CNS
Doctor 2021

Physiology

Modified (4)

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Neurophysiology

Pain

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Pain

- According to the International Association for the Study of Pain, pain is defined as:

Unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage.

Pain

- Pain is more than a direct response to a stimulus. It is a personal, multidimensional experience.

  physical sensory experience transmits through ascending tracts by sensory neurons up toward the CNS, However, these sensory experiences are not solely limited to the transmission of physical sensations; they are also intricately associated with emotional responses.

- It is accompanied by motivated behavioral responses and emotional reactions.

  When a person is in pain, they may experience emotional reactions such as crying, distress, or heightened emotional responses.

- Also, the subjective perception of pain can be influenced by other past or present experiences.

  Like individuals who have dentophobia due to past experiences of pain in dental clinics
  (Pain is a personal experience ,because we may perceive same pain differently.)

Pain Stimuli

Pain isn't a stimulus, it's a perception

nociceptors are free nerve endings, stimulated by :

- Pain can be elicited by multiple types of stimuli, classified as mechanical, thermal, and chemical. ***Whether the stimulus starts as mechanical or thermal, all result in chemical. (because both end with destructed tissues which release chemicals).***

- Some of the chemicals that excite the chemical type of pain are bradykinin, potassium ions, and proteolytic enzymes ,***+ Prostaglandins (are quite important since they do sensitization of the pain receptors (nociceptors) in the damaged areas.)***

Prostaglandins

- All nociceptors can be sensitized by prostaglandins, which greatly enhance the receptor response to noxious stimuli.

- Tissue injury, among other things, can lead to local release of (as ap prostaglandins, which act on nearby nociceptors' peripheral endings to lower their threshold for activation.

As a part of the inflammatory process.

Not like other sensory receptors when they adapt sustained stimulus and decrease a perception, but here same *stimulus tone can elicit a higher perception of pain when nociceptors are sensitized by prostaglandins, so that we give them NSAIDs .*

- NSAIDs inhibit the synthesis of prostaglandins, accounting at least in part for the pain-relieving properties of these drugs.

NSAID ⇒. ↓ prostaglandins ⇒ ↑nociceptors threshold ⇒↓nociceptors activation ⇒ ↓Pain.

Hyperalgesia

normal Stimulus, but when the sensory receptors become highly stimulated, they will perceive this intense normal stimulation as pain stimulation

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

At the level of sensory receptors

- (1) excessive sensitivity of the pain receptors, called primary hyperalgesia (e.g. sunburn). *On the sunburned skin(excessive thermal stimulus), light touch stimulation will be perceived as a painful stimulation.*
- (2) facilitation of sensory transmission, called secondary hyperalgesia.

Out of the scope of this lecture

Occurs in the area surrounding the injured area, not on the same injured area, usually related to the spinal cord & the thalamus.

Remember that pain & temperature are transmitted through the Anteriolateral spinothalamic pathway by two types of nerves;

1. Aδ nerve fibers (fast/acute pain)

2. C fibers (slow/ chronic)

Fast (acute) Pain

- The fast-sharp pain signals are elicited by either mechanical or thermal pain stimuli. متل لما تدعس على مسمار أو تحط ايدك على طنجرة سخنة
- 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.

Fast pain is a protective mechanism, you will do something to remove pain; like withdraw or do any reaction.

Certain books may employ the term "chronic pain," which typically conveys the idea of enduring discomfort over an extended period. However, in clinical contexts, we specifically define chronic pain as persisting for at least six weeks. Conversely, slow pain refers to a gradual onset of discomfort that unfolds within seconds.
Therefore, it may be more accurate to characterize this type of pain as slow pain rather than chronic pain.

Chronic (slow) Pain

- Slow pain can occur in the skin and in almost any deep tissue or organ. *(Remember that fast pain can't be felt in deep tissue/ viscera.)*

- this type of pain is elicited mostly by chemical types of pain stimuli.

  Can be mechanical or thermal, but usually they turn into chemical

- It is transmitted to the spinal cord by type C fibers at velocities between 0.5 and 2 m/sec.

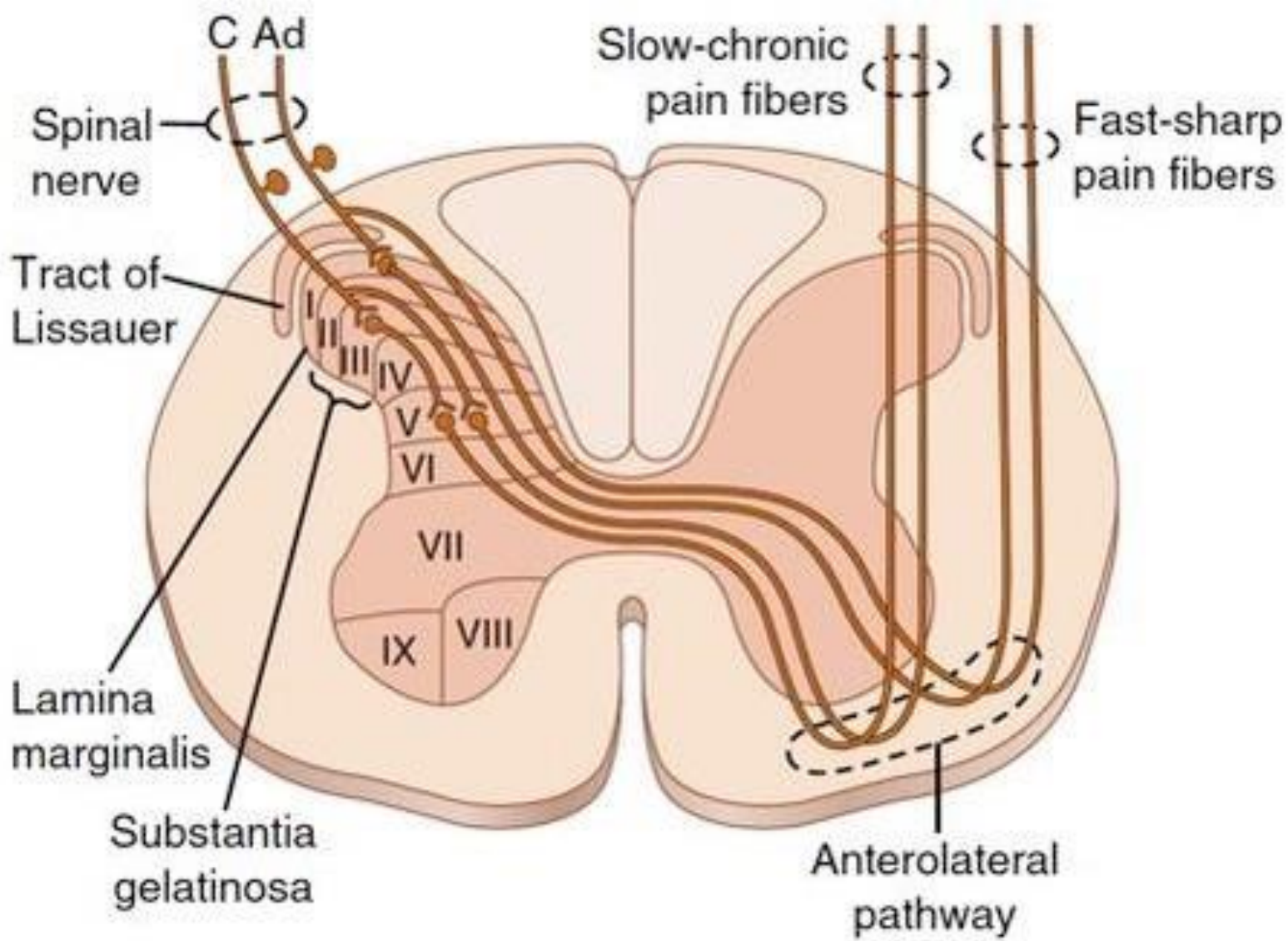
- This feeling is a dull, aching, poorly localized sensation that persists for a longer time and is more unpleasant. *(the suffering type of pain; because it stays for longer duration)*

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. ***It's often very difhcult to discriminate between these two types of pain***

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

Cross- section of spinal cord



Some comments on the previous slide:

*We're concerned about anterolateral spinothalamic tract, the modalities that transmit with pain in the same tract : temperature, itch & tickle.

*Pain either transmit via : Aδ fiber or C fiber.

*sensory information are coming from periphery, cell body in the ganglia, to the spinal cord to the dorsal horn.

*we have two subtypes of the spinothalamic pathway :

1. Neospinothalamic tract Aδ (fast pain)

2. Paleospinothalamic tract C fibers (slow pain)

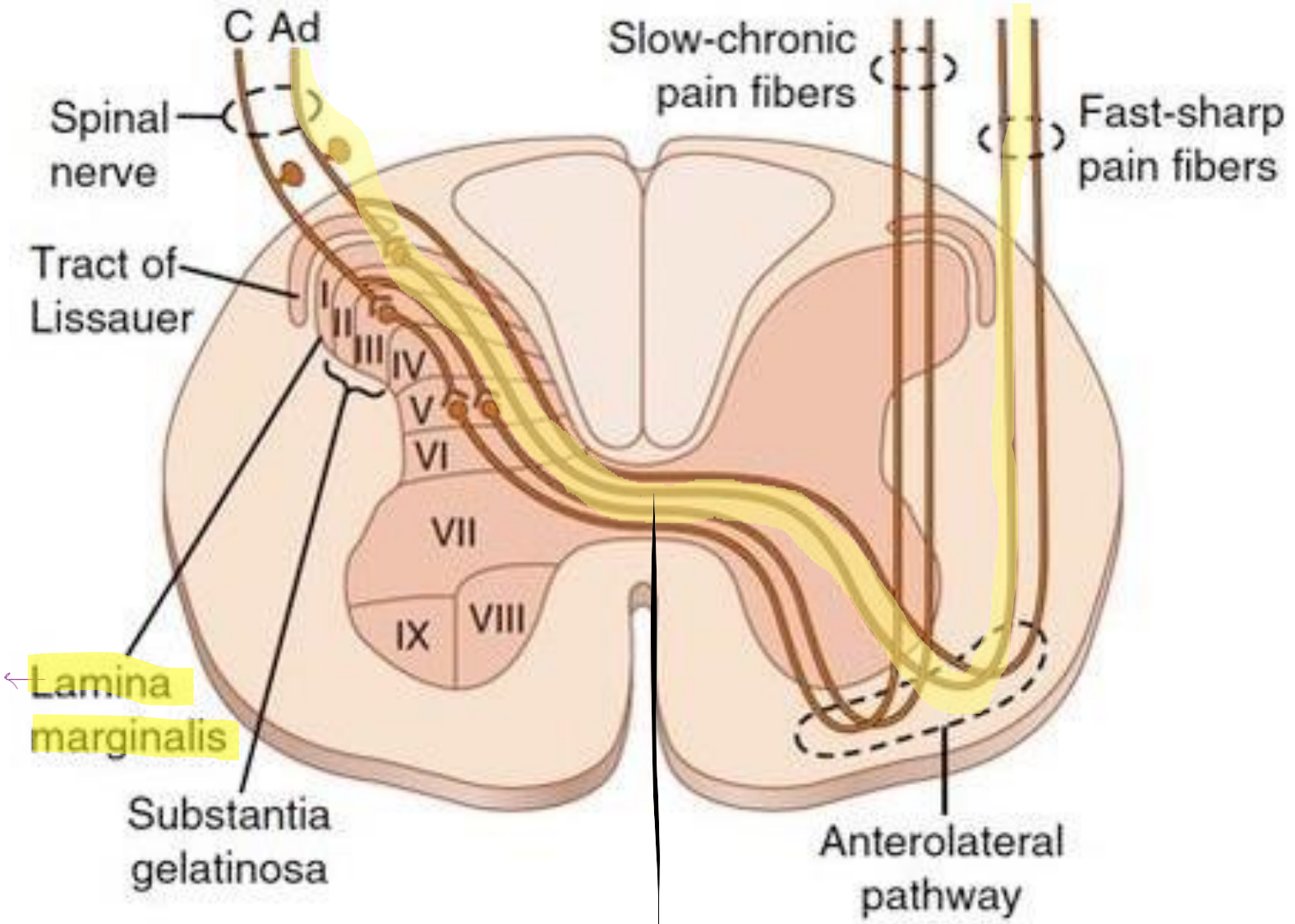
Neospinothalamic tract

- 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.

Cross-section for spinal cord

neospinothalamic pathway is highlighted in yellow



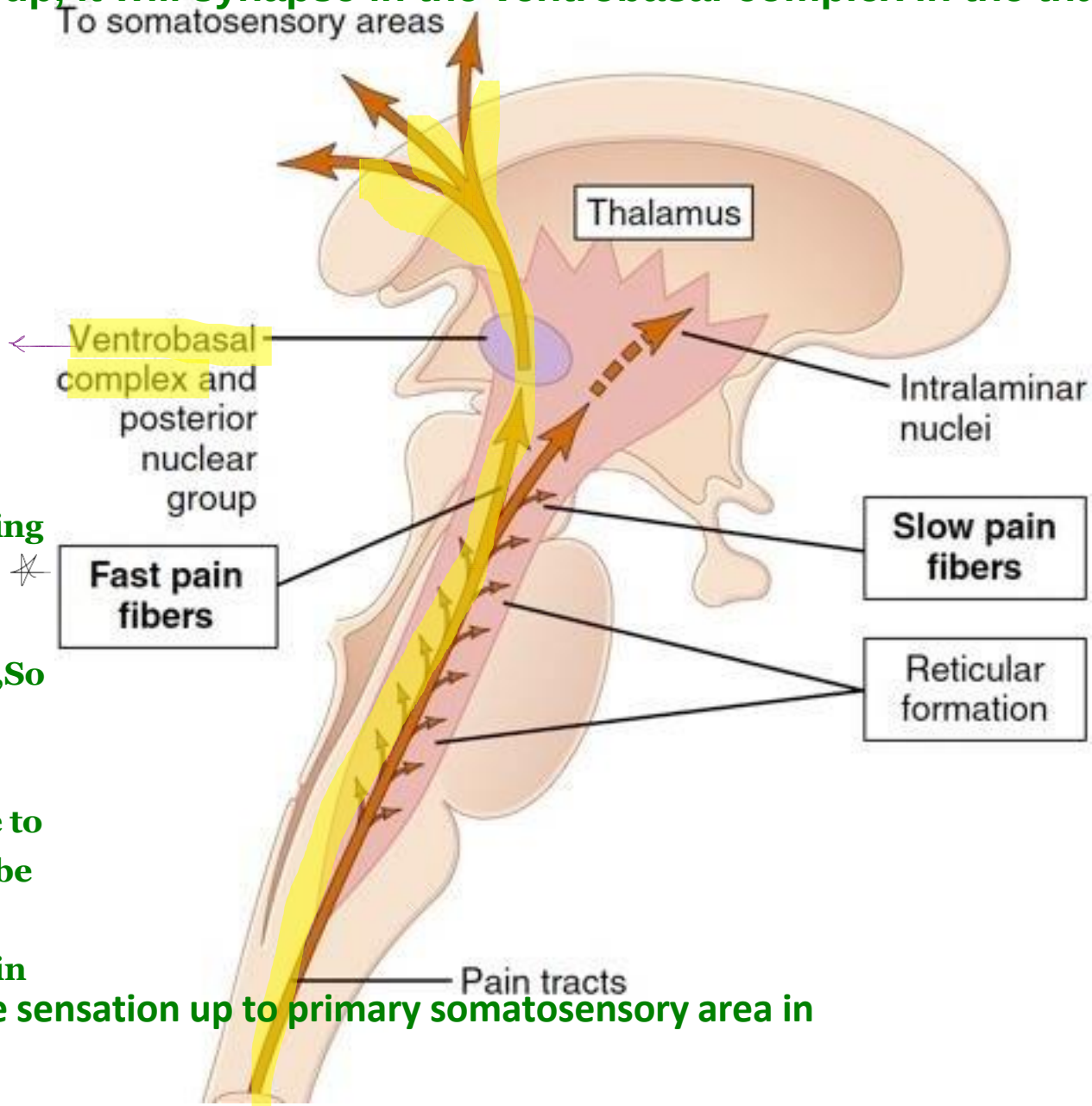
Aδ fiber enters the dorsal horn Where it will synapse with 2nd order neuron in lamina one almost.

Then ,the 2nd neuron will cross to other side(decussation) to go in anterolateral tract to go up towards thalamus.

-When the 2nd neuron go up, it will synapse in the ventrobasal complex in the thalamus

Remember the posterior column pathway (that also synapse in the ventrobasal complex), which serves as a conduit for transmitting various sensory modalities such as proprioception, pressure, vibration, and touch.

- They share the same synapsing point ;this tell us that the localization for fast pain is much better than slow pain ,So that when you stepped on a nail (fast pain), In this situation, you would be able to easily and accurately describe exactly where you felt the prick, again because fast pain sensation will pass with tactile sensation up to primary somatosensory area in cerebral cortex.



الفكرة هون بالمختصر متل لما الوجع بصحيك من النوم ,اللهم عافنا واعفو عنا

→ fast pain fibers *switch On button for consciousness by activating the reticular formation.*

If you're conscious about the pain, the reticular formation is activated, once it's deactivated (in sleep, comatose) you aren't conscious about pain.

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.

the researchers attempted to selectively stimulate fast pain receptors without stimulation for tactile receptors. However, they encountered difficulties in accurately localizing the sensation of pain. As a result, they reached the conclusion that Co-stimulation of tactile pain with fast pain receptors is crucial for precisely localizing pain signals.

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

Paleospinothalamic pathway

Transmit slow pain (C fibers).

- Most of the signals then pass through one or more additional short fiber neurons within the dorsal horns before entering mainly lamina V, also in the dorsal horn.

- Here, the last neurons in the series give rise to long axons that mostly join the fibers from the fast pain pathway, passing to the opposite side of the cord and then upward to the brain in the anterolateral pathway.

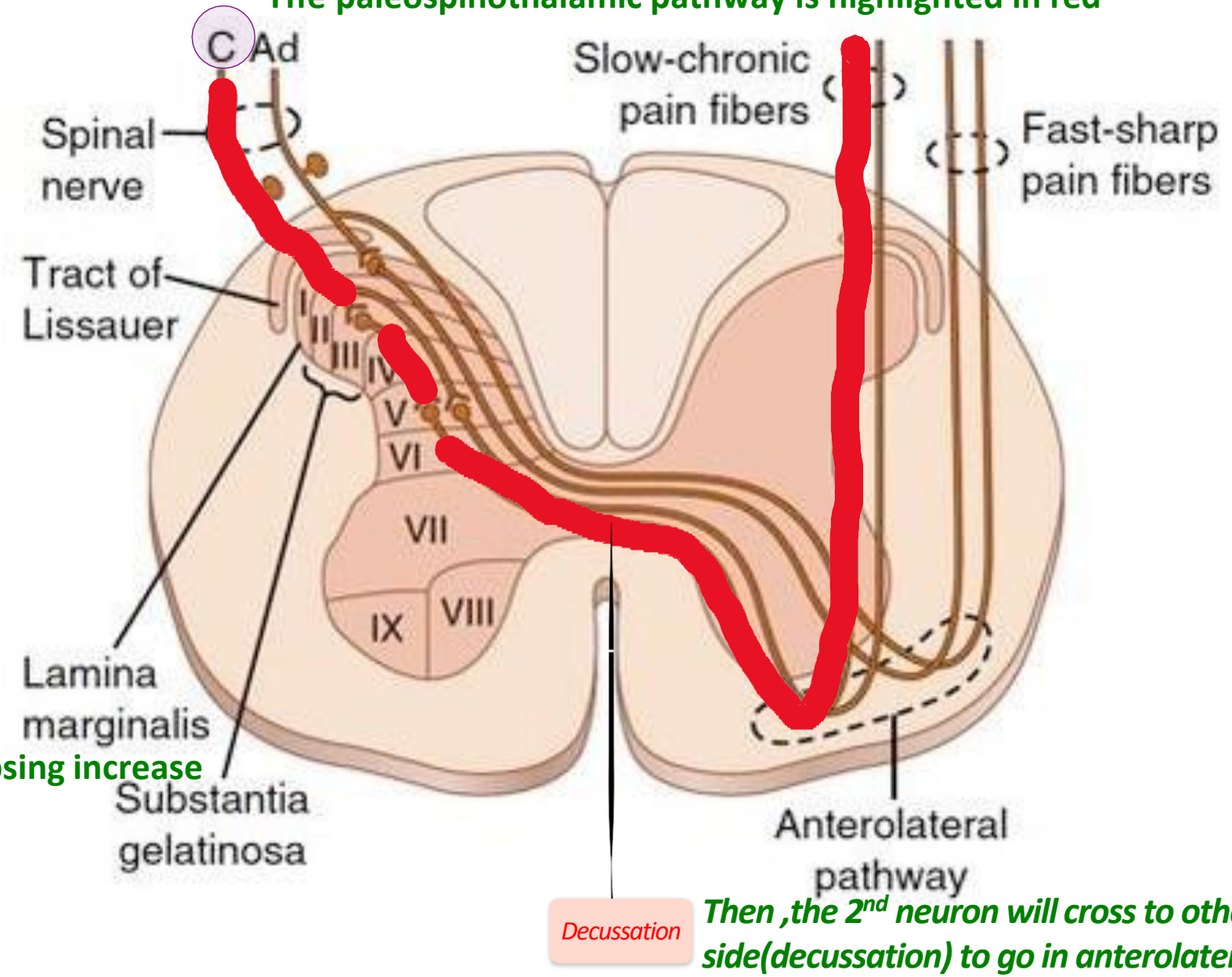
Paleospinothalamic pathway is slow due to:

1. C-fibers; which have low conduction velocity(because they are unmyelinated and small fibers)
2. Slow pain fiber synapse with multiple interneurons when it enters the dorsal horn ,for ex here in the picture it synapses in lamina 3 then in lamina 5

So, when the number of synapsing increase the delay increase.

Cross-section for spinal cord

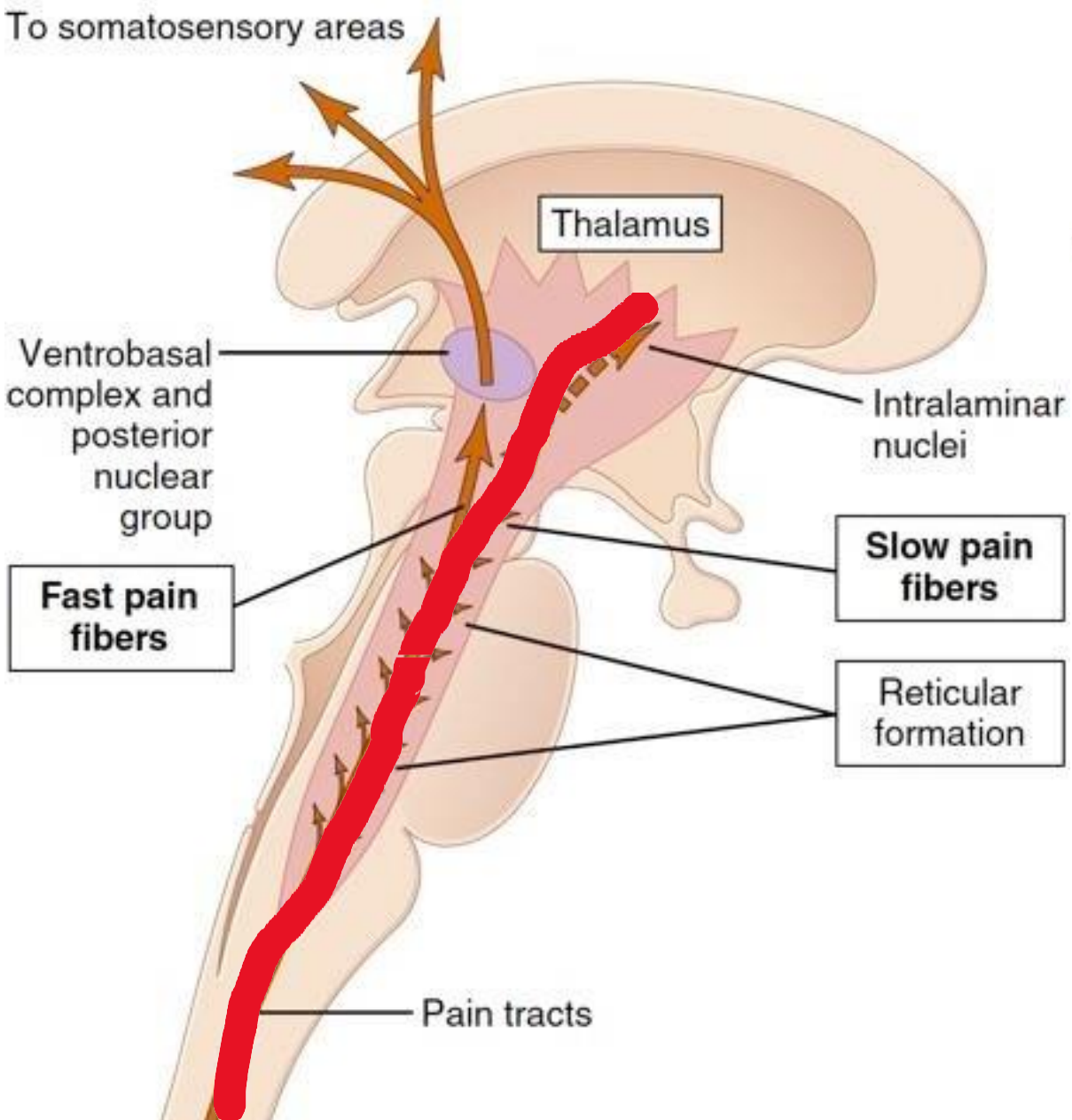
The paleospinothalamic pathway is highlighted in red



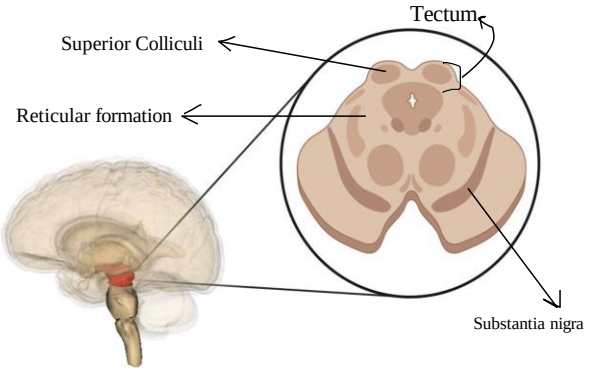
Then ,the 2nd neuron will cross to other side(decussation) to go in anterolateral tract to go up.

❀ Note that the majority of signals did not go to the ventrobasal complex; instead, they were directed towards the reticular nuclei & tectum (the posterior part of the midbrain) which consists of superior & inferior colliculi.

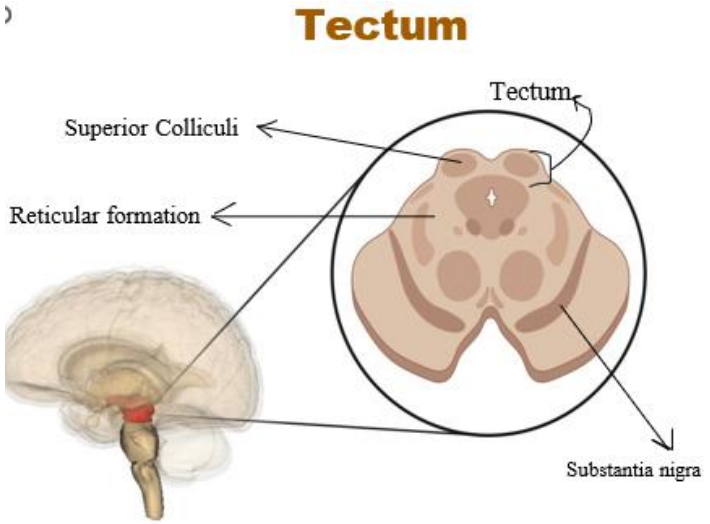
- slow pain is nagging, unpleasant ⇒ reticular nuclei activation.



Tectum



- Superior & inferior colliculi are important for startle reflex; which is an involuntary reaction to a sudden, intense stimulus often a loud noise or sudden movement, It involves certain head & neck movement, rapid muscle contractions, shoulder, and leg muscles.



❀ The startle reflex occurs as a result of stimulation of the tectal nuclei, primarily the superior colliculus.

❀ Furthermore, the signals generated by the startle reflex are transmitted to various brain regions, including the hypothalamus, thalamus (specifically the interlaminar nuclei), and other subcortical areas. Additionally, these signals are conveyed to the limbic system, which is responsible for processing emotions and behaviors associated with the startle response. As a result, the neural pathways involved in the startle reflex branch out extensively and distribute widely throughout the brain, facilitating a coordinated and multi-faceted response to the startling stimulus.

Paleospinothalamic pathway

- Type C pain fiber terminals entering the spinal cord release both glutamate transmitter and substance P transmitter.

- 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.

Neurotransmitters can be categorized into two main groups: small molecules and peptides.

1. small molecules : rapidly acting, ex: glutamate. → mey have relatively fast effects—- contribute to fast pain.

2. peptides : large molecules, ex: substance P. → Peptides are synthesized as larger precursor proteins in the neuronal cell body and then transported to the nerve terminals (need more time)—— contribute to slow pain.

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.

For arousal, attention, and consciousness

- (2) the tectal area of the mesencephalon deep to the superior and inferior colliculi. ***For startle refiex***
- (3) the periaqueductal gray region surrounding the aqueduct of Sylvius.

For the modulation of pain, defensive behaviors, and emotional responses.

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.

The prefix "neo-" means "new" or "recent." In the neospinothalamicathway, it signifies the transmission of fast, sharp pain signals that are perceived quickly, providing a rapid response to acute pain stimuli.

The prefix "paleo-" means "old" or "ancient." In the paleospinothalamic pathway, it denotes the transmission of slow, persistent pain signals that are perceived over a longer duration, associated with chronic or ongoing pain sensations.

Paleospinothalamic pathway

- **Localization** of pain transmitted via the paleospinothalamic pathway is **imprecise**. ***In neospinothalamic → precise localization***
- 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** **and the minority of fibers go to the somatosensory area in cerebral cortex.** It explains why patients often have serious difficulty in localizing the source of some chronic types of pain.

Pain suppression

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

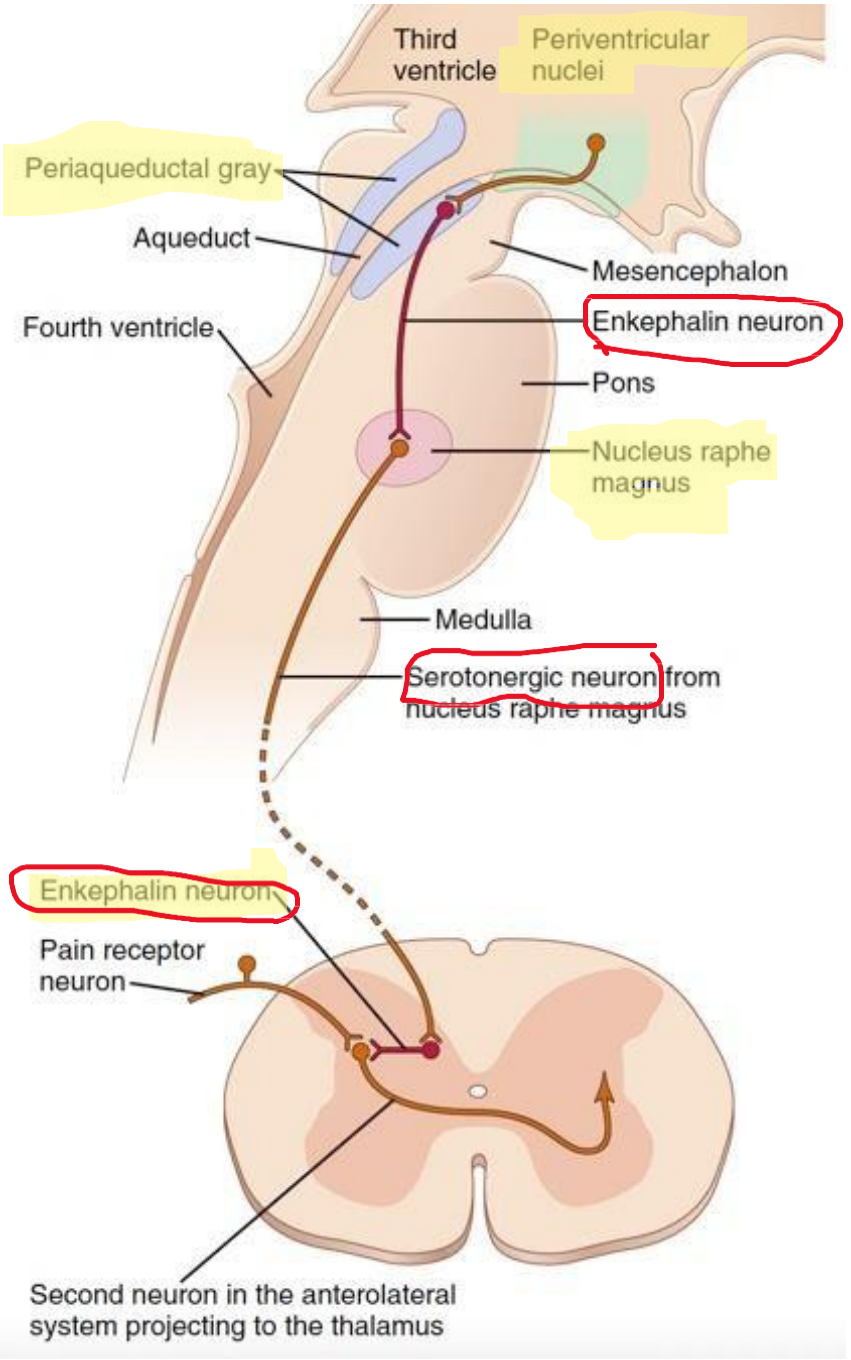
- This variation results partly from a capability of the brain itself to suppress input of pain signals to the nervous system by activating a pain control system, called an **analgesia system**.

We are required to know

- the main areas contribute to the analgesia system, which are :

The main areas that contribute to the endogenous analgesia system are the periaqueductal gray (PAG) and periventricular nuclei(in hypothalamus). These areas are activated by electrical stimulus then they will activate the nucleus raphe, which, in turn, activates the interneurons in the dorsal horn of the spinal cord. These interneurons interact with incoming pain signals and can exert either presynaptic or postsynaptic inhibition, so the pain signals will not go up to the cns.

- neurotransmitters in the pathway (next slide).
- pain inhibitory complex in the dorsal horn = inhibitory interneurons



The endogenous analgesia system

Main areas:

- (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

By postsynaptic or presynaptic inhibition

- (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. ***Opioids & endorphins***

- 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.

How to control pain ?

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

1. Medication for pain control includes two categories: nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids(for cancer end stage patients). It is crucial to be aware that opioids can cause respiratory depression.

❀ morphine overdose (a potent opioid) treated by Naloxone.

2. Electrical stimulation can be utilized to target the periaqueductal and periventricular gray matter regions of the brain in order to induce the endogenous analgesic system.

3. surgical Surgical interventions can involve cutting the pain pathway at a specific point in an attempt to stop or alleviate pain. In some cases, surgeons may even extract a portion of the cortex. However, the effectiveness of surgical options for pain management can vary, and it is not always the ideal choice. This is because the pain pathway consists of numerous interconnections and integrations, making it a complex system to target surgically.

4. Lateral inhibition (like when you put ice, so you activate another modality)

5. Acupuncture (needles when put them on the skin they may triggers the release of endorphin)

6. exercise

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.

Pain control

- Exercise → ***Increases the endorphin, and stimulate tactile sensation as well as increasing oxygen which helps the brain to function better in painful situation.***
- Distraction ***It decrease the perception of pain in the brain; because the brain is working on something else → Lateral inhibition.***
- Deep breathing ***,Meditation,…..***

Pain Assessment

Mnemonic :- SOCRATES

- **S** - Site of pain
- **O** - Onset — How and when the pain did start?
- **C** - Character — اوصف الوجع مثلا حاسس بنغزات ,سكاكين
- **R** - Radiates — هل انتشر الوجع لمكان اخر؟
- **A** - Associated Symt
- **T** - Time/duration
- **E** - Exacerbating — في شيء بزيد شعورك بالالم ؟
- **S** - Severity — Give them a scale to determine the severity like from 1 to 10 how much it hurts ?while for children give them smiley faces .

Doctors-online