Pain: Anatomy and Physiology

Dr Babak Bakhshayesh

Associate Professor of Guillain University of Medical Sciences

Neurologist

Fellowship of Epilepsy

Introduction

- Pain is a subjective sensation, occurs whenever tissues are being damaged and causes the individual to react to remove the pain stimulus.
- Even such simple activities as sitting for a long time → tissue damage because of lack of blood flow to the skin where it is compressed by the weight of the body → the skin becomes painful as a result of the ischemia → the person normally shifts weight subconsciously.
- A person who has lost the pain sense , for example, after a spinal cord injury → fails to feel the pain → fails to shift →total breakdown and desquamation of the skin at the areas of pressure.

FAST PAIN AND SLOW PAIN

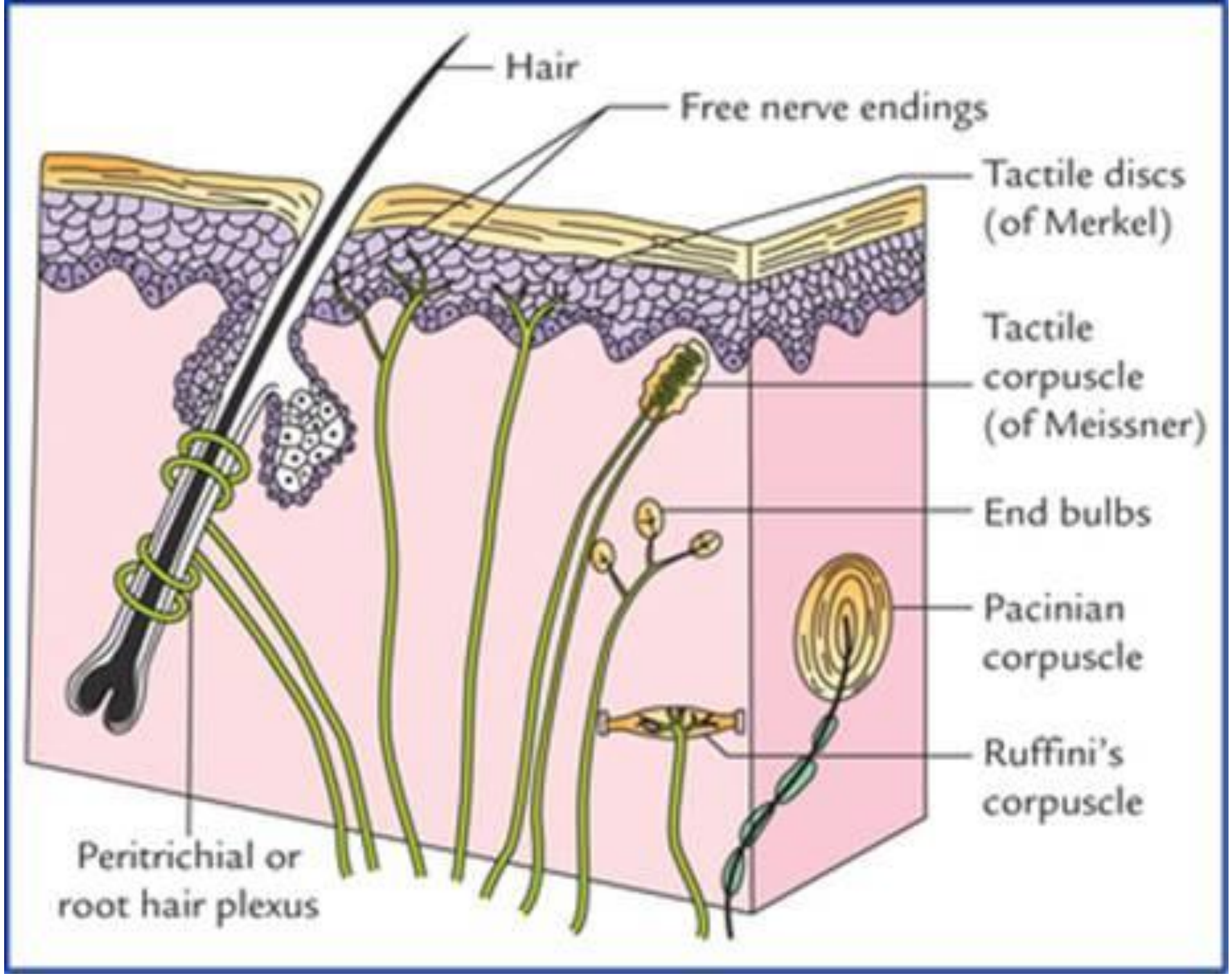
- Pain has been classified into two major types, *fast pain* and *slow pain*
- Fast pain is felt within about 0.1 second after a pain stimulus is applied, whereas slow pain begins only after 1 second or more and then increases slowly over many seconds and sometimes even minutes
- The conduction pathways for these two types of pain are different , each of them has specific qualities

- Many alternative names for Fast pain → *sharp pain, pricking pain, acute pain,* and *electric pain.*
- felt when a needle is stuck into the skin, when the skin is cut with a knife, or when the skin is burned acutely; also when the skin is subjected to electric shock.
- Fast-sharp pain is not felt in most deep tissues of the body.

- Many alternative names for Slow pain → *slow burning pain, aching pain, throbbing pain, nauseous pain,* and *chronic pain.*
- Usually associated with *tissue destruction.*
- Can lead to prolonged, almost unbearable suffering.
- Occur both in the skin and in almost any deep tissue or organ.

PAIN RECEPTORS AND THEIR STIMULATION

- The pain receptors in the skin and other tissues are all free nerve endings.
- They are widespread in the superficial layers of the *skin,* as well as in certain internal tissues, such as the *periosteum,* the *arterial walls,* the *joint surfaces,* and the *falx* and *tentorium* in the cranial vault.
- Most other deep tissues are only sparsely supplied with pain endings
- Nevertheless, any widespread tissue damage can summate to cause the slow, chronic, aching type of pain in most of these areas.


Hair
Free nerve endings
Tactile discs
(of Merkel)
Tactile
corpuscle
(of Meissner)
End bulbs
Pacinian
corpuscle
Ruffini's
corpuscle
Peritrichial or
root hair plexus

Mechanical, Thermal, and Chemical Stimuli

- Pain can be elicited by multiple types of stimuli, classified as *mechanical*, *thermal*, and *chemical pain stimuli.*
- In general, fast pain is elicited by the mechanical and thermal types of stimuli, whereas slow pain can be elicited by all three types.
- Some of the chemicals that excite the chemical type of pain are *bradykinin*, *serotonin*, *histamine*, *potassium ions*, *acids*, *acetylcholine*, and *proteolytic enzymes.*
- *Prostaglandins* and *substance P* enhance the sensitivity of pain endings but do not directly excite them.

Nonadapting Nature of Pain Receptors

- In contrast to most other sensory receptors, pain receptors adapt very little and sometimes not at all
- In fact, under some conditions, excitation of pain fibers becomes progressively greater, especially for slow, aching, nauseous pain, as the pain stimulus continues
- This increase in sensitivity of the pain receptors is called *hyperalgesia.*
- The importance of this → it allows the pain to keep the person apprised of a tissue-damaging stimulus as long as it persists

Rate of Tissue Damage as a Stimulus for Pain

- The average person begins to perceive pain when the skin is heated above 45°C →also the temperature at which the tissues begin to be damaged by heat
- Pain resulting from heat is correlated with → rate at which damage to the tissues is occurring (not with the total damage that has already occurred)
- The intensity of pain is also correlated with → rate of tissue damage from causes other than heat, such as bacterial infection, tissue ischemia, tissue contusion, and so forth

Special Importance of Chemical Pain Stimuli During Tissue Damage

- Extracts from damaged tissue → intense pain when injected beneath the normal skin
- Most of the chemicals listed earlier found in these extracts. One that seems to be more painful is *bradykinin*, might be the agent most responsible for causing pain after tissue damage
- Also, the intensity of the pain correlates with the local increase in potassium ion concentration or the increase in proteolytic enzymes (directly attack the nerve endings and excite pain by making the nerve membranes more permeable to ions)

Tissue Ischemia as a Cause of Pain

- When blood flow to a tissue is blocked, the tissue often becomes very painful within a few minutes.
- The greater the rate of metabolism of the tissue, the more rapidly the pain appears. (For example, Ischemic exercise of the forearm muscles → muscle pain within 15 to 20 seconds → In absence of exercise, within 3 to 4 minutes, even though the muscle blood flow remains zero).
- Suggested causes of pain during ischemia → accumulation of *lactic acid* (anaerobic metabolism) and maybe other chemical agents, such as bradykinin and proteolytic enzymes, formed in the tissues because of cell damage

Muscle Spasm as a Cause of Pain

- Muscle spasm is a common cause of pain and is the basis of many clinical pain syndromes.
- This pain results partially from the direct effect of muscle spasm in stimulating mechanosensitive pain receptors, but it might also result from the indirect effect of muscle spasm to compress the blood vessels and cause ischemia.
- The spasm also increases the rate of metabolism in the muscle tissue, thus making the relative ischemia even greater, creating ideal conditions for the release of chemical pain-inducing substances.

PERIPHERAL PAIN FIBERS—“FAST” AND “SLOW” FIBERS

- The fast-sharp pain signals are elicited by → mechanical or thermal pain stimuli→ They are transmitted in the peripheral nerves to the spinal cord by small type Aδ fibers (velocities between 6 and 30 m/sec).
- The slow-chronic type of pain is elicited 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.

- Double system of pain innervation→ sudden painful stimulus → "double" pain sensation: a fast-sharp pain ,transmitted to the brain by the Aδ fiber pathway, followed a second or so later by a slow pain , transmitted by the C fiber pathway
- The sharp pain → making the person react immediately to remove himself or herself from the stimulus
- The slow pain → become greater over time, eventually producing intolerable pain → making the person keep trying to relieve the cause of pain

- Both pathways → dorsal spinal roots→ spinal cord → relay neurons in the dorsal horns
- Here again, there are two systems for processing the pain signals on their way to the brain

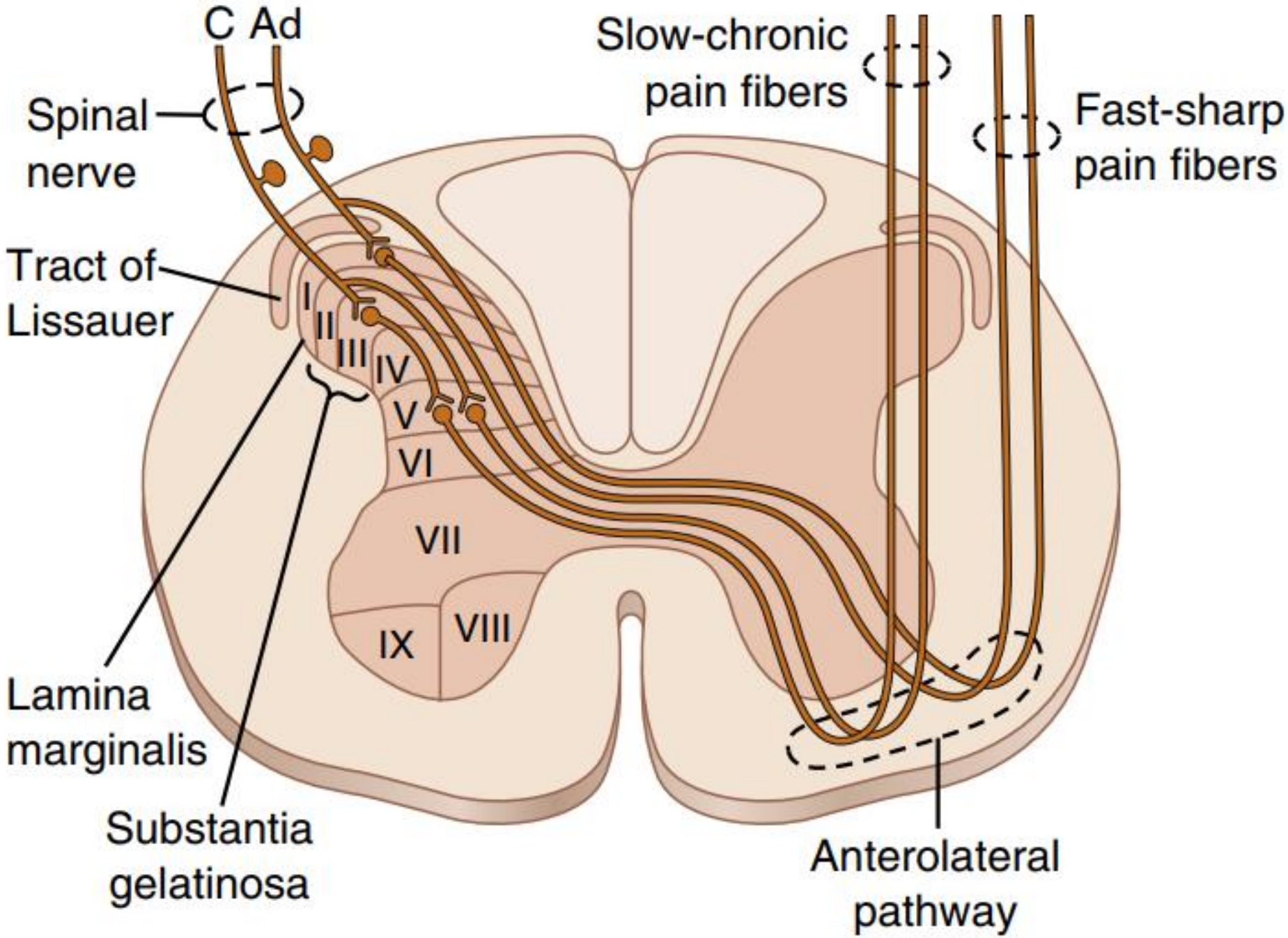
- On entering the spinal cord, the pain signals take two pathways to the brain, through

(1) the Neospinothalamic tract

(2) the Paleospinothalamic tract

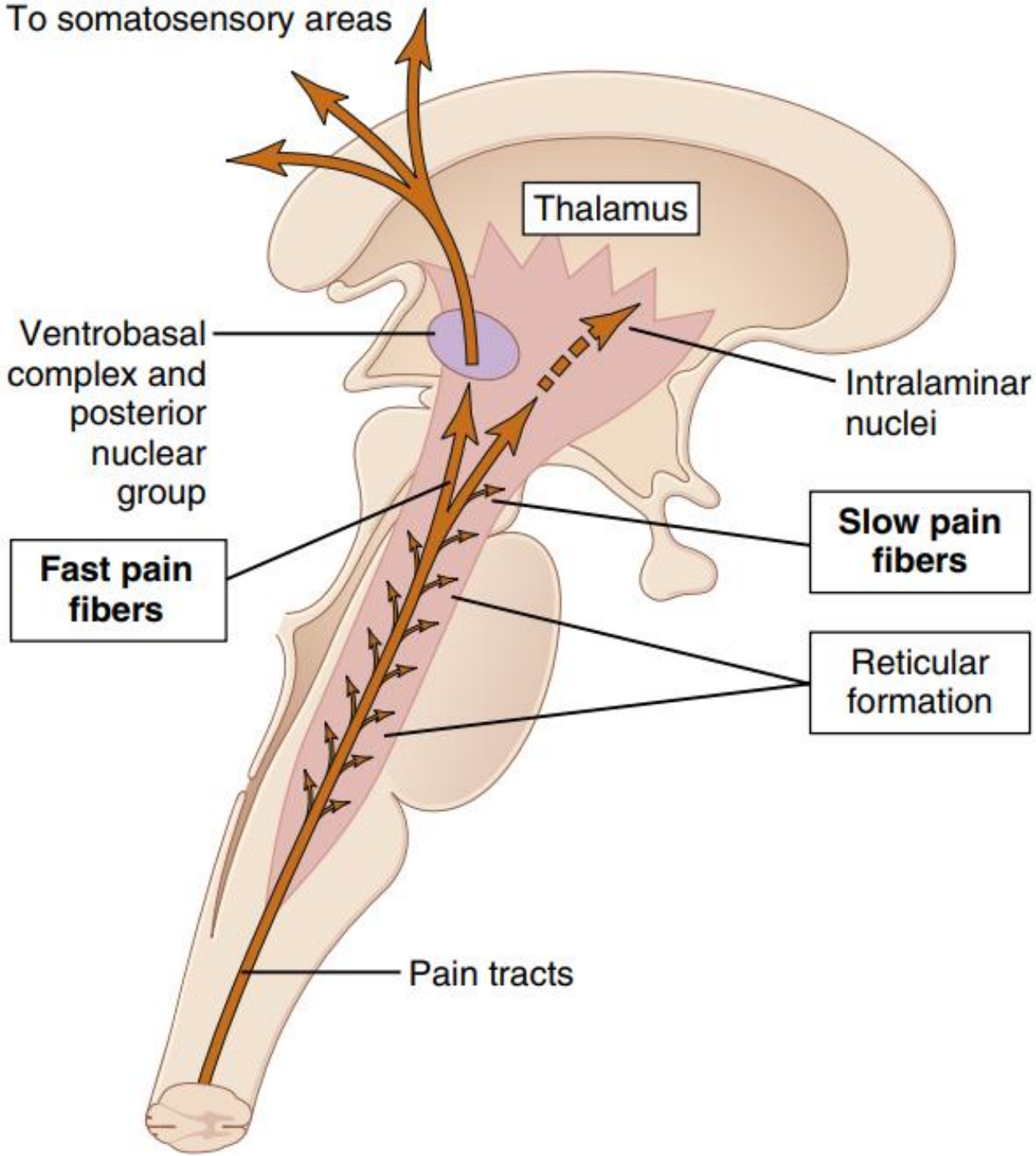
Neospinothalamic Tract for Fast Pain

- The fast type Aδ fibers → terminate mainly in lamina I (lamina marginalis) of the dorsal horns → second-order neurons → long fibers that cross immediately to the opposite side through the anterior commissure → turn upward, passing to the brain in the *anterolateral columns*
- A few fibers terminate in the reticular areas of the brain stem
- Most pass all the way to the thalamus without interruption, terminating in the *ventrobasal complex* along with the dorsal column–medial lemniscal tract for tactile sensations
- A few fibers terminate in the posterior nuclear group of the thalamus
- From these thalamic areas, the signals are transmitted to other basal areas of the brain, as well as to the somatosensory cortex


C Ad
Spinal nerve
Tract of Lissauer
I
II
III
IV
V
VI
VII
VIII
IX
Lamina marginalis
Substantia gelatinosa
Slow-chronic pain fibers
Fast-sharp pain fibers
Anterolateral pathway

The Nervous System Can Localize Fast Pain in the Body

- The fast-sharp type of pain can be localized much more exactly than can slow-chronic pain
- However, when only pain receptors stimulated, without simultaneous stimulation of tactile receptors, even fast pain may be poorly localized, often only within 10 centimeters of the stimulated area
- Yet, when tactile receptors of dorsal column–medial lemniscal system simultaneously stimulated, the localization can be nearly exact
- It is believed that *glutamate* is the neurotransmitter secreted in the spinal cord at the type Aδ pain nerve fiber endings. It has a duration of action lasting for only a few milliseconds


To somatosensory areas
Thalamus
Ventrobasal complex and posterior nuclear group
Intralaminar nuclei
Slow pain fibers
Fast pain fibers
Reticular formation
Pain tracts

Paleospinothalamic Pathway for Slow-Chronic Pain

- Slow-chronic type C pain fibers, and also some Aδ fibers→
- Laminae II and III of the dorsal horns (*substantia gelatinosa)* →
- Most then pass through one or more additional short fiber neurons→
- Entering mainly lamina V→
- The last neurons in the series give rise to long axons →
- Mostly join the fibers from the fast pain pathway, passing through the anterior commissure to the opposite side →
- Upward to the brain in the anterolateral pathway

Substance P, the Probable Slow-Chronic Neurotransmitter of Type C Nerve Endings

- Type C pain fiber entering spinal cord → release both glutamate and substance P. The 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
- In fact, it has been suggested that the "double" pain sensation one feels after a pinprick might result partly from the fact that the glutamate transmitter gives a faster pain sensation, whereas the substance P transmitter gives a more lagging sensation

Projection of Paleospinothalamic Pathway Into the Brain Stem and Thalamus

- The paleospinothalamic pathway terminates widely in the brain stem
- Only 10% to 25% of the fibers pass all the way to the thalamus. Instead, most terminate in one of three areas:

  (1) the reticular nuclei of the medulla, pons, and mesencephalon

  (2) the tectal mesencephalon deep to the superior and inferior colliculi

  (3) the periaqueductal gray region surrounding the aqueduct of Sylvius.
- These lower regions are important for feeling the suffering types of pain.
- Brain stem pain areas → multiple short-fiber neurons → intralaminar and ventrolateral nuclei of the thalamus and certain portions of hypothalamus and other basal regions of the brain

Poor Capability of Nervous System to Localize Precisely Source of Pain in Slow Chronic Pathway

- Localization of pain via the paleospinothalamic pathway is imprecise. For example, to a major part of the body, such as to one arm or leg but not to a specific point on the arm or leg
- This phenomenon is because of the → the multisynaptic, diffuse connectivity of this pathway
- It explains the serious difficulty in localizing the source of some chronic types of pain

Function of the Reticular Formation, Thalamus, and Cerebral Cortex in the Appreciation of Pain

- Complete removal of the somatic sensory areas of cortex → not prevent pain perception → likely impulses entering brain stem reticular formation, thalamus, and other lower centers cause conscious perception of pain
- This does not mean that the cortex has nothing to do with normal pain appreciation; electrical stimulation of cortical somatosensory areas cause a person to perceive mild pain
- Cortex plays an especially important role in interpreting pain quality
- Pain perception is principally the function of lower centers

Special Capability of Pain Signals to Arouse Overall Brain Excitability

- Electrical stimulation in reticular brain stem and intralaminar nuclei of thalamus → strong arousal effect on nervous activity throughout the entire brain
- These two areas → part of the brain's principal arousal system
- This explains why it is almost impossible for a person to sleep when in severe pain

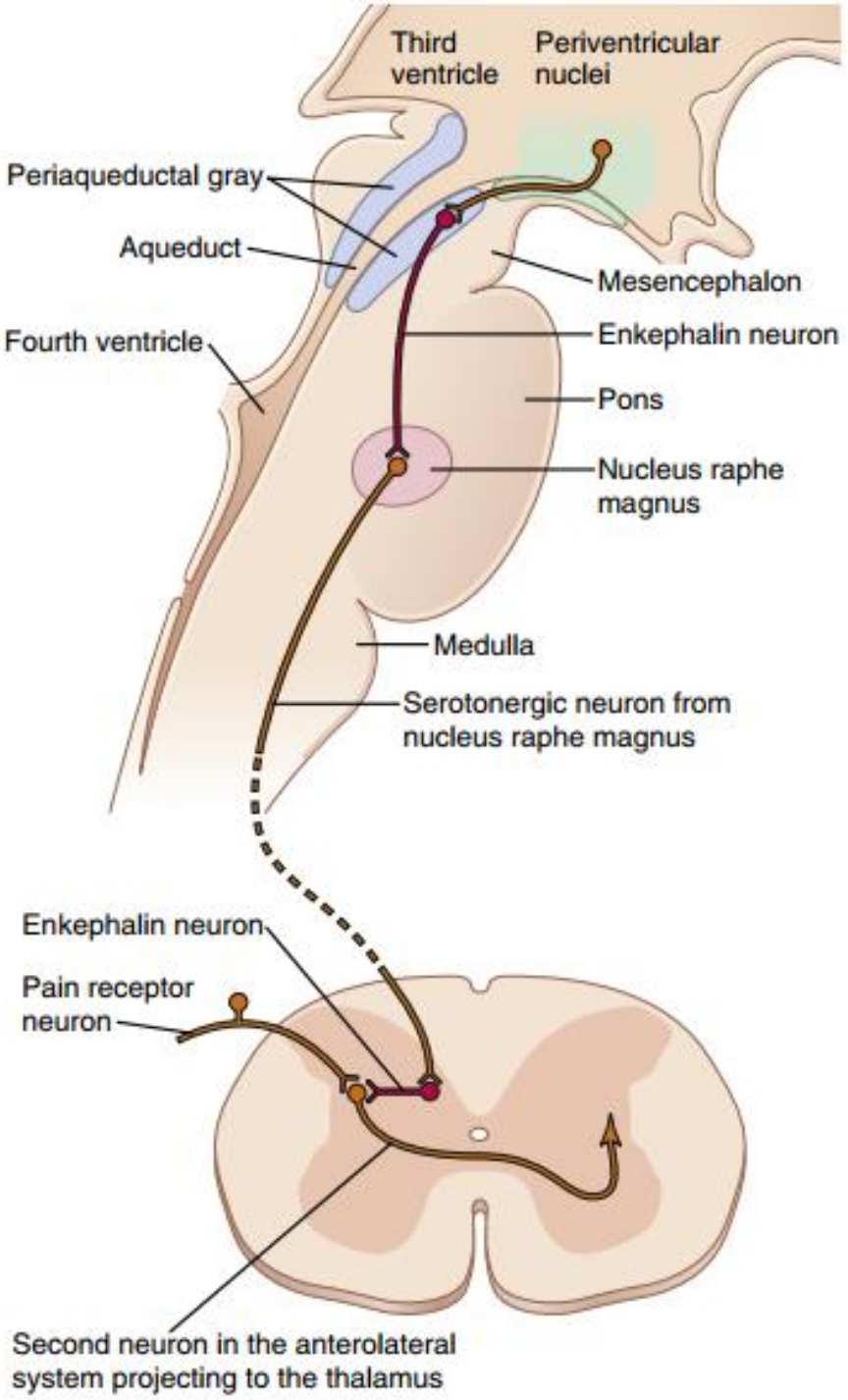
Surgical Interruption of Pain Pathways

- To provide pain relief, the pain nervous pathways can be cut at any one of several points
- In the pain is in the lower part of the body, a cordotomy in the thoracic region often relieves the pain for a few weeks to months. Pain-conducting tracts of the spinal cord on the side opposite to the pain are cut in its anterolateral quadrant to interrupt the anterolateral sensory pathway
- A cordotomy is not always effective for two reasons. First, many pain fibers from upper part of the body do not cross until they have reached the brain. Second, pain frequently returns several months later, partly as a result of sensitization of other pathways that normally are too weak to be effectual (e.g., sparse pathways in the dorsolateral cord)

PAIN SUPPRESSION (ANALGESIA) SYSTEM IN THE BRAIN AND SPINAL CORD

- The degree to which different people react to pain varies tremendously. This results partly from a capability of the brain itself to suppress input of pain signals to by activating a pain control system, called an *analgesia system*.
- The analgesia system, consists of three major components:
- (1) The *PAG* and *PV areas* of mesencephalon and upper pons surround the aqueduct of Sylvius and portions of the third and fourth ventricles. Neurons from these areas send signals to
- (2) the *raphe magnus nucleus*, a thin midline nucleus located in the lower pons and upper medulla, and the *nucleus reticularis paragigantocellularis*, located laterally in the medulla.
- (3) From these nuclei, second-dorder signals transmitted down the dorsolateral columns in the cord to *a pain inhibitory complex located in the dorsal horns of the spinal cord*. **At this point, the analgesia signals can block the pain before it is relayed to the brain**.

- Electrical stimulation either in the PAG area or raphe magnus nucleus → suppress pain signals entering via the dorsal spinal roots.
- Also, stimulation of areas at higher levels of the brain that excite PAG area suppress pain: (1) the PV nuclei of hypothalamus, adjacent to the third ventricle; and, (2) the medial forebrain bundle, also in the hypothalamus.
- PV nuclei and PAG neurons secrete enkephalin. Fibers send signals to the dorsal horns to secrete serotonin at their endings. The serotonin causes local cord neurons to secrete enkephalin as well.
- The enkephalin → both *presynaptic* and *postsynaptic inhibition* of incoming type C and type Aδ pain fibers where they synapse in the dorsal horns.



- The analgesia system can block pain signals at the initial entry point to the cord. It can also block many local cord reflexes that result from pain signals, especially withdrawal reflexes

THE BRAIN'S OPIATE SYSTEM—ENDORPHINS AND ENKEPHALINS

- Injection of minute quantities of morphine either into the PV nucleus around the third ventricle or into the PAG causes an extreme analgesia.
- morphine-like agents, mainly opiates, act at many other points in the analgesia system, including the dorsal horns of spinal cord.
- About a dozen opiate-like substances found at different points of the nervous system. All are breakdown products of three large protein molecules—*pro-opiomelanocortin, proenkephalin,* and *prodynorphin.* The more important are *β-endorphin, met-enkephalin, leu-enkephalin*, and *dynorphin*

Inhibition of Pain Transmission by Simultaneous Tactile Sensory Signals

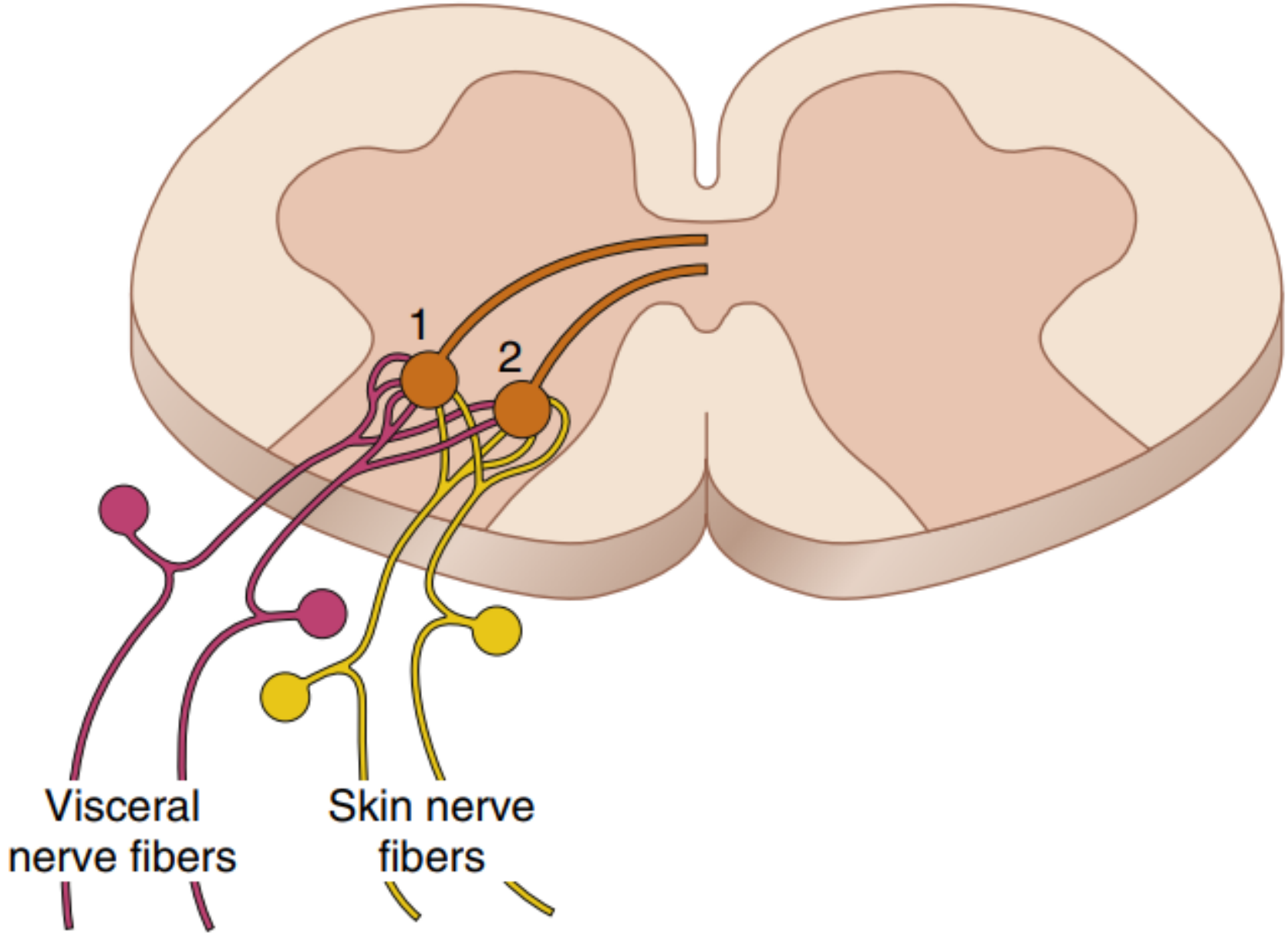
- Stimulation of large-type Aβ sensory fibers from peripheral tactile receptors can depress transmission of pain signals from the same body area.
- It presumably results from local lateral inhibition in the spinal cord.
- It explains why such simple maneuvers as rubbing the skin near painful areas is often effective in relieving pain, also explains why liniments are often useful for pain relief.
- This mechanism and the simultaneous psychogenic excitation of the central analgesia system are probably also the basis of pain relief by acupuncture.

Treatment of Pain by Electrical Stimulation

- Stimulating electrodes are placed on selected areas of the skin or, on occasion, implanted over the spinal cord, supposedly to stimulate the dorsal sensory columns.
- In some, electrodes placed stereotaxically in appropriate intralaminar nuclei of thalamus or in PV or periaqueductal area of diencephalon.
- The patient can personally control the degree of stimulation.
- Dramatic relief has been reported in some. Pain relief reported to last for as long as 24 hours after only a few minutes of stimulation.

REFERRED PAIN

- Often, a person feels pain in a part of the body that is fairly remote from the tissue causing the pain. This phenomenon is called referred pain. For example, pain in one of the visceral organs often is referred to an area on the body surface.
- Referred pain is important in clinical diagnosis because, in many visceral ailments, the only clinical sign is referred pain.
- Visceral pain fibers synapse in the spinal cord on the same second-order neurons that receive pain signals from the skin. When visceral fibers are stimulated, pain signals conducted some same neurons from the skin, and the person has the feeling that the sensations originate in the skin.



Neurons 1 and 2 receive pain signals from the skin as well as from the viscera.

Differences Between Surface And Visceral Pain

- Highly localized types of damage to the viscera seldom cause severe pain → a surgeon can cut the gut entirely in two in a patient who is awake without causing significant pain.
- Any diffuse stimulation of pain nerve endings throughout a viscus causes pain that can be severe → ischemia caused by occluding the blood supply of gut stimulates many diffuse pain fibers at the same time and can result in extreme pain

“PARIETAL PAIN” CAUSED BY VISCERAL DISEASE

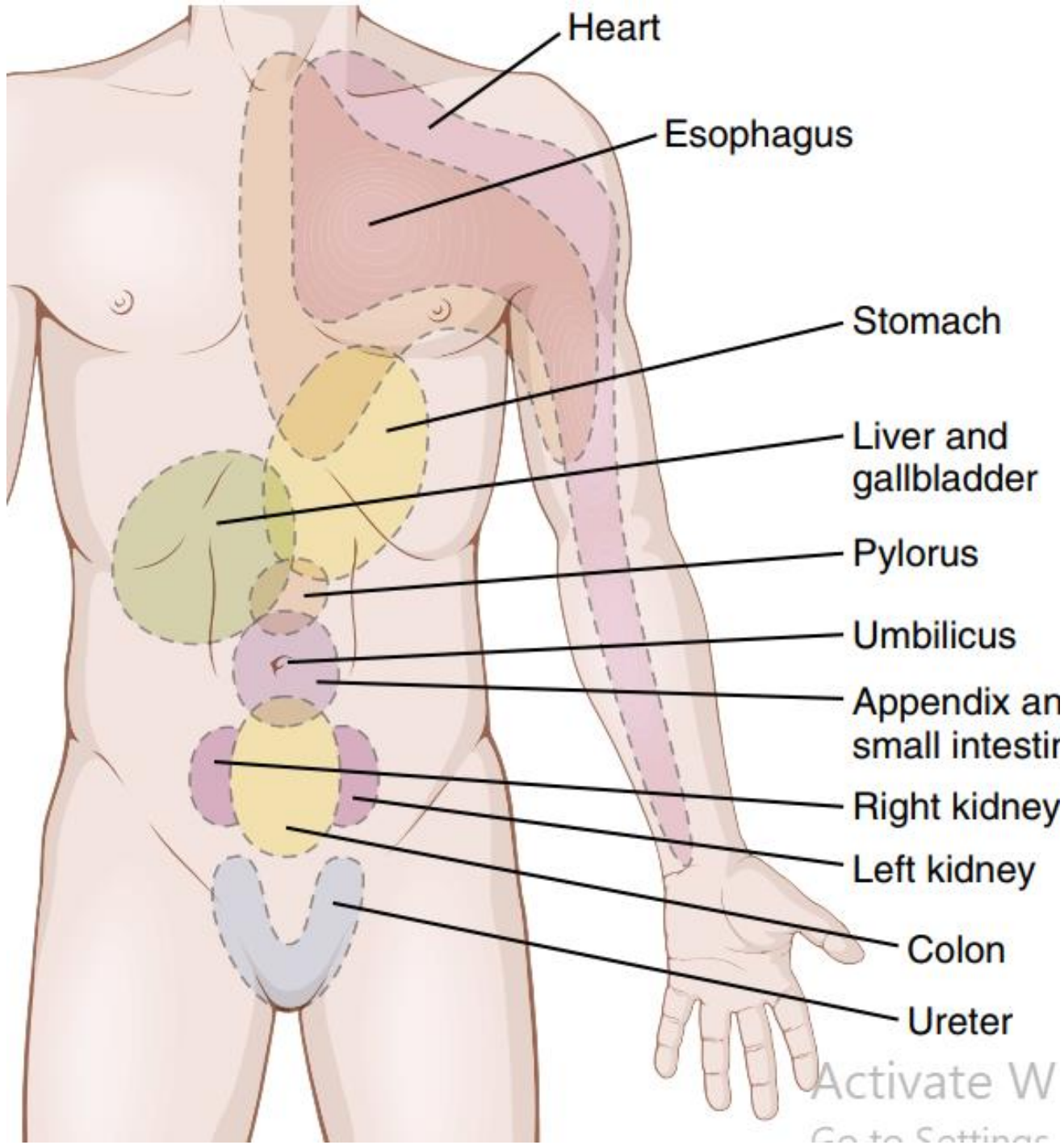
- When a disease affects a viscus, the disease process can spreads to the parietal peritoneum, pleura, or pericardium.
- Parietal surfaces, like the skin, are supplied with extensive pain innervation from the peripheral spinal nerves. Therefore, pain from the parietal wall is frequently sharp.
- A knife incision through the *parietal* peritoneum is very painful, whereas a similar cut through the visceral peritoneum or through a gut wall is not very painful, if it is painful at all.

LOCALIZATION OF VISCERAL PAIN— “VISCERAL” AND “PARIETAL” PAIN TRANSMISSION PATHWAYS

- Pain from viscera is frequently difficult to localize: **First**, the brain does not have firsthand experience that the internal organs exist; so, any pain is localized only generally. **Second**, sensations from the abdomen and thorax are transmitted through two pathways to the CNS, true visceral pathway and parietal pathway.
- True visceral pain is transmitted via pain sensory fibers in the autonomic nerve bundles, and the sensations are referred to surface areas of the body that are often far from the painful organ. Conversely, parietal sensations are conducted directly into local spinal nerves, and are usually localized directly over the painful area.

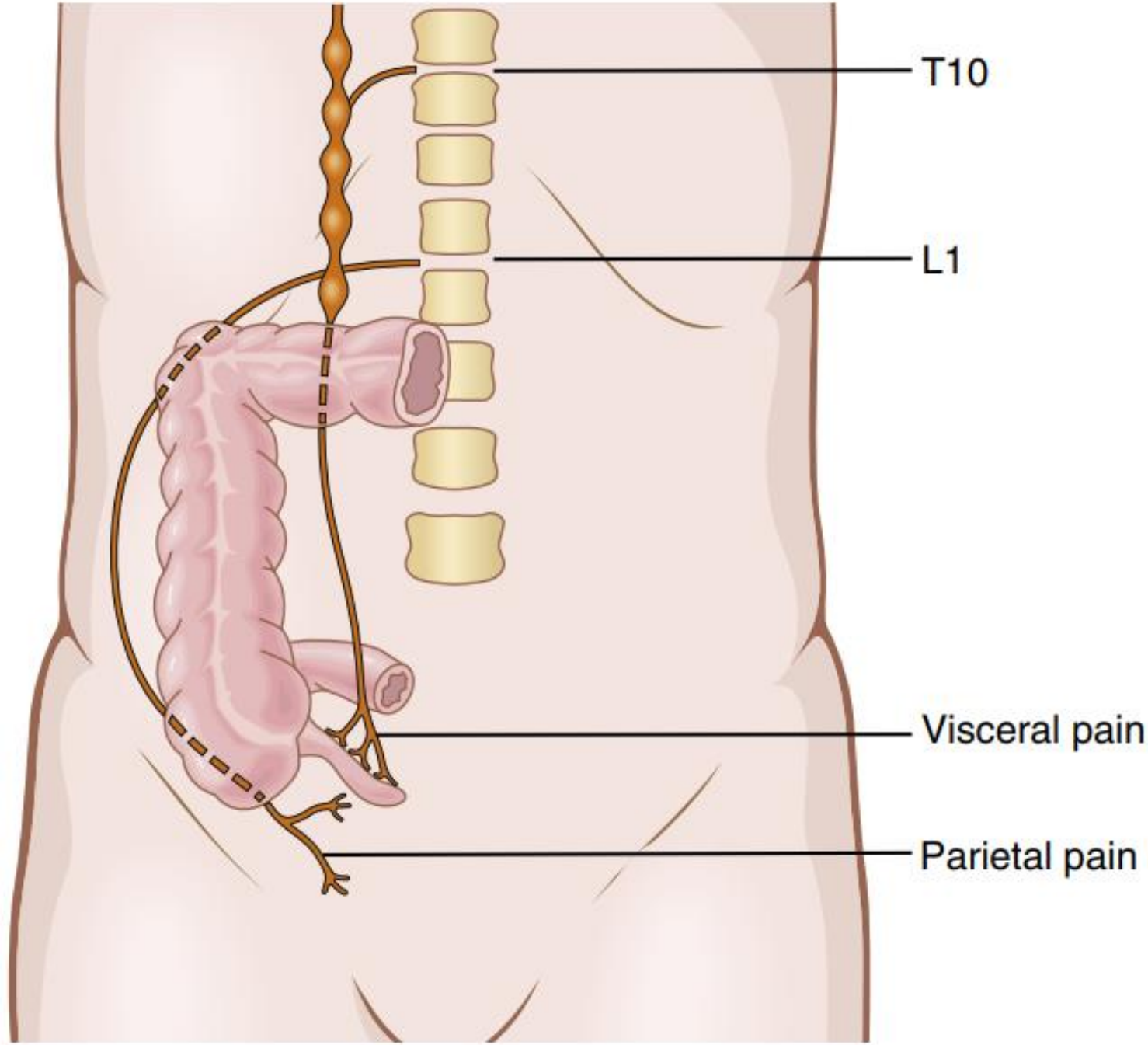
Localization of Referred Pain Transmitted via Visceral Pathways

- Visceral pain is referred to the surface of the body, in the dermatomal segment from which the visceral organ originated in the embryo, not necessarily where the visceral organ now lies.
- **Heart** originated in the neck and upper thorax, so the pain fibers pass along the sympathetic sensory nerves and enter the cord between segments C3 and T5. Therefore, pain is referred to the side of the neck, over shoulder, pectoral muscles, down the arm, and into he substernal area of the upper chest); Usually, on the left because the left side of the heart is much more frequently involved in coronary disease.



Parietal Pathway for Transmission of Abdominal and Thoracic Pain

- Pain impulses pass first from the appendix through visceral pain fibers located within sympathetic nerve bundles → spinal cord at about T10 or T11; referred to an area around the umbilicus and is of the aching, cramping type.
- Pain impulses also often originate in the parietal peritoneum where the inflamed appendix touches→ pain of the sharp type directly over the irritated peritoneum in right lower quadrant of the abdomen.

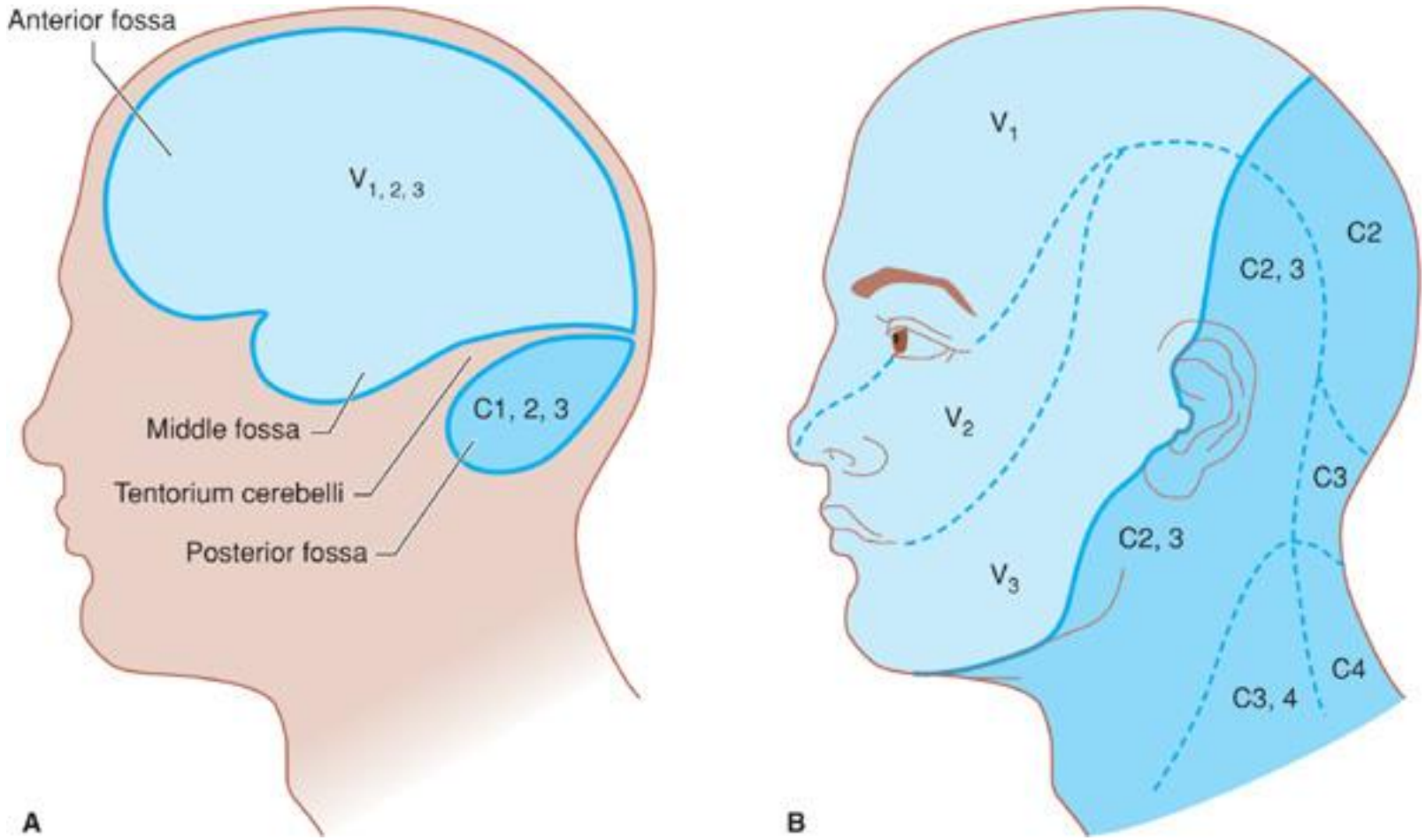

T10
L1
Visceral pain
Parietal pain

Headache

- Headaches are a type of pain referred to the surface of the head from deep head structures.
- Some headaches result from pain stimuli arising inside the cranium, but others result from pain arising outside the cranium, such as from the nasal sinuses.

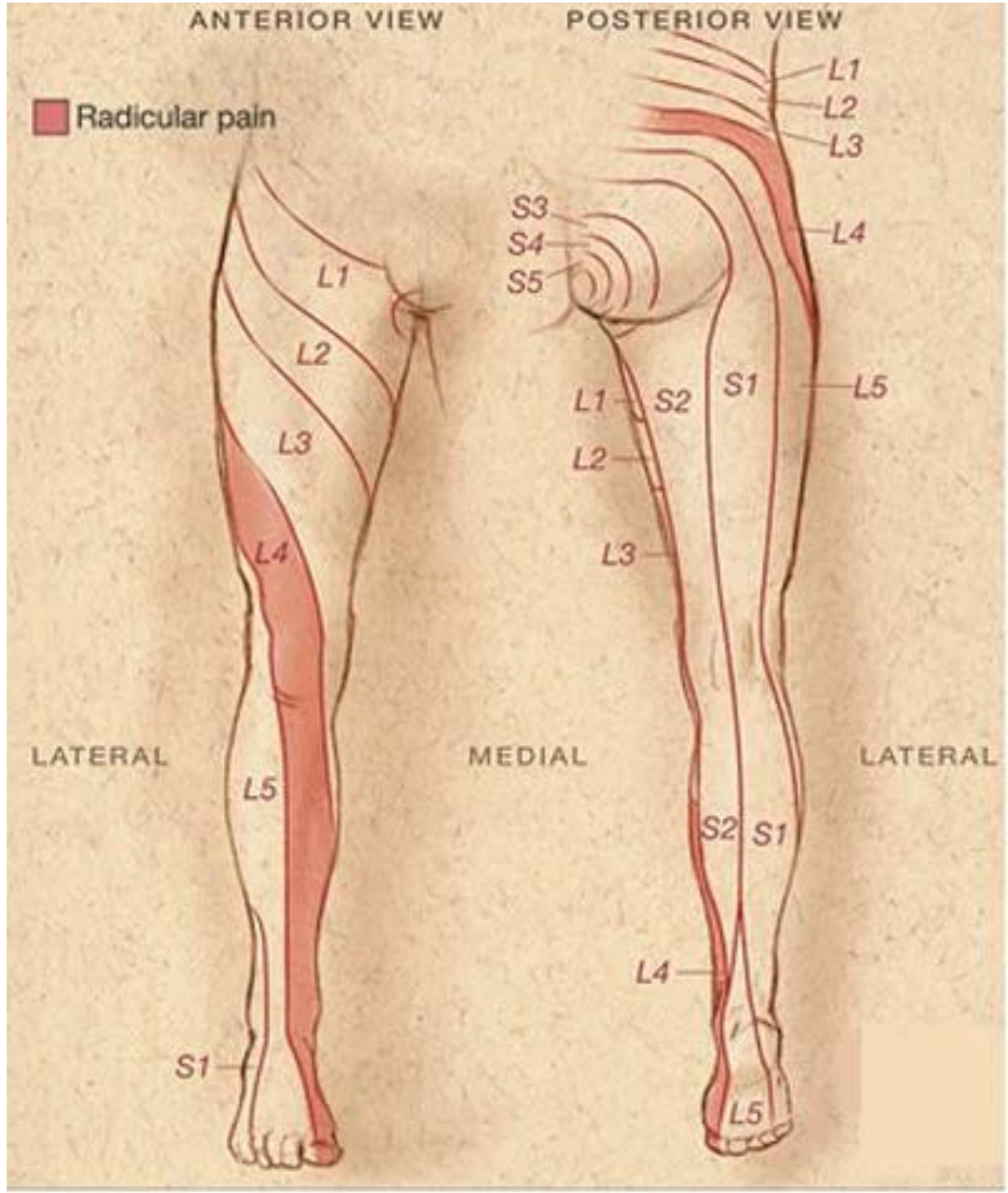
Headache of Intracranial Origin

- The brain tissues → almost totally insensitive to pain. Even cutting or electrically stimulating the sensory areas of the cerebral cortex only occasionally causes pain
- Tugging on the venous sinuses around the brain, damaging the tentorium, or stretching the dura at the base of the brain can cause intense pain that is recognized as headache. Also, almost any type of traumatizing, crushing, or stretching stimulus to the blood vessels of the meninges can cause headache. An especially sensitive structure is the middle meningeal artery; neurosurgeons are careful to anesthetize this artery specifically when performing brain operations with use of local anesthesia.


Anterior fossa
$V_{1, 2, 3}$
C1, 2, 3
Middle fossa
Tentorium cerebelli
Posterior fossa
A
V_1
C2
C2, 3
V_2
C3
C2, 3
V_3
C4
C3, 4
B

Radicular pain

- Is pain "radiated" along the dermatome (sensory distribution) due to inflammation or other irritation of the nerve root (radiculopathy) at its connection to the spinal column
- A common form of radiculitis is sciatica – radicular pain that radiates along the sciatic nerve from the lower spine to the lower back, gluteal muscles, back of the upper thigh, calf, and foot as often secondary to nerve root irritation from a spinal disc herniation or from osteophytes in the lumbar region of the spine

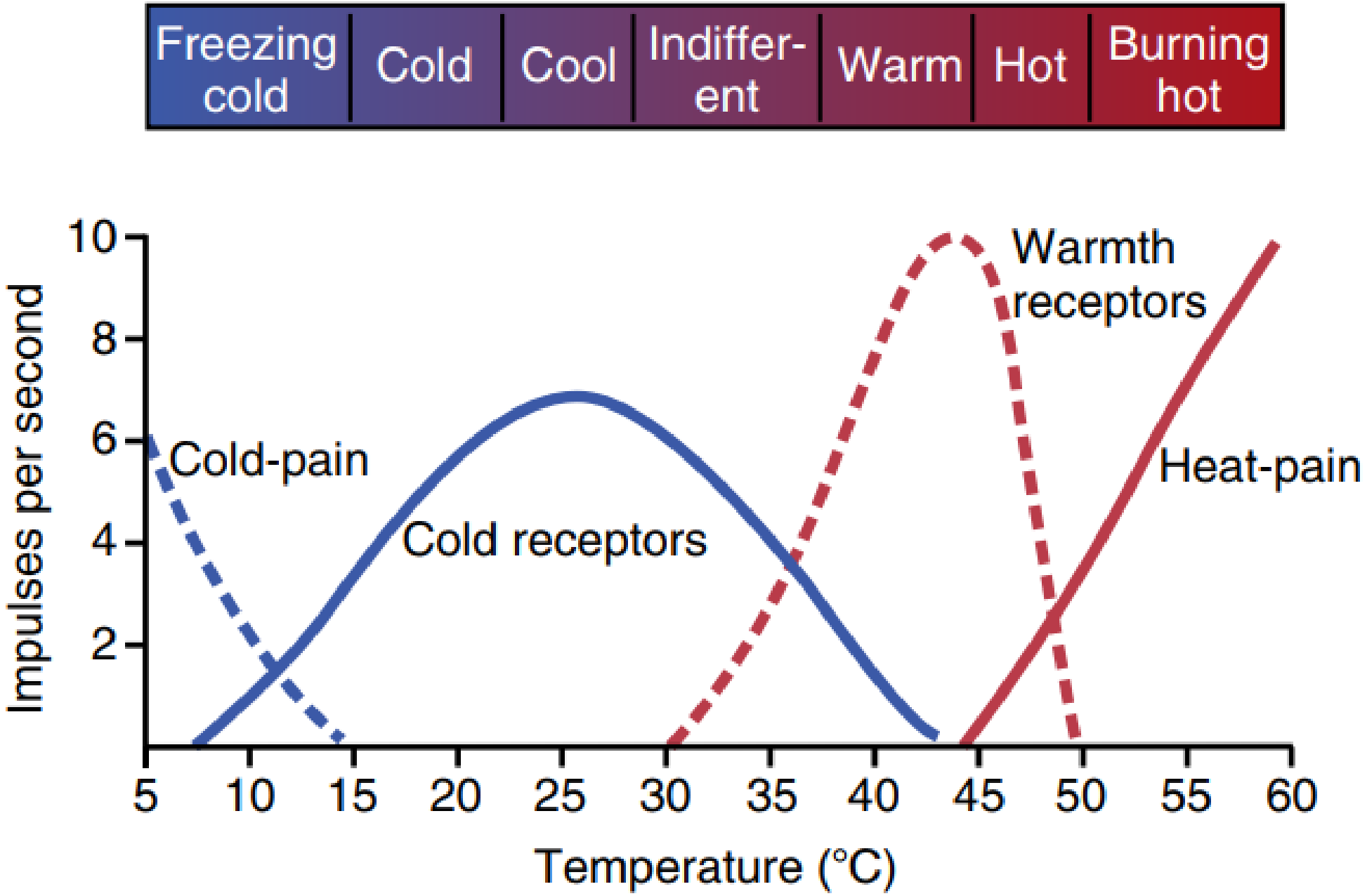

ANTERIOR VIEW
POSTERIOR VIEW
Radicular pain
L1
L2
L3
L4
L5
S1
S2
S3
S4
S5
LATERAL
MEDIAL
LATERAL

Hyperalgesia—Hypersensitivity to Pain

- A pain nervous pathway sometimes becomes excessively excitable, which gives rise to hyperalgesia.
- Possible causes of hyperalgesia are the following:

  (1) excessive sensitivity of pain receptors, called primary hyperalgesia→ An example is extreme sensitivity of sunburned skin, results from sensitization of the skin pain endings by local tissue products from the burn—histamine, prostaglandins, and others

  (2) facilitation of sensory transmission, called secondary hyperalgesia, frequently results from lesions in the spinal cord or the thalamus


Freezing cold
Cold
Cool
Indiffer-ent
Warm
Hot
Burning hot
Impulses per second
10
8
6
4
2
Cold-pain
Cold receptors
Warmth receptors
Heat-pain
5
10
15
20
25
30
35
40
45
50
55
60
Temperature (°C)

THANKS

FOR YOUR ATTENTION