Physiology

Modified no. 4

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Neurophysiology

Color code

- Slides
- Doctor
- Additional info
- Important

Pain

اللهم عَافِ كل مبتلى, واشفِ كل مريض يتألم من مرض جسدي أو نفسي أو علة من العلل, لايقدر على علاجها وشفائها إلا أنت، آمين يارب العالمين

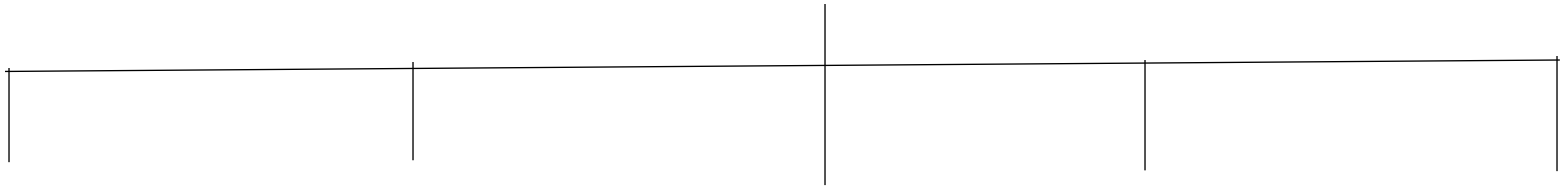
Please note that the slides have been rearranged to make them easier for u to understand. Also, Dr read almost everything so make sure u don’t miss anything ✨

Fatima Ryalat, MD, PhD

Welcome again in the 4th physiology lec in the CNS

Topics for today's lec :)

"Pain"



- Classification (Fast vs. Slow) (Somatic vs. Visceral).
- Pathways (Neospinothalamic, Paleospinothalamic).
- Referred Pain.
- Endogenous Analgesia System.
- Pain Control (Lateral Inhibition, Acupuncture, etc)

In this lecture the doctor introduced us to pain classification and pathways, it will be easy if you understand the concept of somatosensory pathways,
say بسم الله and let's go

Pain Classification

- **<u>There are Two types of pain : fast pain , and slow pain</u>**

- Stimulus
- Receptor
- Nerve fiber
- Neurotransmitter
- Ascending Pathway
- Localization
- Character of pain
- Significance

🩹 We have discussed multiple sensory modalities that carry informative sensations. However, pain is not only an informative sensation but also a protective one.

What is the stimulus for pain?

Excessive mechanical, thermal, or chemical stimulation can induce pain by activating pain receptors (nociceptors), which are free nerve endings.

These **free nerve endings** are part of nerve fibers. Which type of nerve fibers?

- **A-delta fibers**: Larger in diameter, myelinated, and fast-conducting.
- **C fibers**: Smaller in diameter, unmyelinated, and slow-conducting.

We have two types of pain: fast pain and slow pain. Each type differs in its stimulus, nerve fiber type, and neurotransmitters utilized. We will discuss them in the next slide.

🐌 **Slow pain: Transmitted via C fibers.**

🚀 **Fast pain: Transmitted via A-delta fibers, allowing sensory input to reach the cortex more quickly.**

Now, Remember from general physiology:

- **Types of Neurotransmitters:**

1. Small-molecule, rapidly acting neurotransmitters:

1. Stored in vesicles at the nerve terminal.
2. Released immediately when an action potential reaches the nerve ending.
3. Example: **Glutamate**.

2. Peptides:

1. Synthesized in the axon.
2. Take longer to be available.
3. Example: **Substance P**.

- Since **A-delta fibers** are responsible for fast pain transmission, they primarily use **rapidly acting small-molecule neurotransmitters** to serve their function.
In contrast, **C fibers**, which transmit slow pain, rely on **peptides** as their main neurotransmitters.

Pain

- Even though all pain receptors are free nerve endings, these endings use two separate pathways for transmitting pain signals into the central nervous system.

- The two pathways mainly correspond to the two types of pain:
- a fast-sharp pain pathway.
- a slow-chronic pain pathway.

Fast (acute) Pain

- The fast-sharp pain signals are elicited by either mechanical or thermal pain stimuli.
- Fast-sharp pain is not felt in most deep tissues of the body.
- They are transmitted in the peripheral nerves to the spinal cord by small type Aδ fibers at velocities between 6 and 30 m/sec.
- a fast-sharp pain is followed a second or so later by a slow pain.
- The sharp pain plays an important role in making the person react immediately to remove himself or herself from the stimulus.

Chronic (slow) Pain

- Slow pain can occur in the skin and in almost any deep tissue or organ.
- this type of pain is elicited mostly by chemical types of pain stimuli.
- It is transmitted to the spinal cord by type C fibers at velocities between 0.5 and 2 m/sec.
- This feeling is a dull, aching, poorly localized sensation that persists for a longer time and is more unpleasant.

Pain Classification

- **Somatic : Cutaneous : like in the skin, Deep: muscles and joints**
- **Visceral: internal organs, they have a relatively scarce distribution of nerve fibers to sense the pain in these organs**(not present in some tissues like: liver, alveoli, brain tissue)
- **Parietal** (sharp, localized), more number of pain sensors (e.g: pluera).
- **Neuronal** (hyperalgesia vs allodynia)

- Causes
- Localization and innervation density.
- Pain intensity and rate of tissue damage
- Autonomic responses

Explanation about the previous slide:

For example, let's imagine this is a part of the **small intestine** supplied by a blood vessel:

Patient 1

Had a **thrombosis**, which led to **ischemia** (impaired blood supply), causing the release of **chemical signals**. These are transmitted as **slow pain** through **C-fibers**.

Pain characteristics: No localization of pain, but the patient feels **suffering** 😖.

Reason: Ischemia → Release of chemicals → Increased pain intensity → More fibers transmitting the pain → **Spatial summation**.

Patient 2

Had **dissection surgery** on the small intestine due to a pathology like perforation, **without ischemia**.

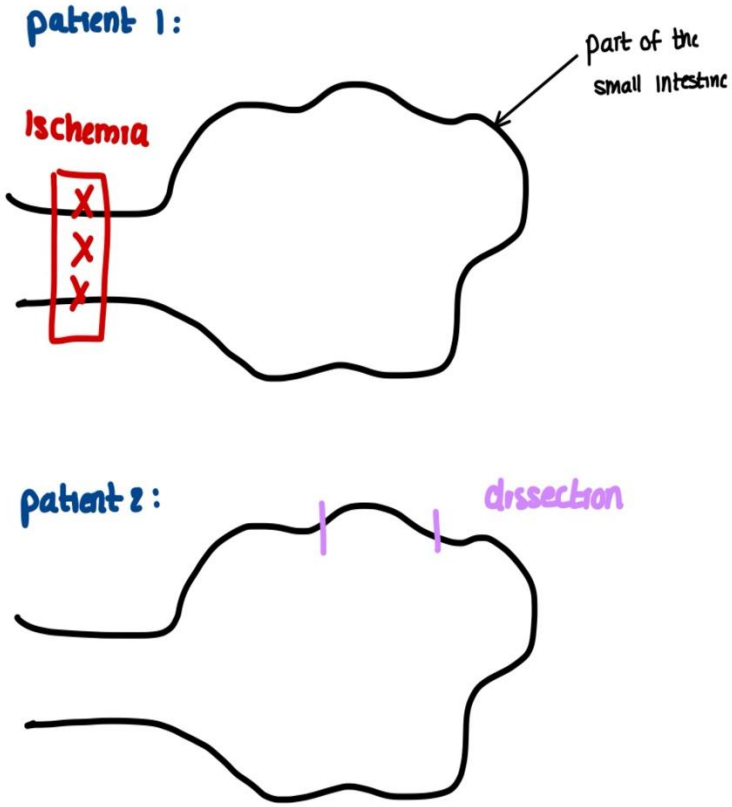
Pain characteristics: Mild pain 😌.

Reason: No nerve supply for pain in deep tissues like the small intestine, so no strong pain perception.

Which patient feels more pain?

Patient 1 with ischemia will feel **more pain** due to the **chemical neurotransmitters** released and increased **surface area**, which increases the intensity of pain and number of fibers involved.

Patient 2 will feel **mild pain** because the **nerve supply** in the deep tissues is limited.

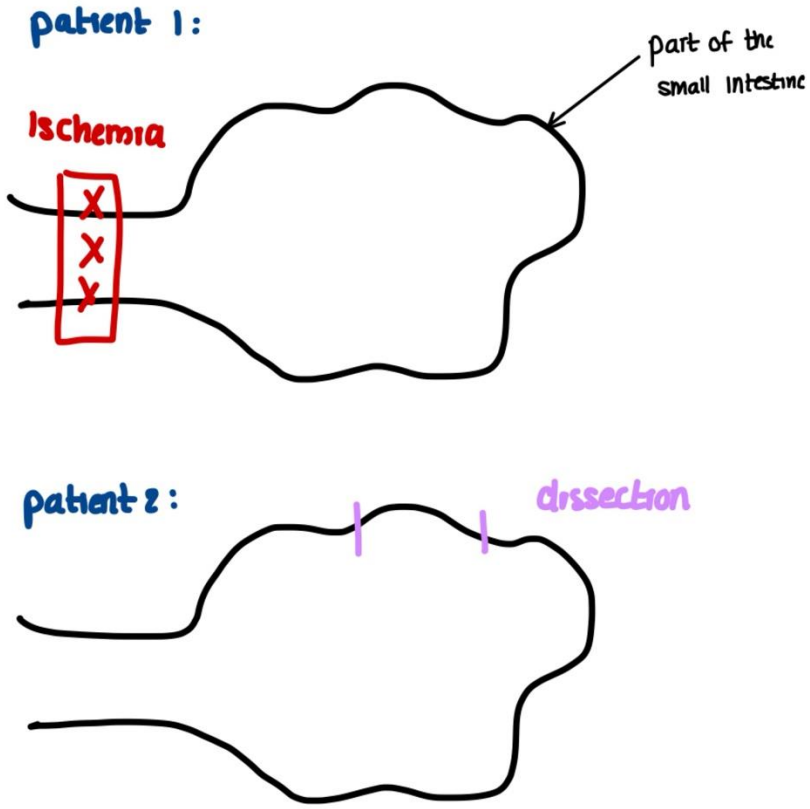


الخلاصة من السلايد السابق:

هي إنه فيه فرق في شدة الألم في الأمعاء حسب نوع الإصابة:

1. **الألم بسبب نقص الدم (ischemia)**: هذا الألم بكون أقوى لأنه لما الأمعاء ما يوصلها دم كافي، بتطلّع مواد كيميائية بتنشط أعصاب الألم بشكل أكبر وبتسبب ألم شديد.
2. **الألم بسبب الجراحة (dissection surgery) في الأمعاء**: هذا الألم بكون أخف لأنه ما في نقص في التروية، والألم بيكون ناتج عن التضرر الميكانيكي فقط، والأعصاب اللي بتشعر بالألم مش بنفس الكثافة زي لما يكون في نقص بالدم.

بالمختصر، الألم الناتج عن نقص الدم **"ischemia"** بكون أقوى بسبب المواد الكيميائية، أما الجراحة من دون نقص دم فالألم بكون أخف لأنه ما في تفاعل كيميائي قوي



Visceral pain

- Essentially all visceral pain that originates in the thoracic and abdominal cavities is transmitted through small type C pain fibers and, therefore, can transmit only the chronic, aching, suffering type of pain.

- One of the most important differences between surface pain and visceral pain is that highly localized types of damage to the viscera seldom cause severe pain.

- Conversely, any stimulus that causes diffuse stimulation of pain nerve endings throughout a viscus causes pain that can be severe.

Visceral pain

- Any stimulus that excites pain nerve endings in diffuse areas of the viscera can cause visceral pain.

- Such stimuli include ischemia of visceral tissue, chemical damage to the surfaces of the viscera, spasm of the smooth muscle of a hollow viscus, excess distention of a hollow viscus, and stretching of the connective tissue surrounding or within the viscus.

Visceral pain

- A few visceral areas are almost completely insensitive to pain of any type.
- These areas include the parenchyma of the liver and the alveoli of the lungs
- Yet, the liver capsule is extremely sensitive to both direct trauma and stretch, and the bile ducts are also sensitive to pain. In the lungs, even though the alveoli are insensitive, both the bronchi and the parietal pleura are very sensitive to pain.

Visceral Pain

- 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.

- Pain from the viscera is frequently localized to two surface areas of the body at the same time because of the dual transmission of pain through the referred visceral pathway and the direct parietal pathway.

Parietal pain

- When a disease affects a viscus, the disease process often spreads to the parietal peritoneum, pleura, or pericardium.

- These parietal surfaces, like the skin, are supplied with extensive pain innervation from the peripheral spinal nerves.

- parietal sensations are conducted directly into local spinal nerves from the parietal peritoneum, pleura, or pericardium, and these sensations are usually localized directly over the painful area and sharp.

Causes of Pain:

1.Ischemia (the most common cause)

2.Stretching and distention of blood vessel walls

👉 Anyways, When thinking about the causes of pain, you should consider:

1.Etiology (vascular, inflammation, infection, trauma)

2.Anatomical distribution (where the pain is coming from)

👉 Don't forget:

Poor localization of pain: Seen in **visceral** (internal organs) and **deep** pain.

Very well localized pain: Seen in **cutaneous** (skin) and **parietal** (body walls) pain.

🥼 U should keep in mind that PAIN is the most thing we will deal with as doctors, especially the chronic slow pain.

(Your body is communicating with you through pain, so you should listen to your body's signs and warnings)

pathways

✅ Neospinothalamic pathway

Paleospinothalamic pathway

✅ The first pathway is called the neospinothalamic pathway and it’s for fast pain transmission.

Let's revise :

Here, we have a **pain receptor** on an **A-delta nerve fiber**, which is now transmitting pain signals.

1.First-order neuron:

- Carries the pain signal to the **dorsal root** of the spinal cord.
- Synapses with the **second-order neuron** in the spinal cord.

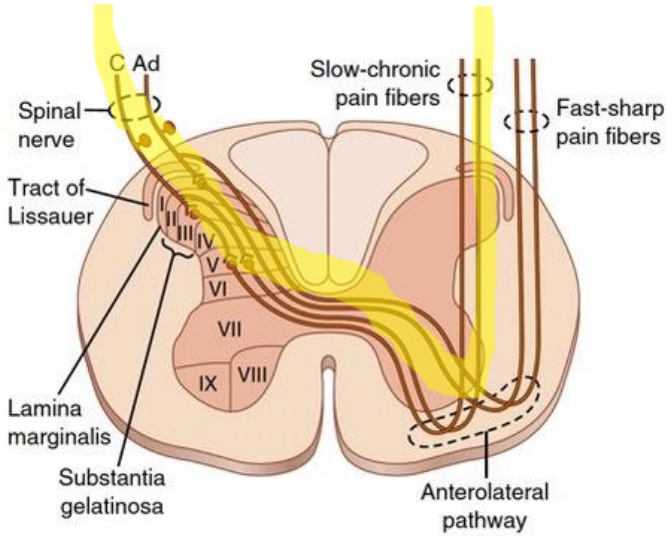
2.Second-order neuron:

- **Decussates** (crosses to the opposite side).
- Ascends to the **thalamus** and synapses at the **ventrobasal complex (VBL)** with the **third-order neuron**.

3.Third-order neuron:

Transmits the signal from the thalamus to the **primary somatosensory cortex**.

📍 This region of the cortex contains a **somatotopic map (homunculus)**, where each body part is represented in an organized manner. Since the pain stimulus reaches the cortex, we become **conscious of the pain sensation**.



Withdrawal reflex: The withdrawal reflex is a **protective spinal reflex pathway** that transmits pain signals even faster than the normal pain pathway. Its purpose is to **alert the brain and trigger a rapid motor response**, causing the affected organ to move away from the danger source. This mechanism helps **minimize tissue damage**.

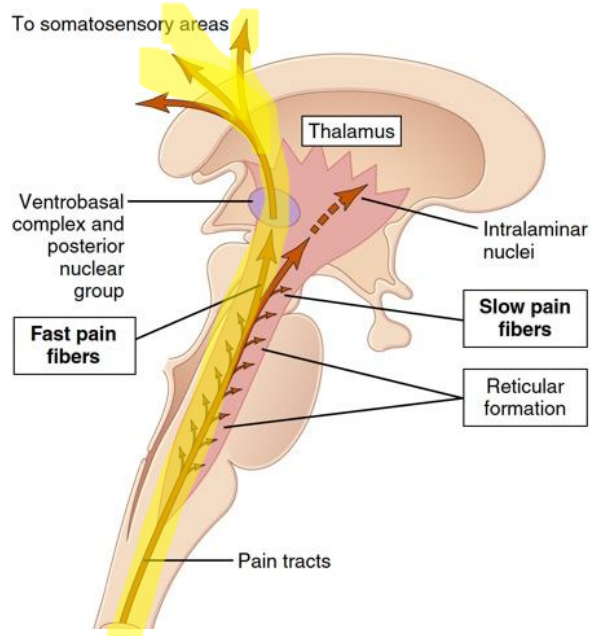
Example: Imagine you're cutting vegetables to make fattoush 🥗😋 and accidentally you cut your finger. The withdrawal reflex will activate, causing you to pull your hand away even before you consciously feel the pain. This happens because the reflex bypasses the brain initially, allowing for an immediate response. The pain sensation reaches the cortex slightly later, making you realize the injury after you've already moved your hand.

🚩 Effect of diabetes on the Withdrawal Reflex:

In **advanced diabetes**, the nervous system may fail to properly receive pain signals due to **peripheral neuropathy**. This can result in a **delayed or absent withdrawal reflex**.

Consequences:

1. Increased risk of **unnoticed injuries**, such as burns and cuts.
2. **Reduced pain perception**, preventing the protective withdrawal response.
3. Higher likelihood of **chronic wounds and infections**, as injuries may go untreated.

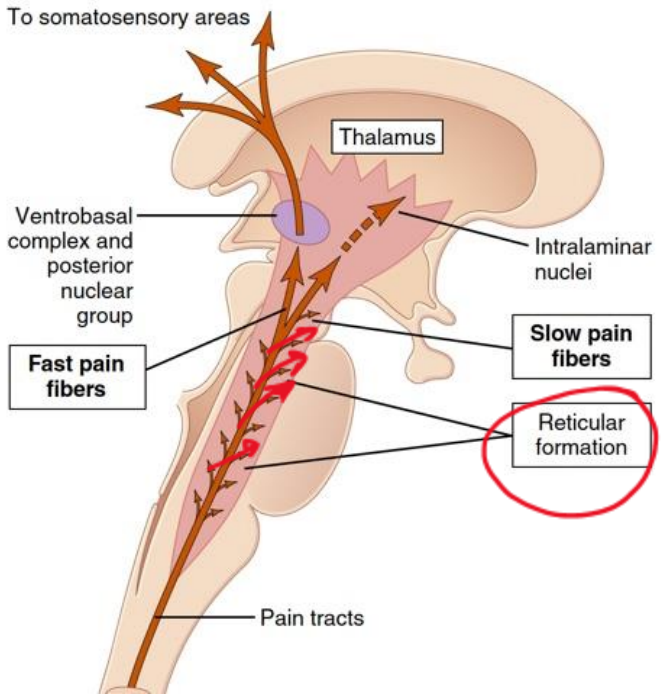


- Look at the red arrow, where do these branches go?

The branches indicated by the red arrow project to a specialized, rounded structure located between the upper spinal cord and the lower part of the diencephalon. This network of white and gray matter is called the reticular formation, often referred to as the "switch-on button" of consciousness.

Purpose of This Pathway

This pathway enhances alertness in response to fast, acute pain by activating the reticular formation, which in turn stimulates the perception of pain in the cortex. By doing so, the brain remains aware of the pain stimulus, ensuring a heightened state of alertness in response to potential danger. The reticular formation is active when we are awake and alert. It is switched off during sleep or coma, meaning pain perception and alertness are significantly reduced in these states.



Neospinothalamic tract

- A 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, terminating in the ventrobasal complex along with the dorsal column–medial lemniscal tract for tactile sensations.

- A few fibers also 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.

Localization of fast pain

- The fast-sharp type of pain can be localized much more exactly in the different parts of the body than can slow-chronic pain.

- When tactile receptors that excite the dorsal column–medial lemniscal system are simultaneously stimulated, the localization can be nearly exact.

- It is believed that glutamate is the neurotransmitter substance secreted in the spinal cord at the type Aδ pain nerve fiber endings.

pathways

Neospinothalamic pathway

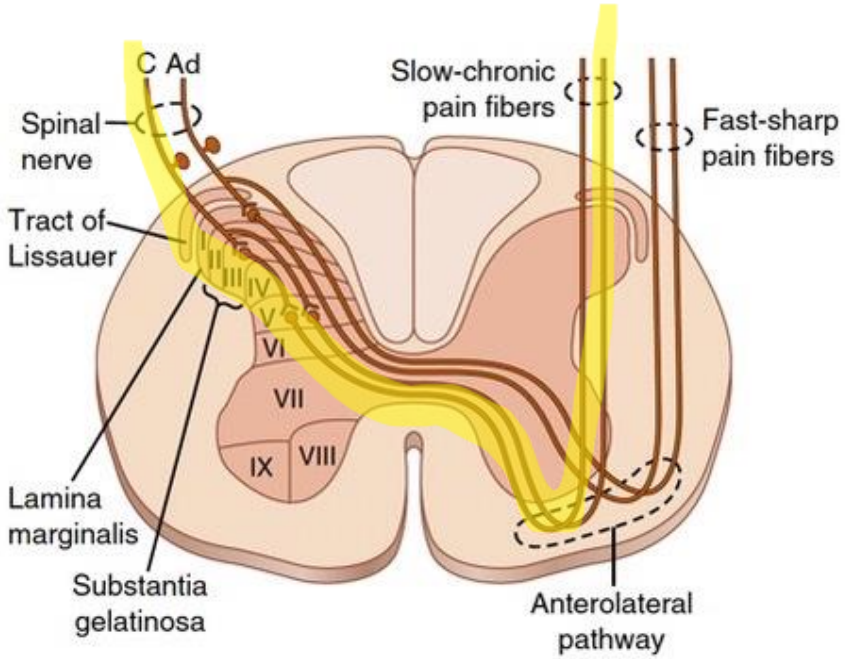
✅ Paleospinothalamic pathway

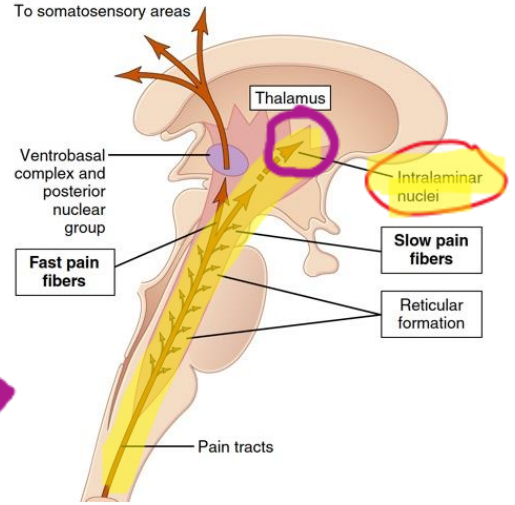
✅ The pleospinothalamic pathway is related to the Slow and chronic type of pain.

Pathway of C-Fibers and the Emotional Response to Pain
First, the C-fibers enter the dorsal root and synapse at the substantia gelatinosa, specifically at lamina II and III of the spinal cord.
Then, the second-order neurons decussate and ascend to the thalamus.
But guess what? Unlike fast pain, where the third-order neurons project to the somatosensory cortex, here they follow a different route!

Where Do The Third Order Neurons Go?
Instead of reaching the primary somatosensory cortex, the third neurons project to the intralaminar nuclei in the subcortical region.

Why?
This divergence occurs because slow pain requires an emotional and behavioral responses, integrating with the limbic system rather than triggering a rapid reflex.
This is why pain affects people differently: some may cry, others may become angry, and some may even appear calm.
Additionally, some C-fibers send signals to the reticular formation, ensuring conscious awareness of the pain.





So! 💡
Fast Pain (A-delta fibers) → Localization of pain → Do Action
Slow Pain (C-fibers) → Suffering → Emotional/Behavioral Response

Paleospinothalamic pathway

- The slow-chronic 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 area of the mesencephalon deep to the superior and inferior colliculi.
- (3) the periaqueductal gray region surrounding the aqueduct of Sylvius.

Paleospinothalamic pathway

- These **lower regions of the brain** appear to be important for feeling the **suffering types of pain**.

- From the brain stem pain areas, multiple short-fiber neurons relay the pain signals upward into the intralaminar and ventrolateral nuclei of the thalamus and into certain portions of the hypothalamus and other basal regions of the brain.

Paleospinothalamic pathway

- Electrical stimulation in the reticular areas of the brain stem and in the intralaminar nuclei of the thalamus, the areas where the slow-suffering type of pain terminates, has a strong **arousal effect** on nervous activity throughout the entire brain.

- This explains why it is almost impossible for a person to sleep when in severe pain.

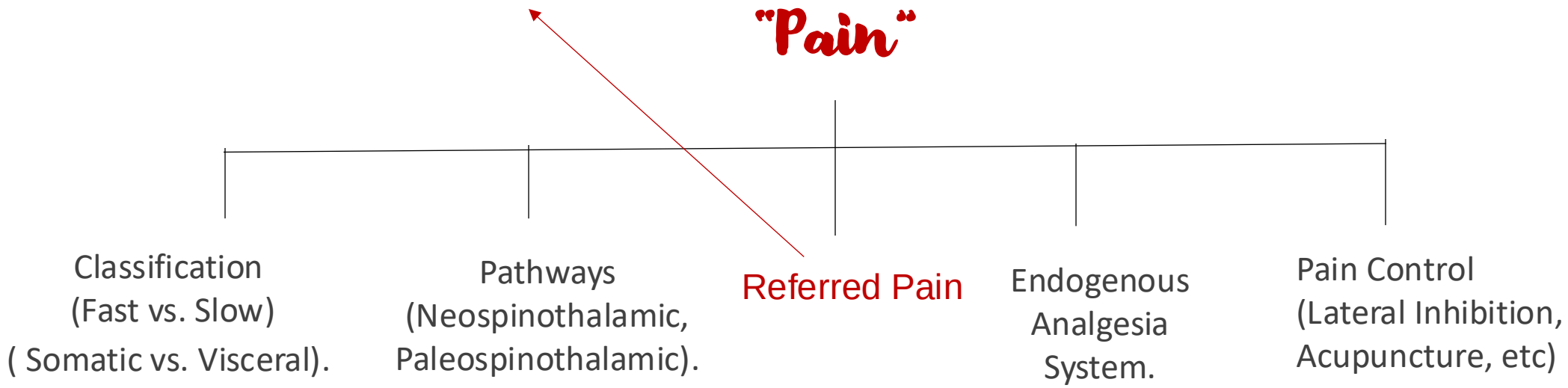
Paleospinothalamic pathway

- **Localization** of pain transmitted via the paleospinothalamic pathway is **imprecise**.
- For example, slow-chronic pain can usually be localized only 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 in keeping with the **multisynaptic, diffuse connectivity of this pathway.** It explains why patients often have serious difficulty in localizing the source of some chronic types of pain.

Referred Pain

🎯 **Note: We're here now :)**



Imagine a patient who comes to your clinic or ER complaining of left shoulder pain. What is the first thing you should do, from most to least important?

1.Taking a history

2.Physical examination (changes in skin or range of motion)

3.ECG, cardiac enzyme tests

👉Here we can conclude the definition of referred pain: the localization of pain in an area far from the source of the pain (in this case, the origin of the pain is in the heart, but it is referred to the left shoulder)

Referred pain

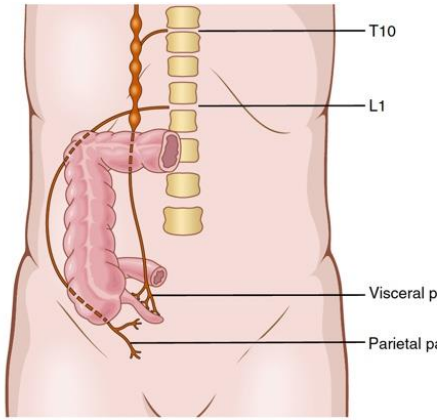
- When visceral pain is referred to the surface of the body, the person generally localizes it in the **dermatomal** segment from which the visceral organ originated in the embryo, not necessarily where the visceral organ now lies.

- For example, the heart originated in the neck and upper thorax, so the heart’s visceral pain fibers pass upward along the sympathetic sensory

Mechanism of referred pain

- branches of visceral pain fibers are shown to synapse in the spinal cord on the same second-order neurons that receive pain signals from the skin.

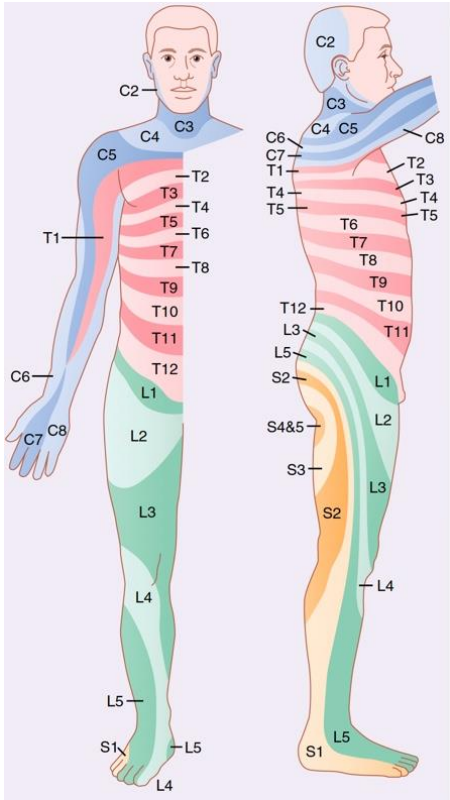
- When the visceral pain fibers are stimulated, pain signals from the viscera are conducted through at least some of the same neurons that conduct pain signals from the skin, and the person has the feeling that the sensations originate in the skin.

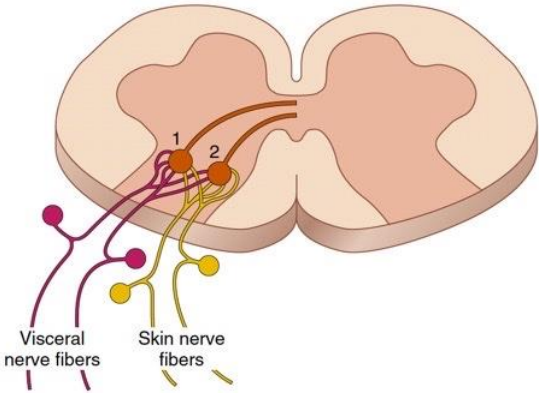


👉 The signal from the left shoulder and the heart both travel to the same level in the spinal cord, where they share the same spinal segment. The first-order sensory neurons from both the heart and the left shoulder **synapse at the same location in the spinal cord,** a phenomenon called **convergence**. As a result, the second-order neuron carries the signal up to the brain. According to the **labeled line theory**, the brain interprets this signal as coming from the left shoulder because the pathways are mapped in a way that corresponds to the location of the body part.

However, the brain **cannot distinguish** the true source of the pain, so it perceives it as being from the left shoulder even though the pain originates from the heart.

But Why does this happen at the same level? This occurs because both the heart and the left shoulder develop from the same **embryonic** segment, or **dermatome**, meaning they share common neural pathways that can lead to referred pain.



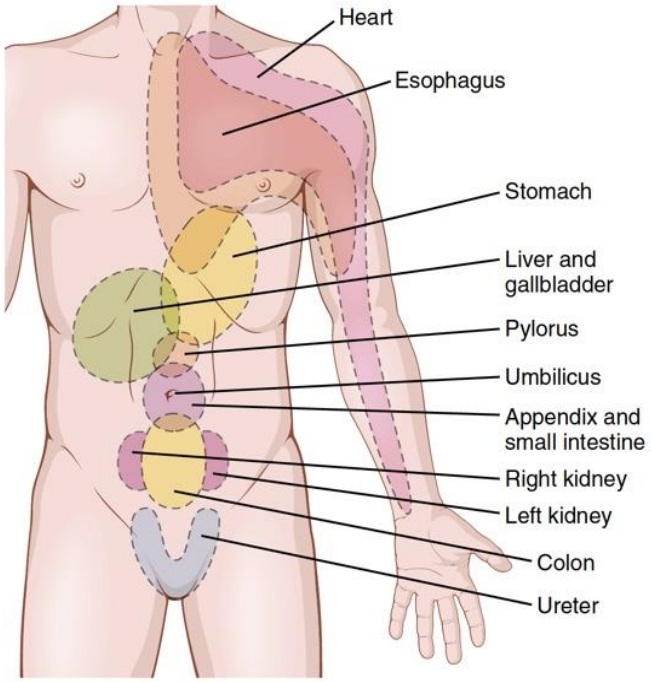


Examples of referred pain and their causes:

Periumbilical pain: This could indicate appendicitis or inflammation of the small intestine (enteritis).
In the case of appendicitis, the release of chemicals triggers pain receptors (nociceptors). The pain signal travels to the autonomic plexus at the level of T10 around the umbilicus (site of referred pain from the appendix)

Then, the pain becomes localized to the lower quadrant at the L1 level (the level of the appendix) when the inflammation reaches and irritates the parietal peritoneum, activating somatic neurons at the L1 level.
When examining the patient, you may notice rigidity of the abdominal muscles as a protective mechanism, known as **guarding rigidity**.

Areas of different referred pain:



1. **Appendicitis** → Release of chemicals → Stimulate nociceptors.
2. Nociceptors → Signal travels to **autonomic plexus** at **T10**
3. Inflammation of the appendix → Pain signal travels to **peritoneum**.
4. **Peritoneum irritation** → Activates **somatic neurons at L1**.
5. Pain → Radiates to **lower right quadrant** (at **L1**).
6. On examination → **Guarding rigidity** (abdominal muscle rigidity as a protective mechanism).

Endogenous analgesia system

- In stressful situations where we need to prioritize things over pain, like when someone's house is burning and he had survived but there are still other people inside the house, so the survived one will not feel the pain of being burned at that moment, this kind of stress will activate an endogenous analgesic system which will suppress the pain at that moment in order to act quickly and try to save the people that are still in the house. -سبحان الله-

An exception: the disaster girl meme

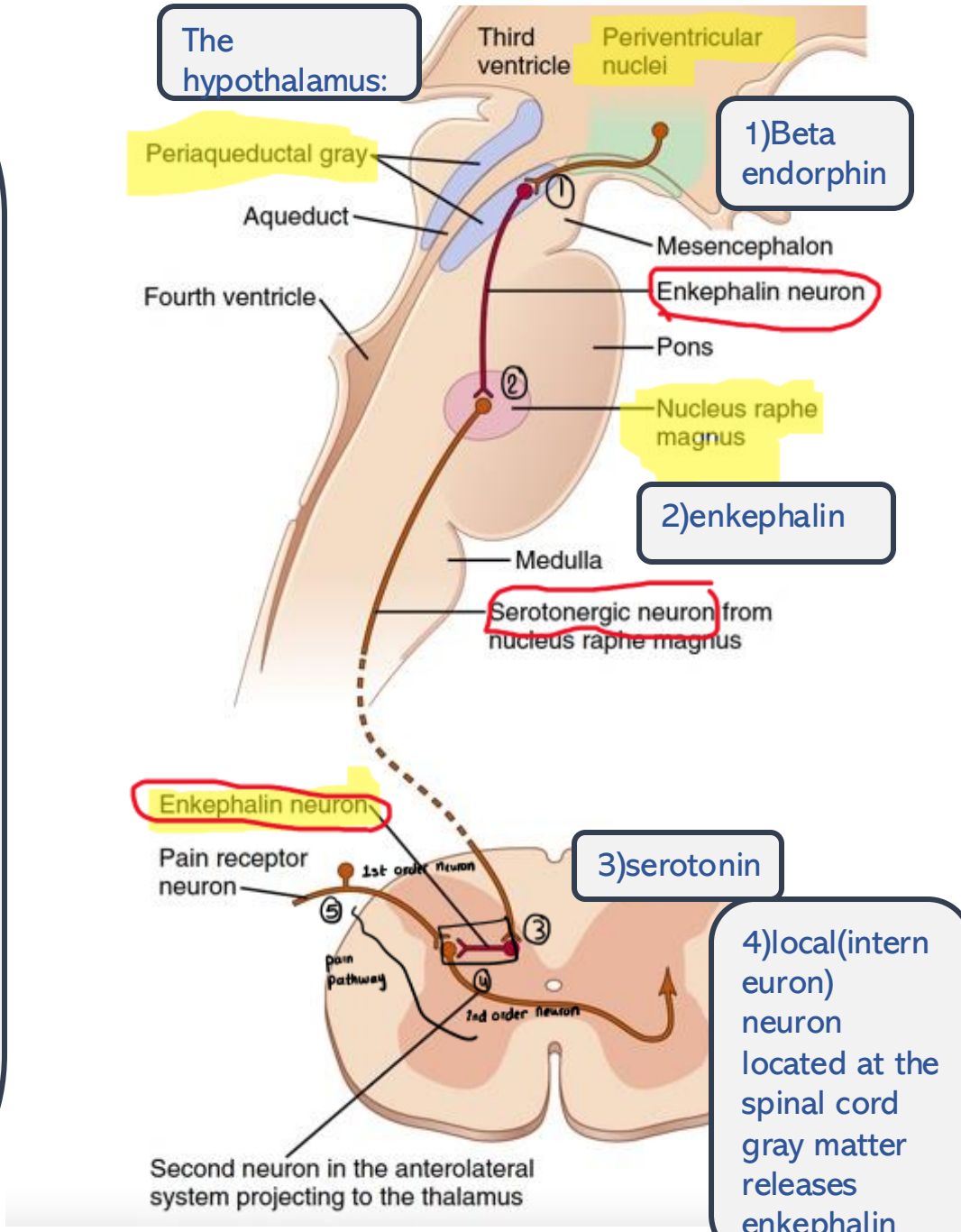
💡 The mechanism of action of our endogenous analgesic system:

- Occurs at higher centrals in the CNS at the periventricular nuclei at the hypothalamus (hypothalamus is very related to stress) which activates theses neurons releasing neurotransmitters(beta endorphin)

- The neurotransmitters go and synapse with another neuron located at the periaqueductal gray area which releases enkephalin and descends to synapse with another neuron located at the nucleus raphe magnus

- Then descends to the spinal cord and releases serotonin which acts on a local neuron in the spinal cord and does a presynaptic inhibition to the pain pathway as an interneuron and releases enkephalin.

So, this pathway will cause inhibition of the pain pathway and will inhibit the pain sensation, that's the reason why they do pharmacologically external opioids and sometimes they are used for addiction.



Summary for prev. Slide :)

1. Stress → activates paraventricular nuclei in the hypothalamus

   ↓

2. Paraventricular nuclei → release beta-endorphins

   ↓

3. Beta-endorphins → synapse with neurons in the periaqueductal gray area

   ↓

4. Periaqueductal gray → releases enkephalins

   ↓

5. Enkephalins → descend and synapse with neurons in the nucleus raphe magnus

   ↓

6. Nucleus raphe magnus → sends signal down to the spinal cord

   ↓

7. Serotonin → released in the spinal cord

   ↓

8. Serotonin → acts on local neurons in the spinal cord, causing presynaptic inhibition on the pain pathway

   ↓

9. Enkephalins → released, inhibiting the pain sensation

The endogenous analgesia system

- (1) The periaqueductal gray and periventricular areas of the mesencephalon and upper pons. Neurons from these areas send signals to
- (2) the raphe magnus nucleus, located in the lower pons and upper medulla, and the nucleus reticularis paragigantocellularis, located laterally in the medulla. From these nuclei, second order signals are transmitted down the dorsolateral columns in the spinal cord to
- (3) 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.

The endogenous analgesia system

- Several transmitter substances, especially **enkephalin and serotonin**, are involved in the analgesia system.

- The enkephalin is believed to cause both **presynaptic and postsynaptic inhibition** of incoming type C and type Aδ pain fibers where they synapse in the dorsal horns.

Pain control

- Lateral inhibition [as we have taken before, like inserting pressure on the pain area /cold compression/using acupunctures]
- Acupuncture
- Pharmacological
- Surgical
- Stress [stimulus the endogenous analgesic system]
- Exercise [when a patient suffers from chronic pain but has limited range of movement ,it is preferred to start exercise, because it will induce certain changes, like stress changes and activate the endogenous analgesic system]

Pain suppression

- The degree to which different **people react to pain varies** tremendously.

- This variation results partly from a capability of the brain itself to suppress input of pain signals to the nervous system by activating a pain control system, called an **analgesia system**.

Pain control

- Electrical stimulation either in the periaqueductal gray area or in the raphe magnus nucleus can suppress many strong pain signals entering via the dorsal spinal roots.

- Also, stimulation of areas at higher levels of the brain that excite the periaqueductal gray area can also suppress pain. Such as the periventricular nuclei in the hypothalamus.

Pain control

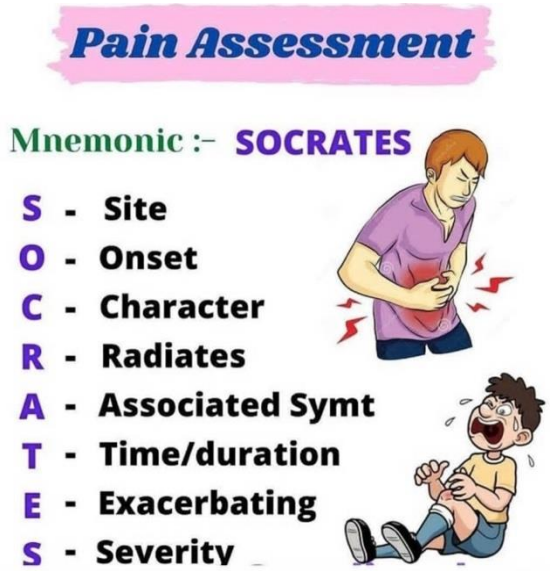
- Stimulation of large-type Aβ sensory fibers from peripheral tactile receptors can depress transmission of pain signals from the same body area.

- This effect presumably results from local lateral inhibition in the spinal cord.

Pain control

- Acupuncture is based on the idea that vital energy called qi (pronounced chee) flows through the body along pathways called meridians.

- According to one theory, acupuncture relives pain by activating sensory neurons that ultimately trigger the release of neurotransmitters that function as analgesics such as endorphins, enkephalins, and dynorphins.



اللهمّ اجعلنا فيه من الفائزين برضوانك، الرّاجين لعفوك وغفرانك، اللهمّ قرّبنا فيه إليك، اللهمّ آنِسنا فيه بقربك، وأتمِم علينا به نعمك، وأكرمنا فيه من واسع فضلك يا حي يا قيوم يا سميع يا عليم. 🌙✨

VERSIONS	SLIDE #	BEFORE CORRECTION	AFTER CORRECTION
V1→ V2	35,37		highlighted
V2→V3			

امسح الرمز و شاركنا بأفكارك لتحسين أدائنا !!