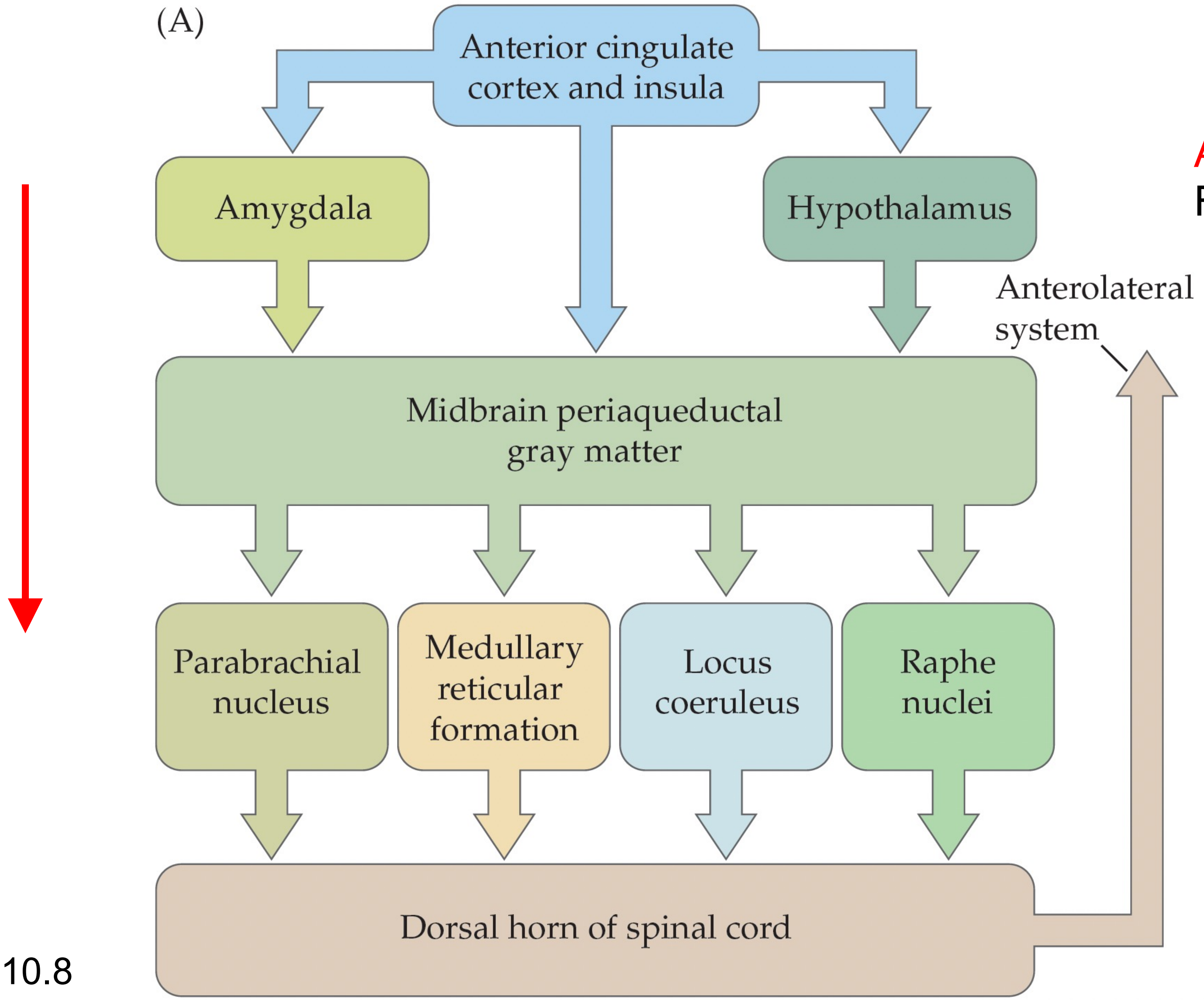
Unpleasant feeling, fear, anxiety

Spinothalamic pathway to the discriminative system

More "complex" pathway to the "limbic" thalamus and finally to limbic/emotional systems (hypothalamus / amygdala / insular cortex)

Purves, Figure 10.5

Descending information from the brain is involved in endogeneous mechanisms of analgesia



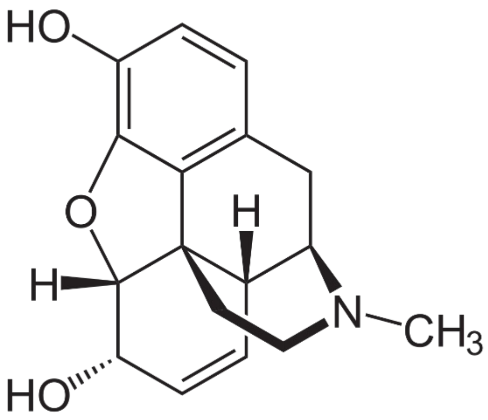
Analgesia is the reduced feeling of pain.
Found upon electrical stimulation of PAG

Purves, Figure 10.8

Mechanisms of opiate action and the descending control of pain

- There are <u>four opioid receptors</u>, these are G-protein coupled receptors: μ , δ , κ and orphan

- Morphine activates μ – opioid receptors



Morphine

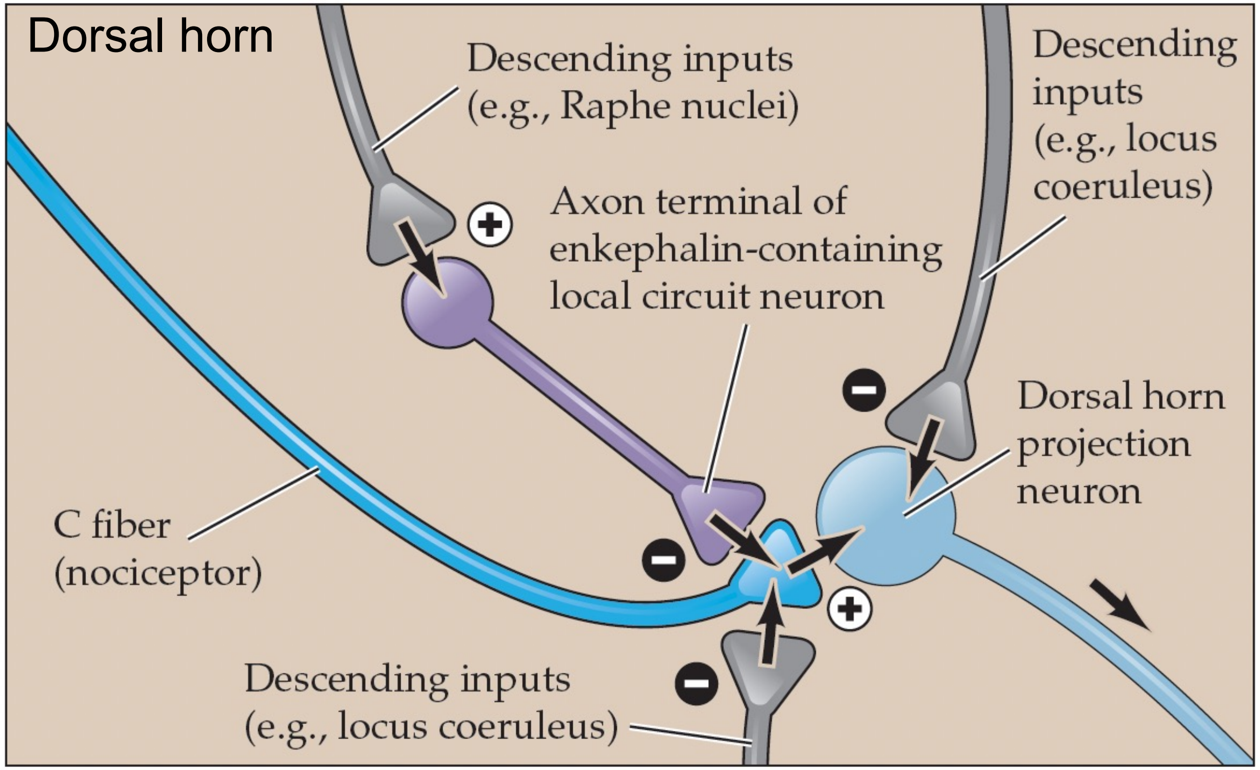
- μ – opioid receptors are highly expressed in the spinal cord <u>dorsal horn</u> and <u>PAG</u>

Mechanisms for the descending control of pain

E.g., during extreme physical strain (marathon) or context (wounded in battle)

- Inputs from Raphe nuclei to the dorsal horn *recruit* enkephalin-containing interneurons.
- The resulting enkephalin release onto the nerve terminals of C-fibers *reduces the release of glutamate* at the DRG → dorsal horn synapse (by binding to presynaptic μ receptors).

Information transfer from the C-fiber to dorsal horn secondary sensory neurons **is weakened.**



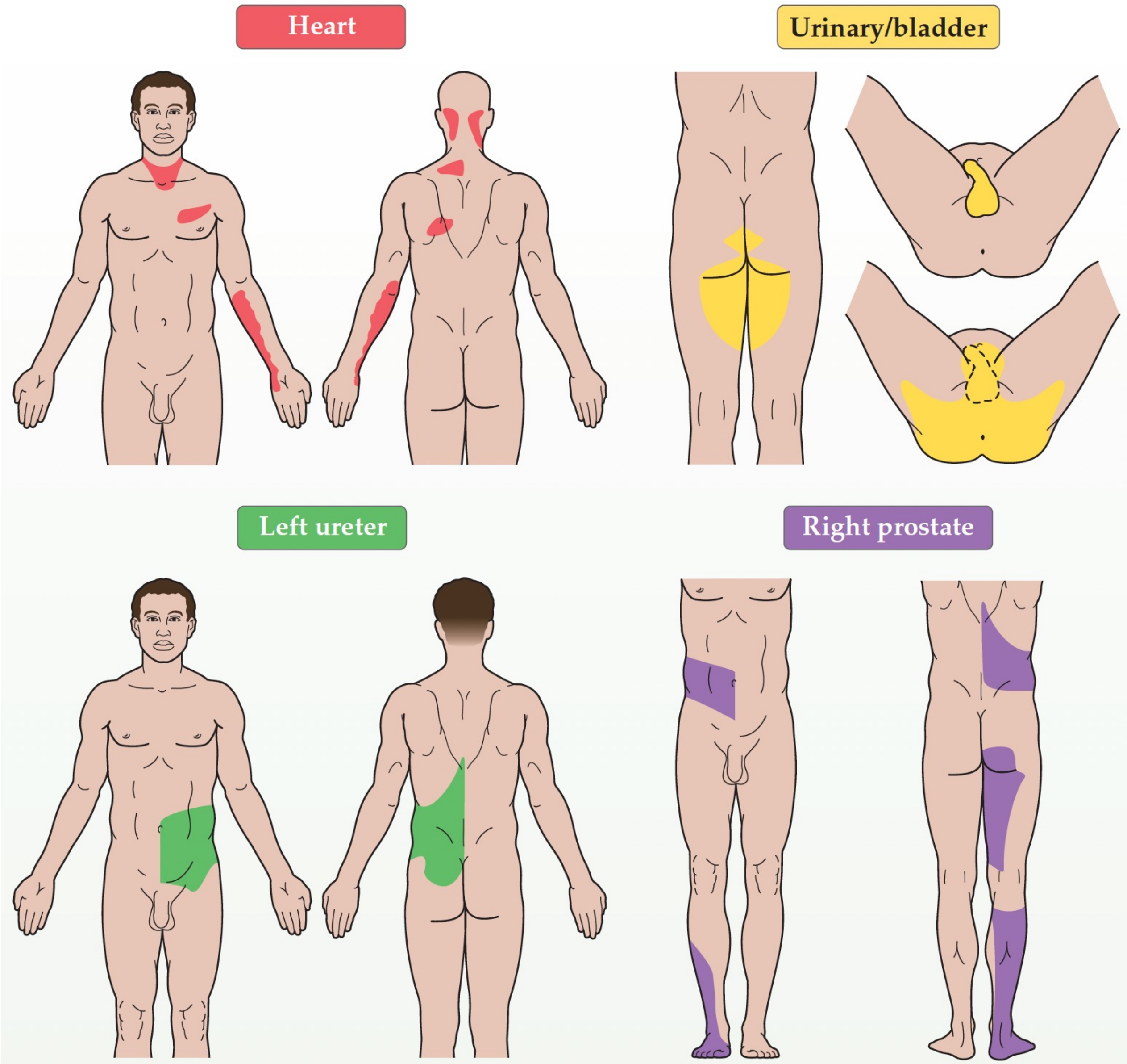
Endogenous opioids: Enkephalins, endorphins, dynorphins

Purves, Figure 10.8

Clinically relevant pain phenomena

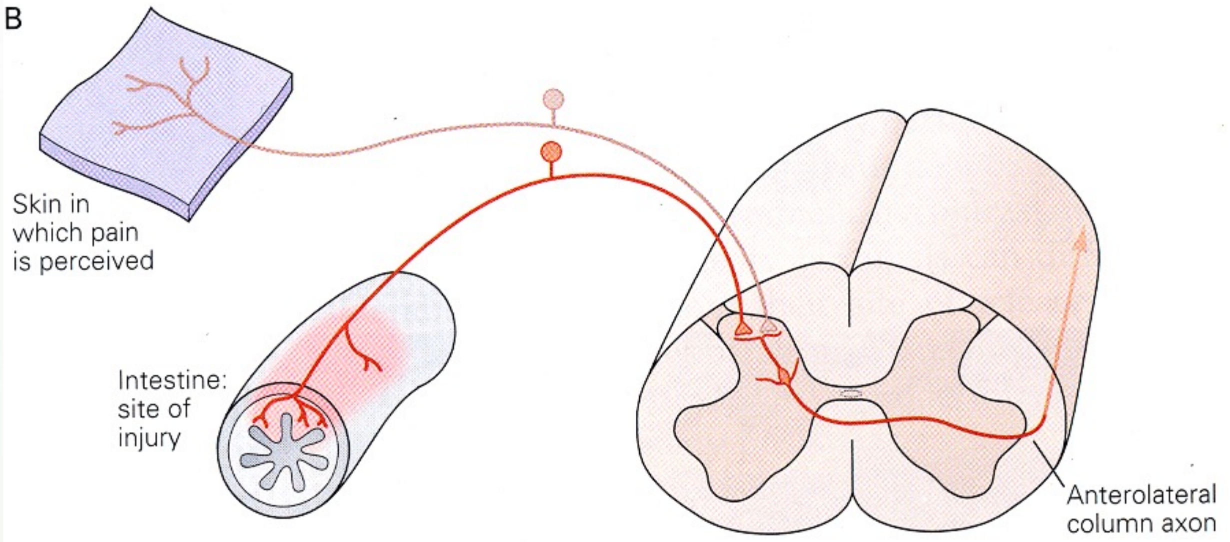
- Referred pain
- Phantom limb pain
- Peripheral and central sensitization
- Gate theory of pain

Referred pain: Due to dorsal horn neurons that process both visceral and cutaneous nociceptive input



Purves, Box 10B

<u>Warning symptom of a heart attack</u>:
When heart muscle is not adequately perfused with blood. This results in arm and chest pain

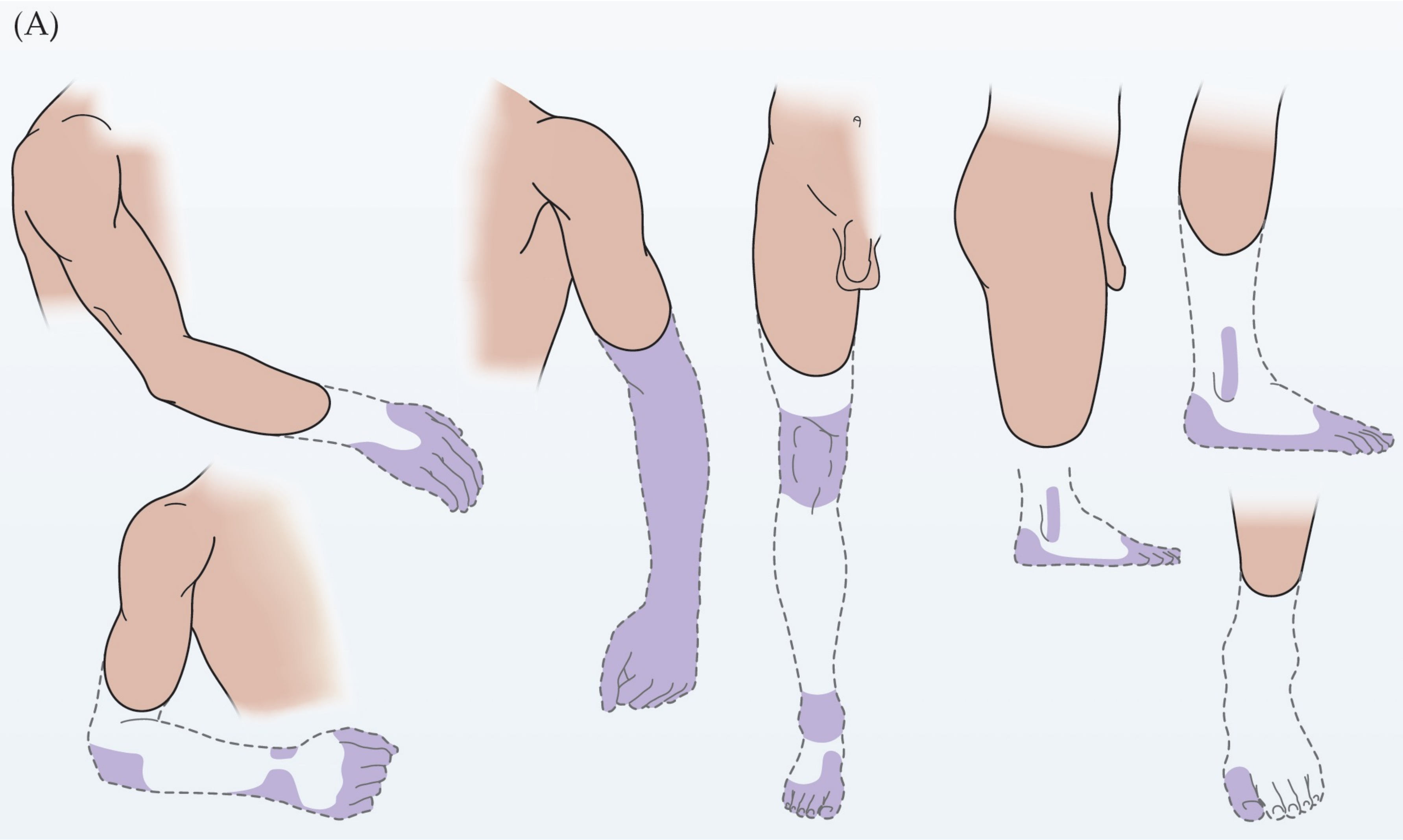


Kandel, Figure 24.3

Phantom limbs and phantom pain: misperception of missing limbs

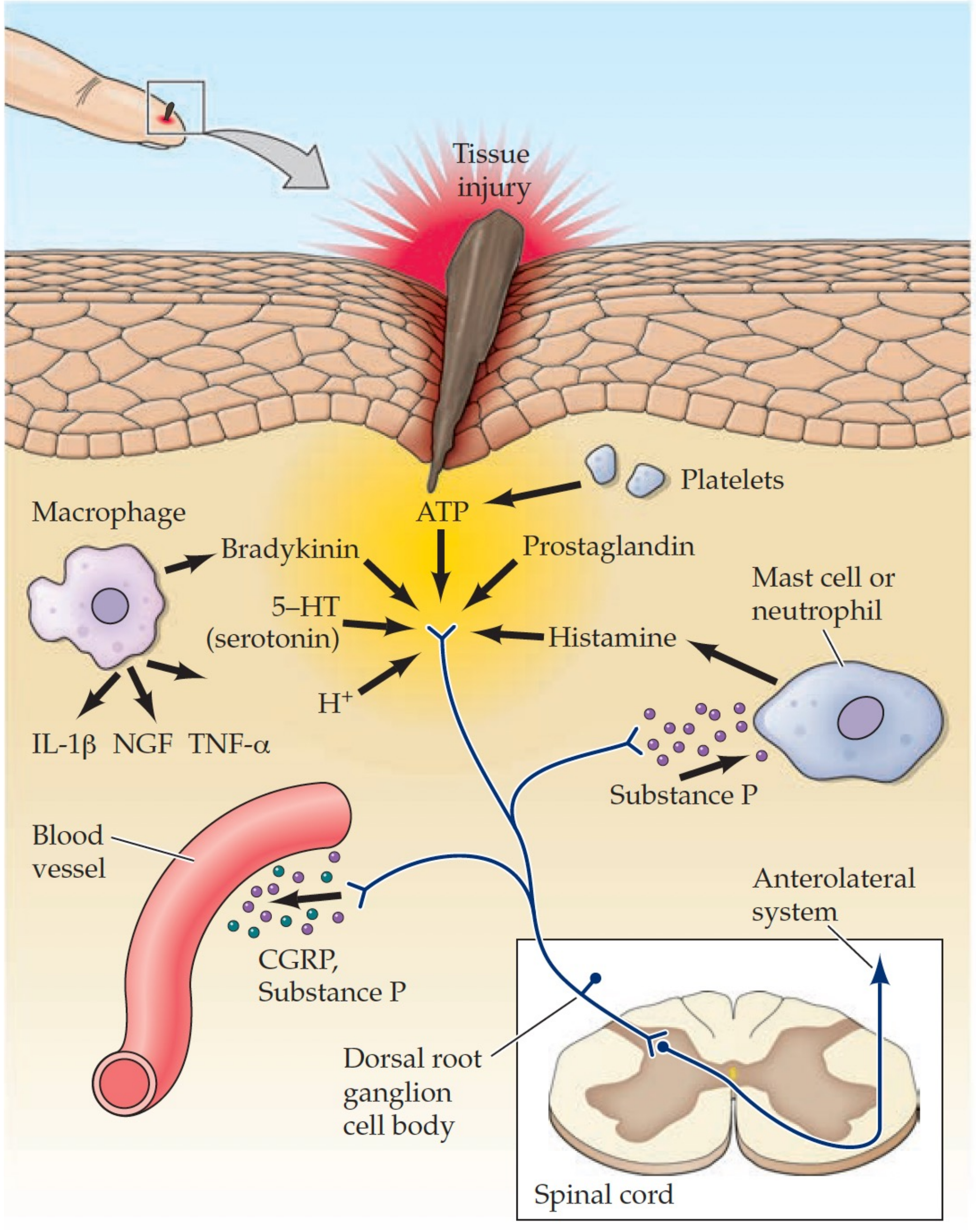
Purple areas: areas of patient reports of phantom limbs after limb loss/amputation

Mechanism: delayed rearrangement of cortical receptive maps;
plasticity of receptive fields



Purves, Chapter 10 ‘Clinical Applications’

Sensitization at inflammatory site of tissue damage



Sensitization:

- Hyperalgesia (increased pain perception) in the area of injury

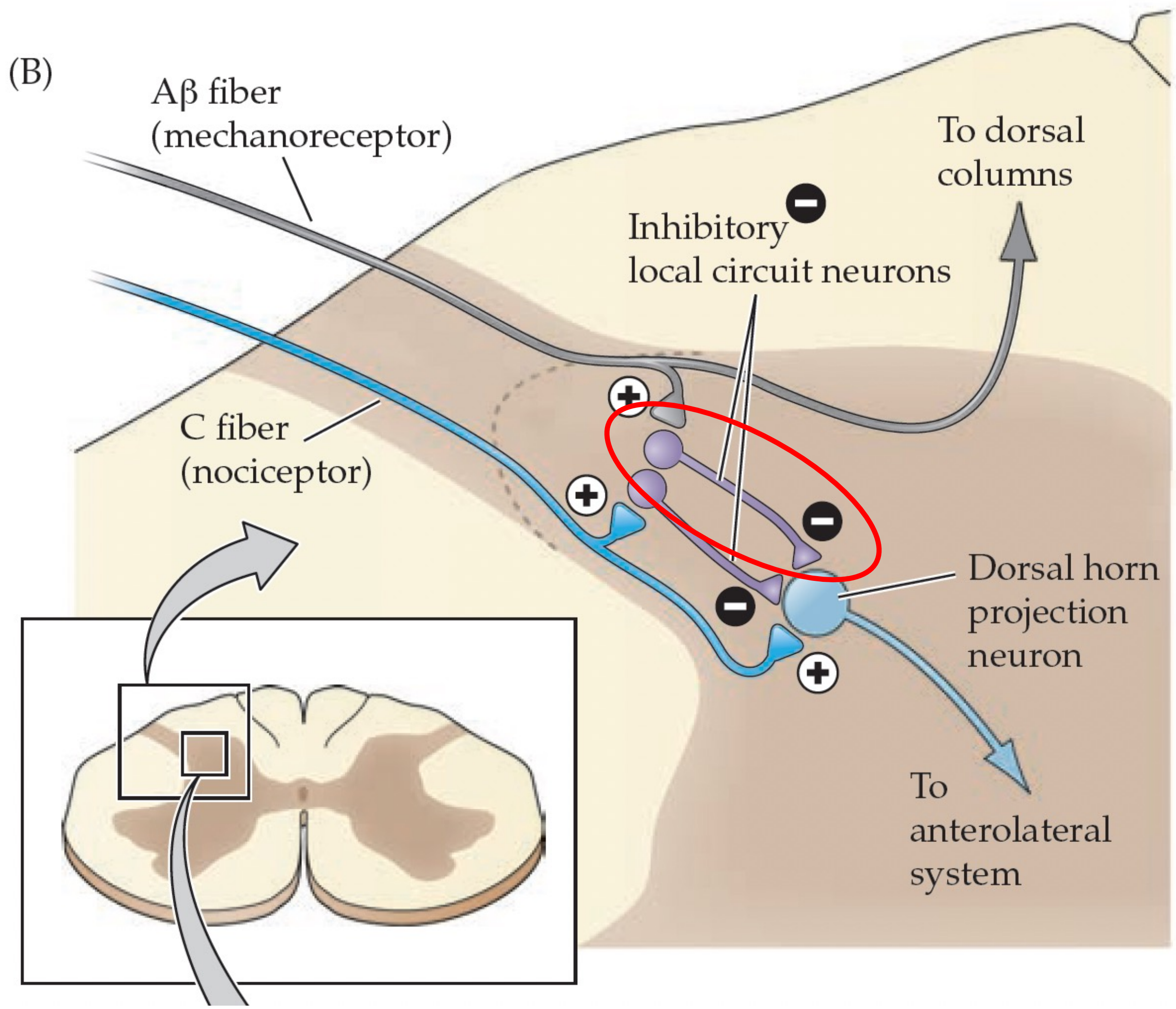
(1) Peripheral sensitization:

‘Inflammatory soup’ (e.g., Bradykinin, ATP, H^+ , histamin, Prostaglandins) cause TRV1 receptors to be potentiated etc.

(2) Central sensitization in the spinal cord dorsal horn via windup (e.g., removal of NMDA Mg^{2+} block)

Purves, Figure 10.7

Gate theory of pain: Activating mechanoreceptors modulates nociceptive processing in the spinal cord dorsal horn



Purves, Figure 10.8

- **Aβ and C-fibers** (carrying nociceptive info) both project to the dorsal horn.
- In the dorsal horn, Aβ fibers make **collateral** synapses onto local inhibitory interneurons
- *The latter* inhibit dorsal horn projection neurons of the nociceptive system

*This is why "rubbing" **reduces** the subjective feeling of pain*

Summary: The Nociceptive System

Important concepts and keywords

- Early and late pain (due in part to AP conduction velocities)
- Sensing through TRP ion channels (activated by which stimuli; ionic permeability)
- Principal anatomical organization (spinothalamic tract). Consequences for clinical diagnosis after spinal cord hemisection.
- Ascending pathways giving rise to two different perceptions of pain
- Descending control of pain and endogenous opioids
- Mechanisms behind Referred pain
- The gate theory of pain