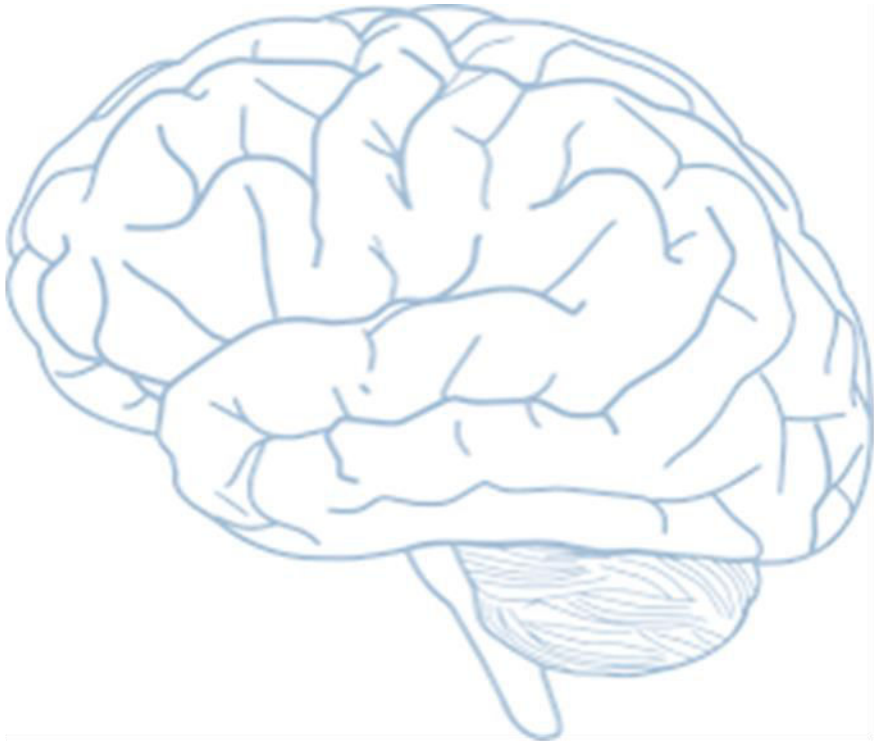
MEDICINE
KING SAUD UNIVERSITY

تمت المراجعة
شوق الأحمري & عبدالعزيز العنقري



Physiology Team 436

CNS PHYSIOLOGY

- Text
- Important
- Formulas
- Numbers
- Doctor notes
- Notes and explanation

Lecture No.28

"Be Proud Of Every Step You Take Toward Reaching The Goal"

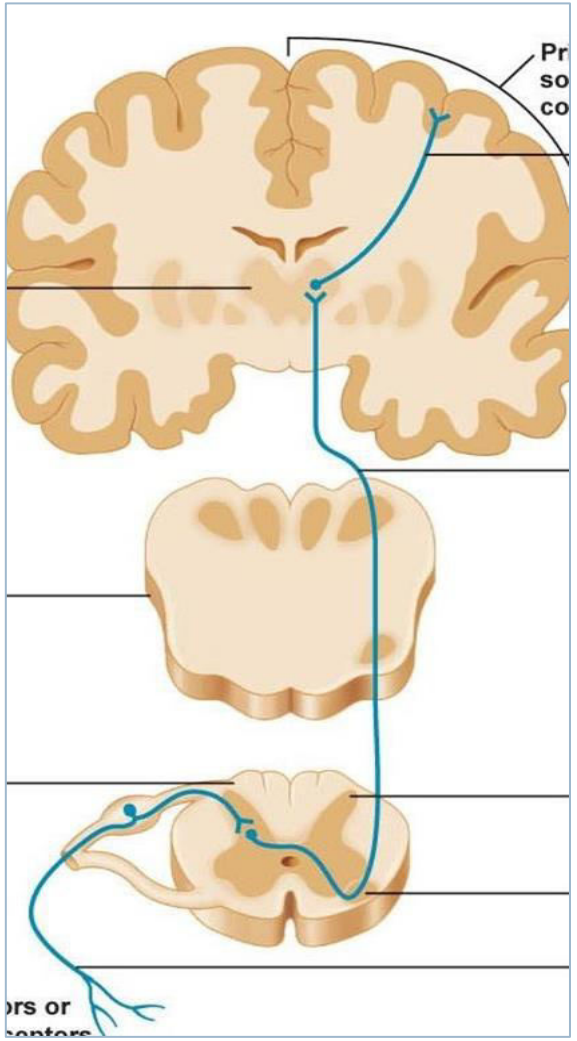
Physiology of the pain

Objectives:

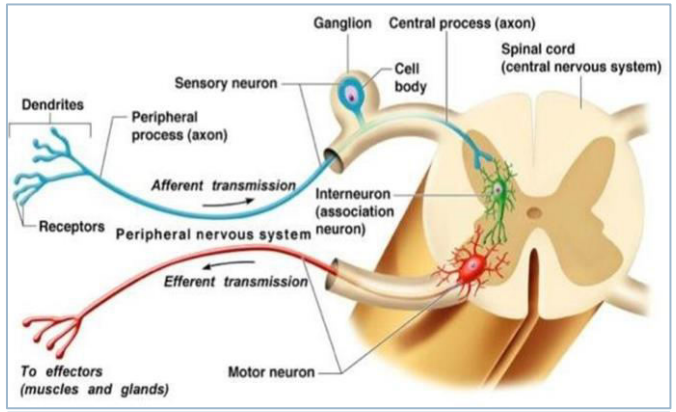
1. To know about the receptor of pain.
2. The types of neuron responsible for conduction of impulses ex: A-delta and C- types.
3. Two types of pain ex: fast and slow.
4. Know the tracts involved and its functions.
5. Know the role of thalamus and cortex in the perception of pain.

Definitions

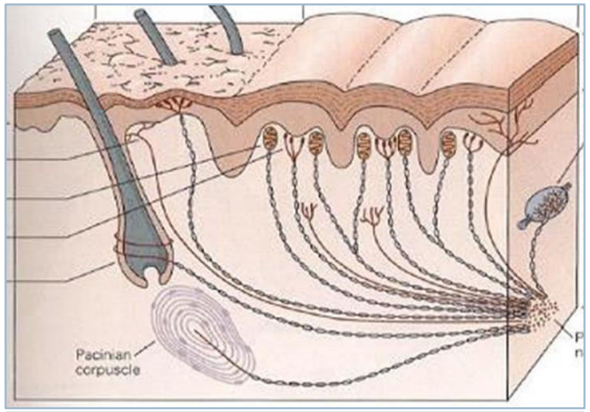
Primary sensory (afferent) neurons	First order neurons in the sensory system responsible for transmitting sensory information from the periphery to the CNS
Sensory receptors	Are specialized peripheral endings of primary afferent neurons.
Noxious stimulus	Any stimulus (mechanical, chemical or thermal) that produces tissue damage or threatens to do so (≠ innocuous).
Nociceptors (Pain receptors)	Primary afferent receptors that respond selectively to noxious stimuli.
Polymodal nociceptors	Respond to various noxious stimuli.
Adequate stimulus	The form of energy to which a specific receptor is most sensitive
Somatic pain	Pain originating from skin, joints, muscles, and other deep tissues
Visceral pain	Pain originating from the internal organs
Allodynia	Pain caused by a stimulus that is not normally painful (e.G. Touch)
Hyperalgesia	An increased sensitivity to a stimulus that is Normally painful.
Spontaneous pain	Stimulus independent pain (ongoing pain)



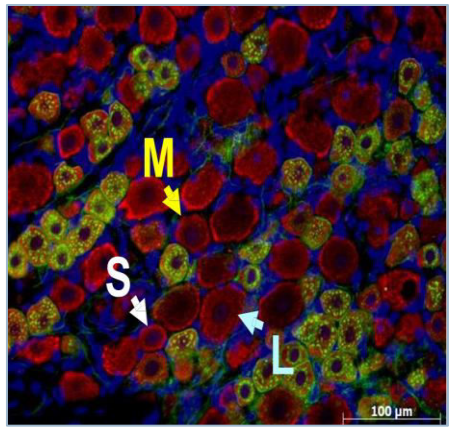
Afferent & Efferent neurons



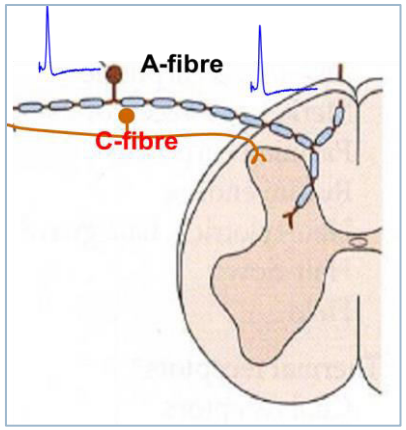
All pain receptors are free nerve endings of unmyelinated type C fibers and small diameter type Aδ fibers.



Small: <30μm
Medium: 31-40μm
Large: >40μm



Nociceptors (small/medium)
Non-nociceptors (large)



Classification of nerve fibers

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- Types of nerve fibers:
  - Myelinated (a-fiber).
  - Aα (thickly myelinated).
  - Aβ (intermediate m.).
  - Aδ (thinly myelinated).
  - Unmyelinated (c-fiber).

Type	I	II	III	IV
Type	Aα	Aβ	Aδ	C
Diameter (μm)	10-20	5-10	2-5	0.5-2
Conduction Velocity (m/s)	70-120	30-70	5-30	0.5-2

ONLY IN FEMALES' SLIDES

Pain & Nociception

- What is nociception?

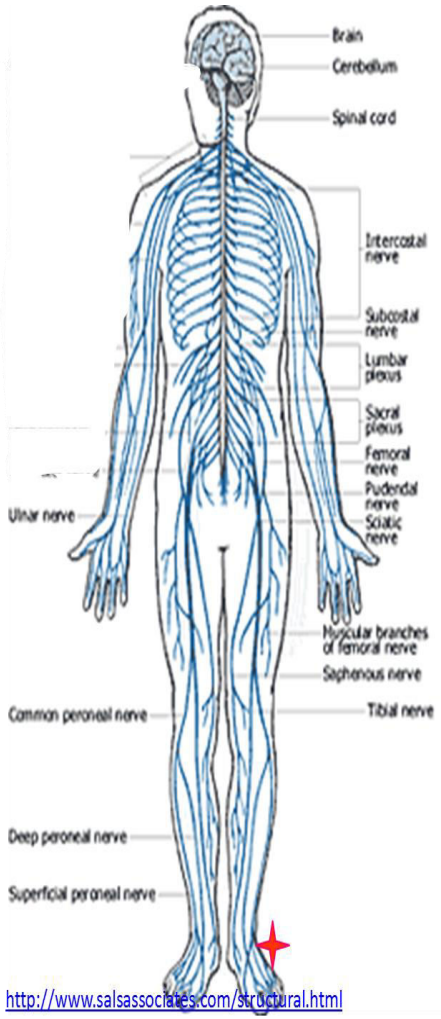
Refers to the transmission of signals evoked by activation of nociceptors from periphery to the CNS.

- What is pain?

Is perception of unpleasant sensation that originates from a specific body region.

- Formal definition:

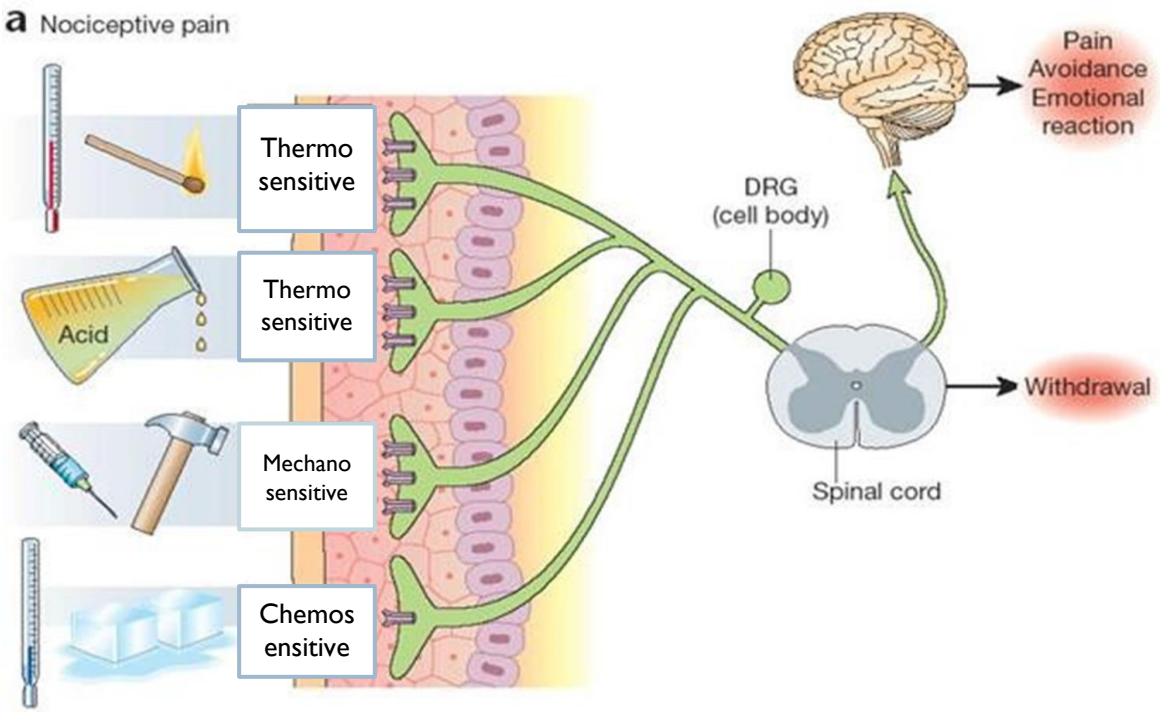
Is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage (International Association Study of Pain).



http://www.salsassociates.com/structural.html

Types of Nociceptors

- Polymodal nociceptors:
  - Mechanosensitive
  - Thermosensitive
  - Chemosensitive



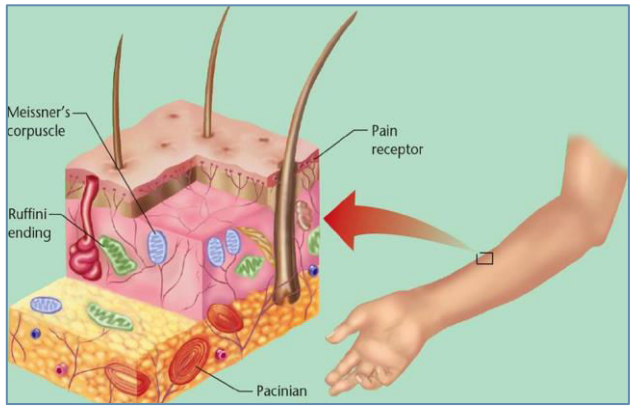
Pain receptors(nociceptors)

- " Are special receptors that respond only to noxious stimuli and generate nerve impulses which the brain interprets as "pain".
- They are specific (have adequate stimulus) in that pain is not produced by overstimulation of other receptors.
- They are most widely distributed.
- They are high threshold receptors i.e.. Painful stimuli must be strong and noxious to produce tissue damage.
- Heat pain threshold > 43 °c.
- Do not adapt (or very little) to repetitive stimulation (can be sensitized by various agents, ex: Prostaglandins)(it allows the pain to keep the person apprised of a tissue damaging stimulus as long as it persists).

Sir Charles Scott herrington (1857-1952)

Distribution of pain receptor(nociceptors)

- Nociceptors are widespread in superficial layers of skin.
- Fewer in deep tissue and absent in brain tissue.



- They are found in largest no. & density in skin, periostium joint surface, arterial wall & duramatar.
- pain receptors are activated by 3 types of stimuli:

1. Mechanical- they elicit fast pain.
2. Thermal- they elicit also fast pain.
3. Chemical- they produce slow pain.

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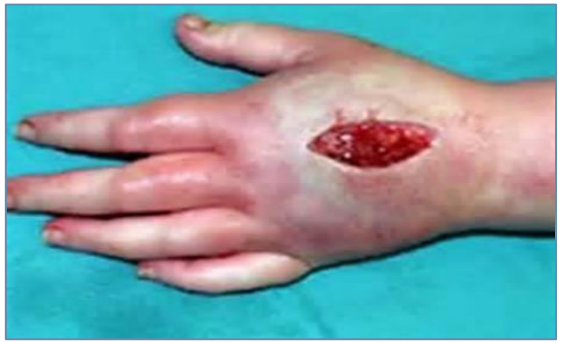
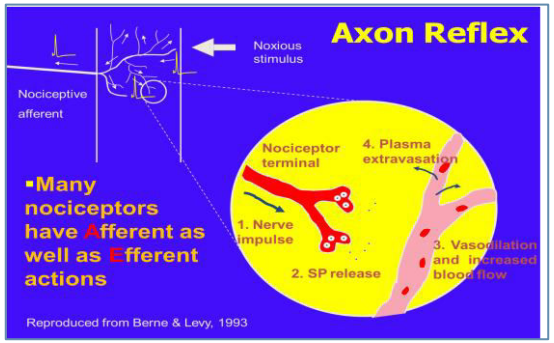
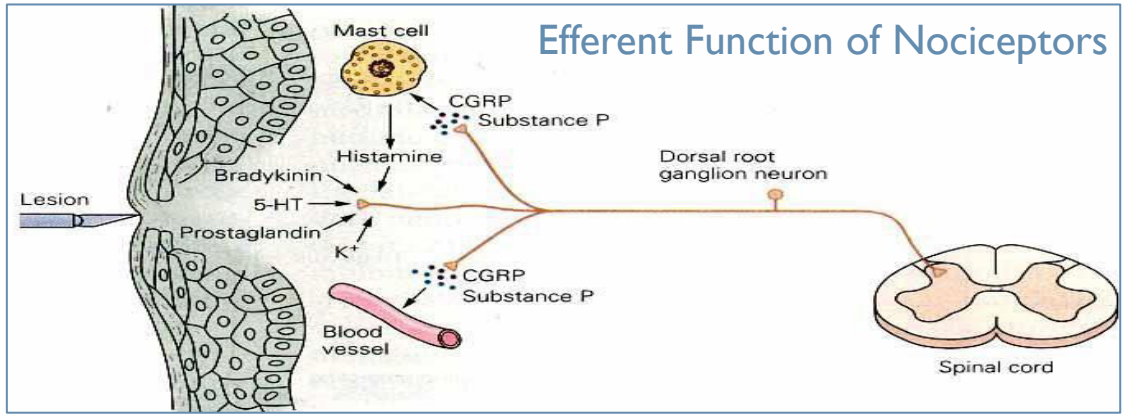
Pain mediators after tissue damage

- Nociceptive neurons release peptides ex: substance P and CGRP (Calcitonin gene related peptide) which stimulate mast cells and blood vessels (via axon reflex).







Vasodilation
Extravasation

Significance of pain: why do we feel pain?

- It is a protective mechanism that make us aware that tissue damage is occurring or is about to occur:

1. Avoid noxious stimuli.
2. Remove body parts from danger.
3. Promote healing by preventing further damage.
4. Storage of painful experiences in memory helps us to avoid potentially harmful event in the future.

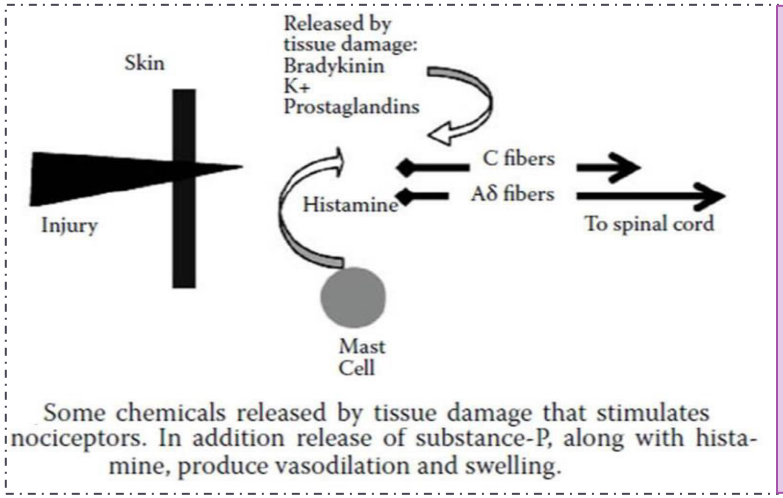
- The sensation of pain may be accompanied by behavioral responses (withdrawal, defense) as well as emotional responses (crying or fear).

- Pain is perceived at both cortical and thalamic levels.

• Brown color refer to (ONLY IN Males' SLIDES)

Mechanism of stimulation of nociceptors

- Pain receptors are depolarized either directly or through the production of pain producing substances from damaged tissues as a result of inflammation (also called inflammatory mediators).
- Ex: Bradykinin, histamine, substance P, calcitonin gene - related peptide (CGRP), interleukins, prostaglandins, K+, ach, proteolytic enzymes, acids.
- PGs & substance – P enhance the sensitivity of pain receptors.



Some chemicals released by tissue damage that stimulates nociceptors. In addition release of substance-P, along with histamine, produce vasodilation and swelling.

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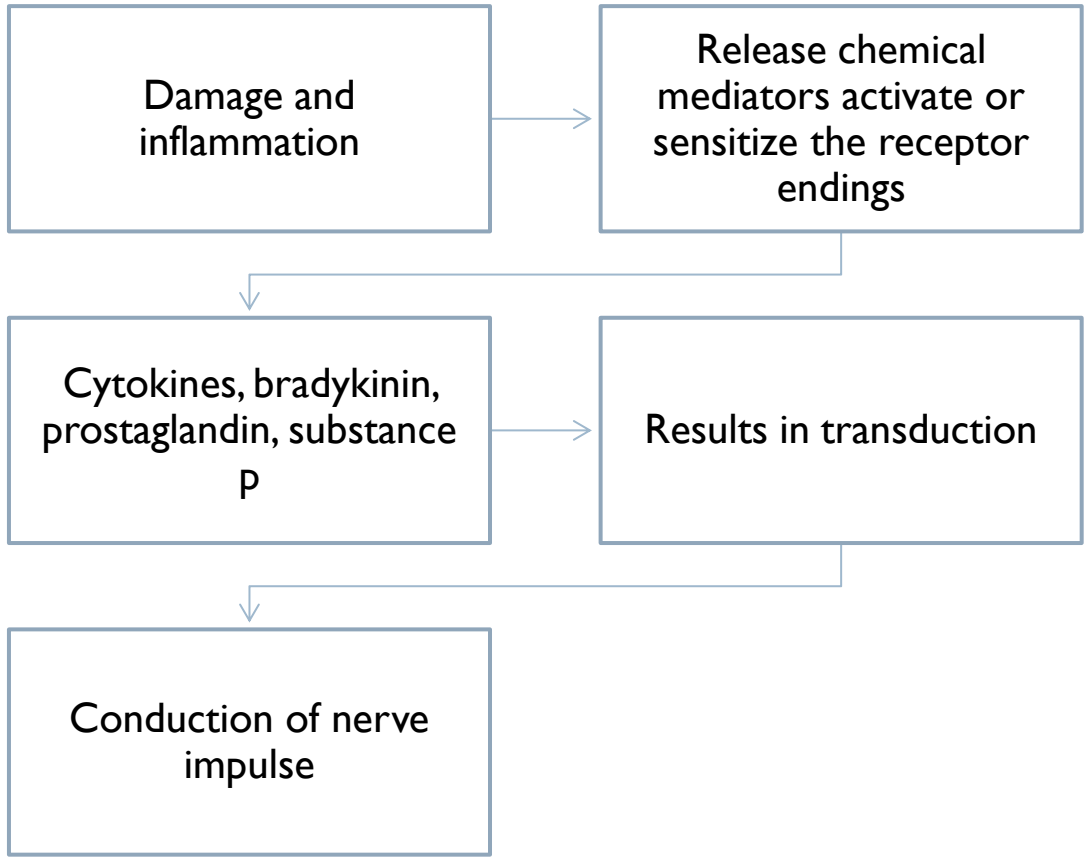

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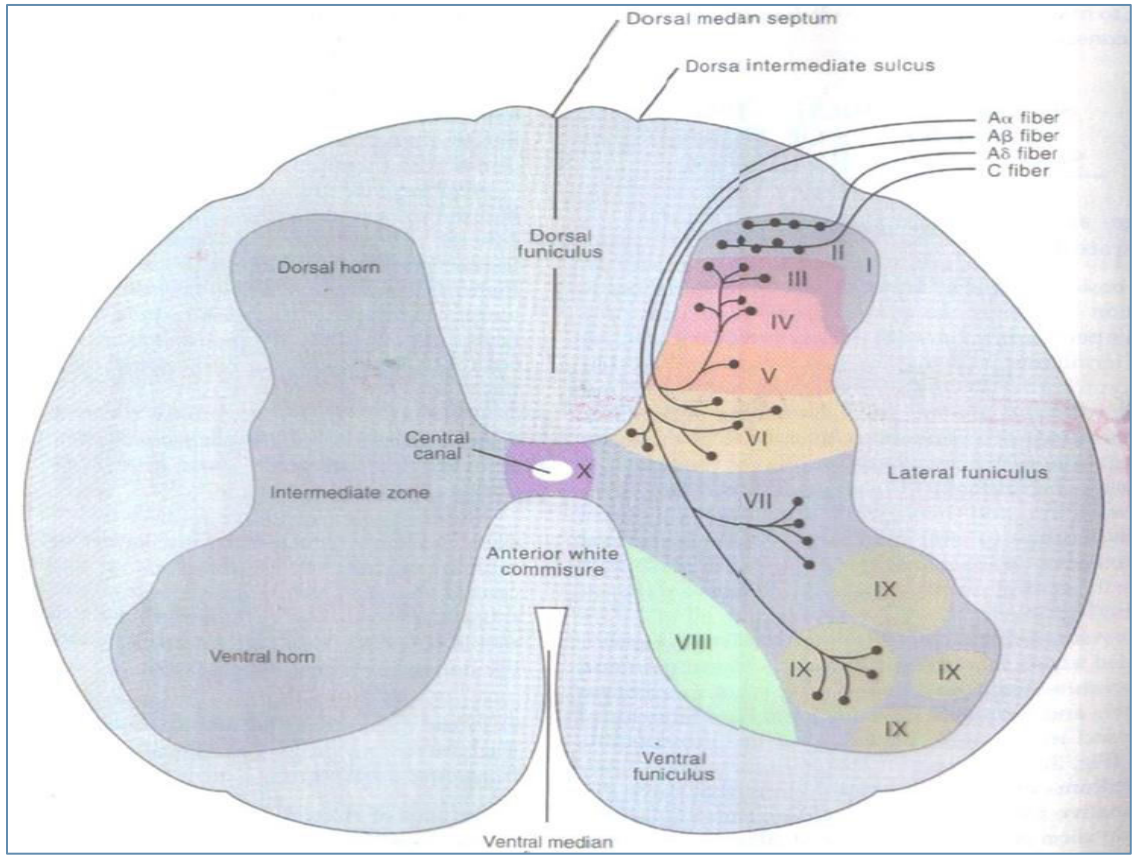
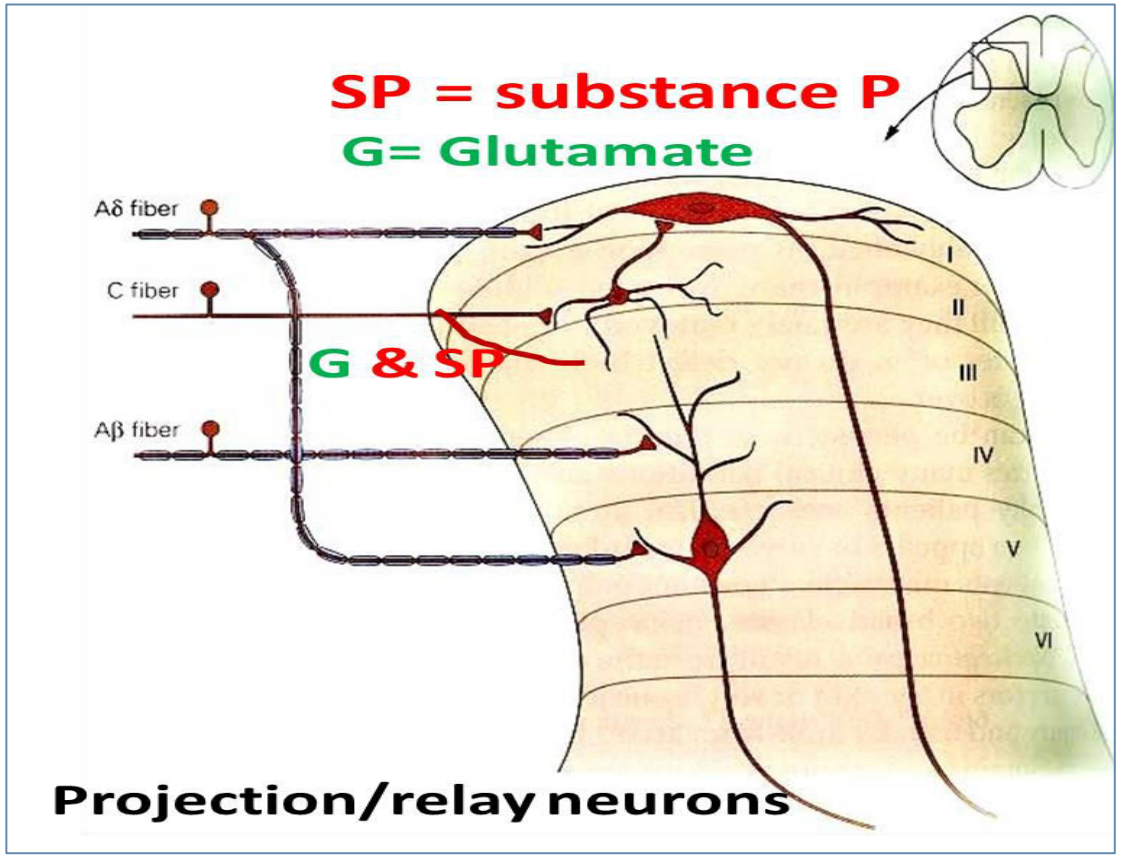
Chemical substance released during tissue damage	
Substance	Source
K^+	Damaged cells
Serotonin	Platelets
Bradykinin	Plasma
Histamine	Mast cells
Prostaglandins	Damaged cells
Leukotrienes	Damaged cells
Substance P	Primary nerve afferents

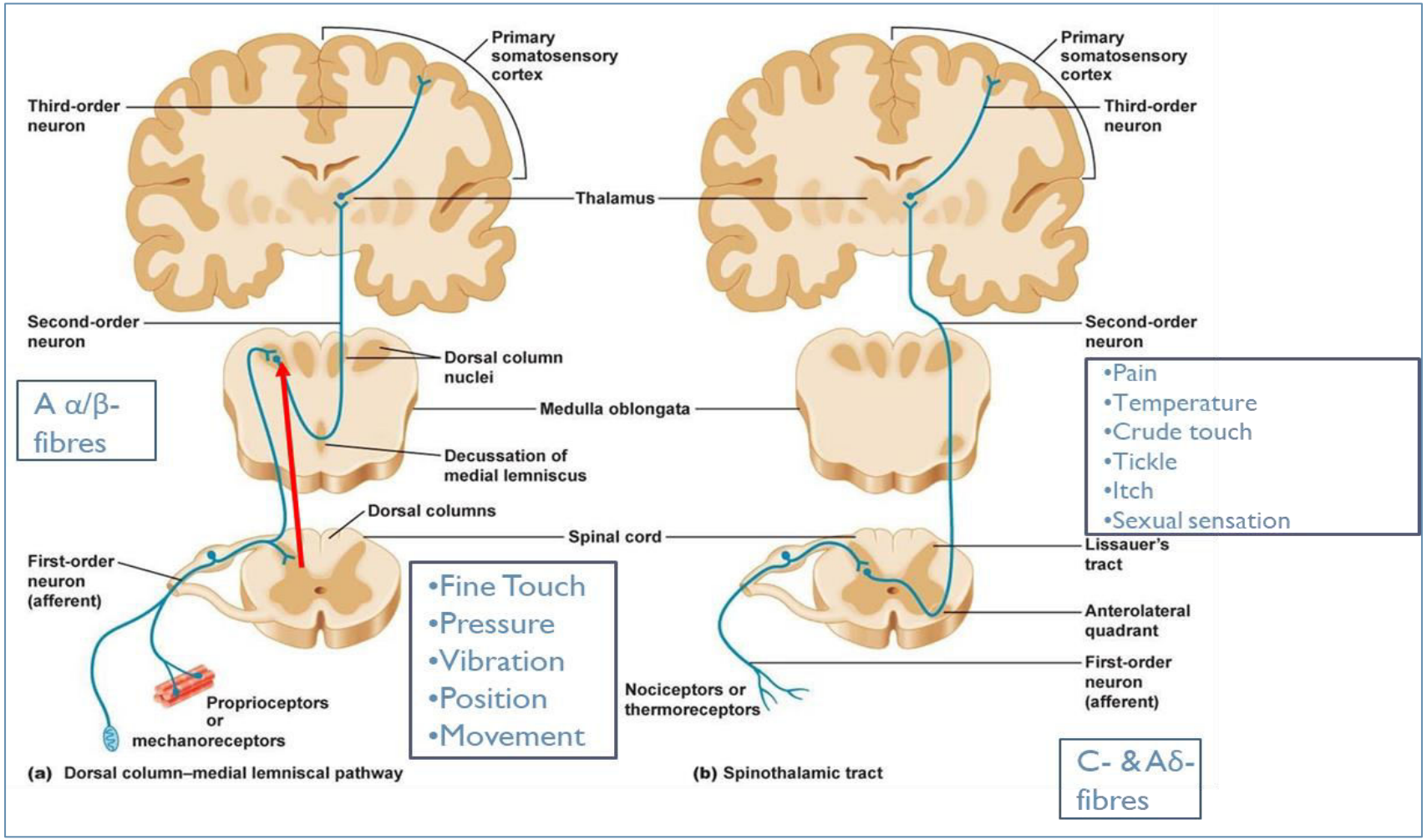
Nociceptive input to the spinal cord





- Aδ-fibers terminate in lamina I and V (fast pain) and neurotransmitter is glutamate.
- C-fibers terminate in lamina II and III (substansia gelatinosa) (slow pain) and neurotransmitter is substance P

Nociceptive vs non-nociceptive pathways



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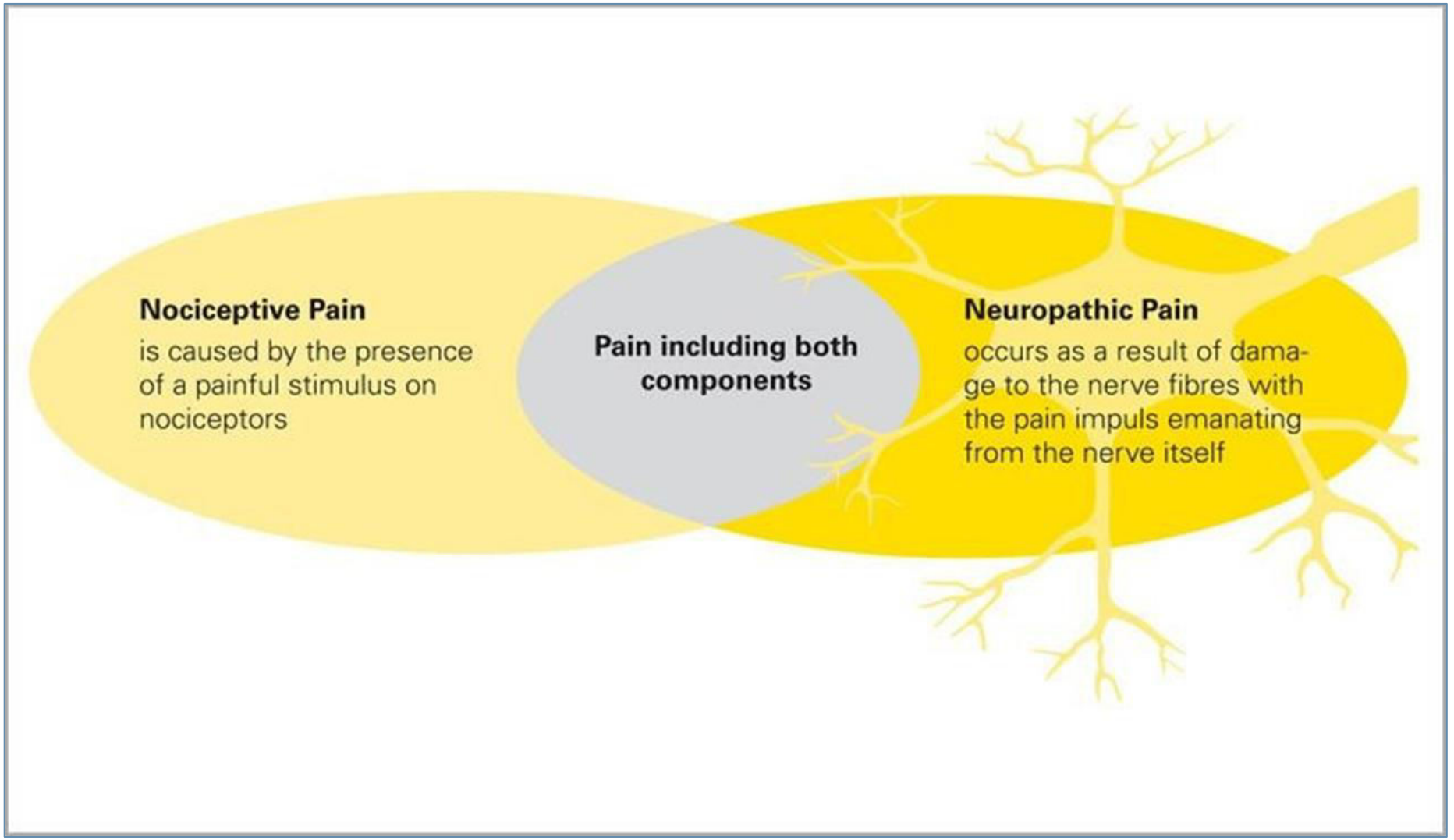

Nociceptive Pain
is caused by the presence of a painful stimulus on nociceptors
Pain including both components
Neuropathic Pain
occurs as a result of damage to the nerve fibres with the pain impuls emanating from the nerve itself

Dual Pain Pathways

- Pain signals take 2 pathways to the brain.
- Most of the slow pain fibers project to reticular formation & then proceed to thalamus (posterior nuclei) .
- Reticular system project to all parts of brain but specially to cerebral cortex therefore they cause arousal from sleep.

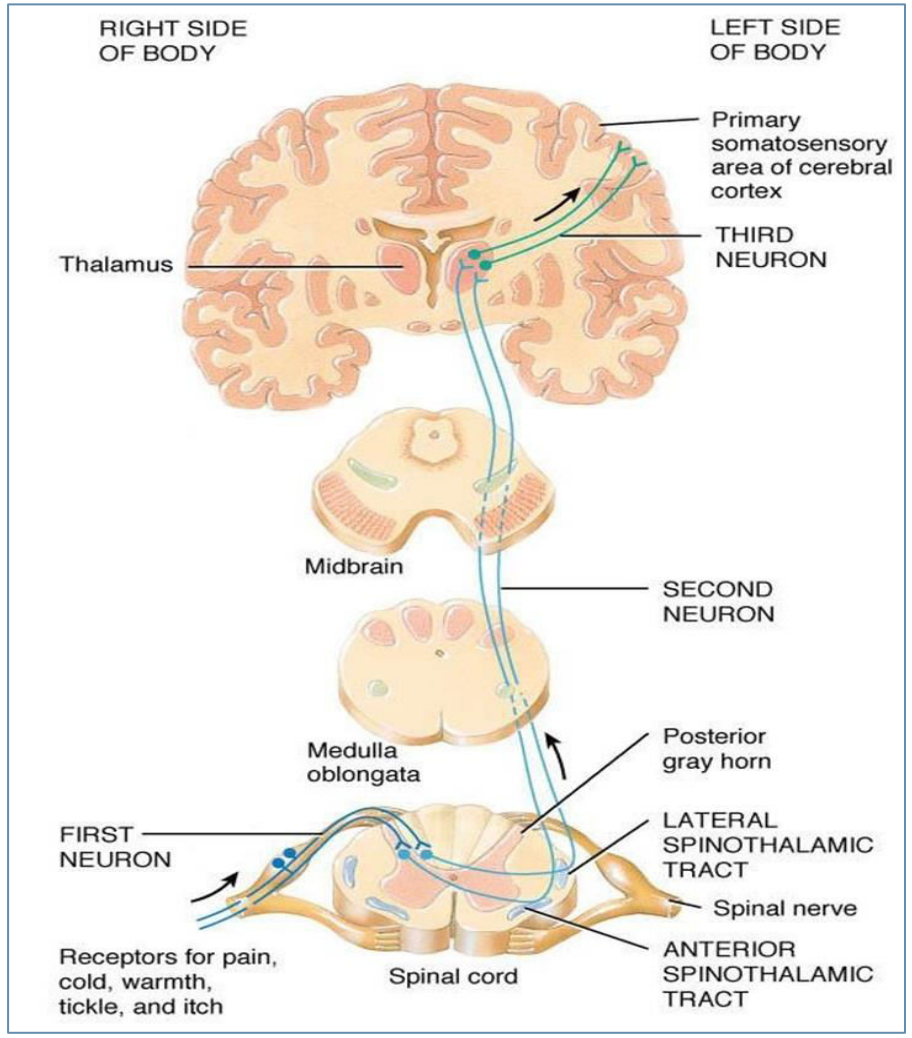
1. Neospinothalamic (lateral STT):

- Fast pain (aδ-type).
- Thermal pain (acute type).

2. Paleospinothalamic (ventral STT):

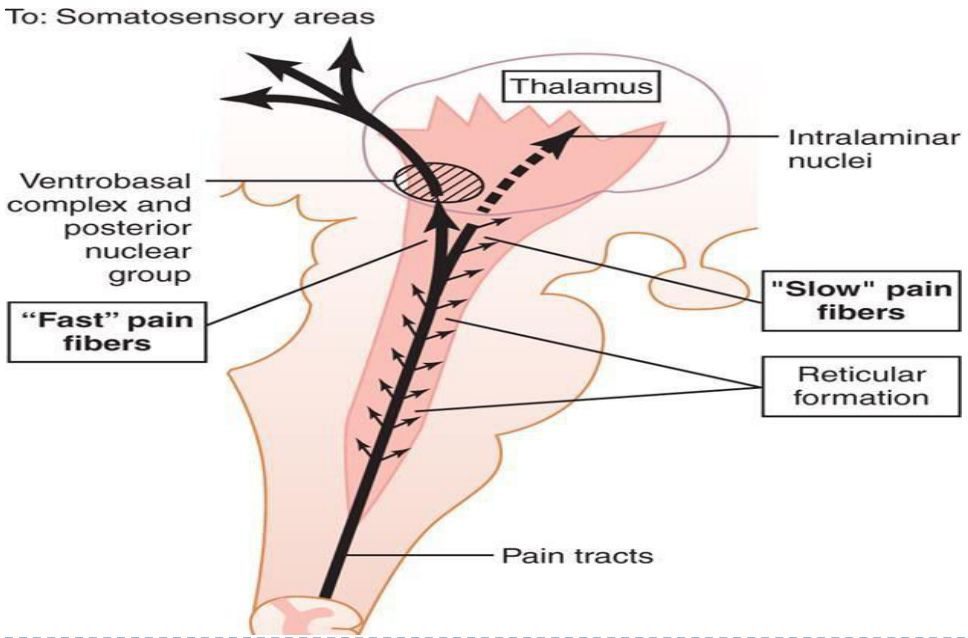
- Slow pain (c-type) plus some aδ.
- Crude touch & pressure.
- Itch & tickle.
- Sexual sensations.

- 1/10 to 1/4 of the fibers pass all the way to the thalamus.
- Most terminate reticular nuclei the tectal area & periaqueductal.
- gray region feeling the suffering types of pain.



Where do fibers of lateral & ventral STT terminate?

- Most pain fibers of lateral STT (L-STT) pass all the way to thalamus:
- Ventrobasal complex.
- Posterior nuclear group.
- Only few pain fibers of ventral STT pass all the way to thalamus: they project to
- Brain stem reticular formation.



Difference between pain reception and perception

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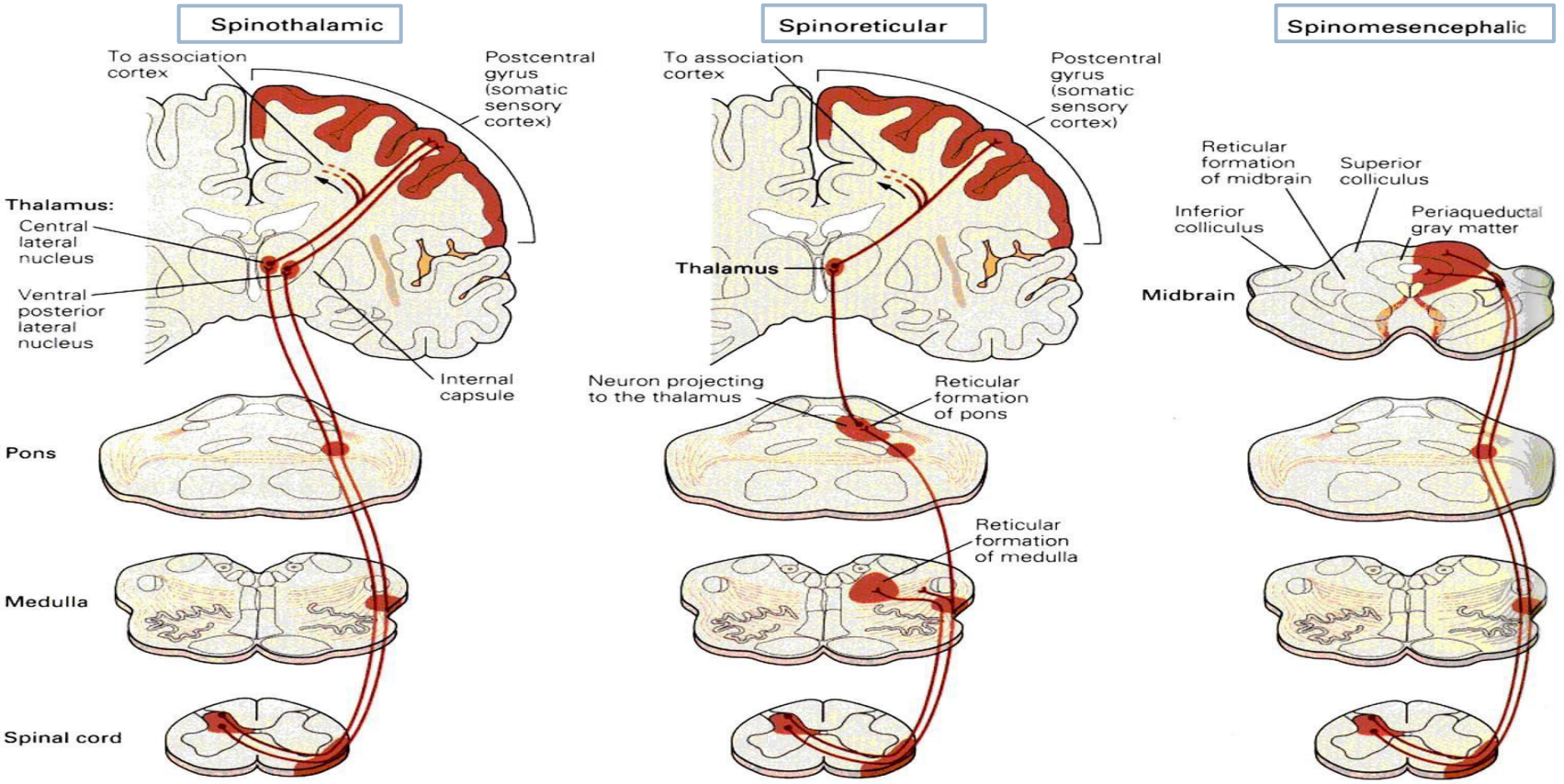
- Reception: Response of nerve receptors in the skin and tissues to stimuli resulting from actual or potential tissue damage.
- Perception: he process by which pain is recognized and interpreted by the brain.

Other ascending pain pathways



Pain pathways that provide different brain regions with information for processing different aspects of pain.

Qualities of pain

- (Phenomenon of double-pain).
- Fast / Sharp / immediate (1st) pain vs slow / diffuse / delayed (2nd) pain.

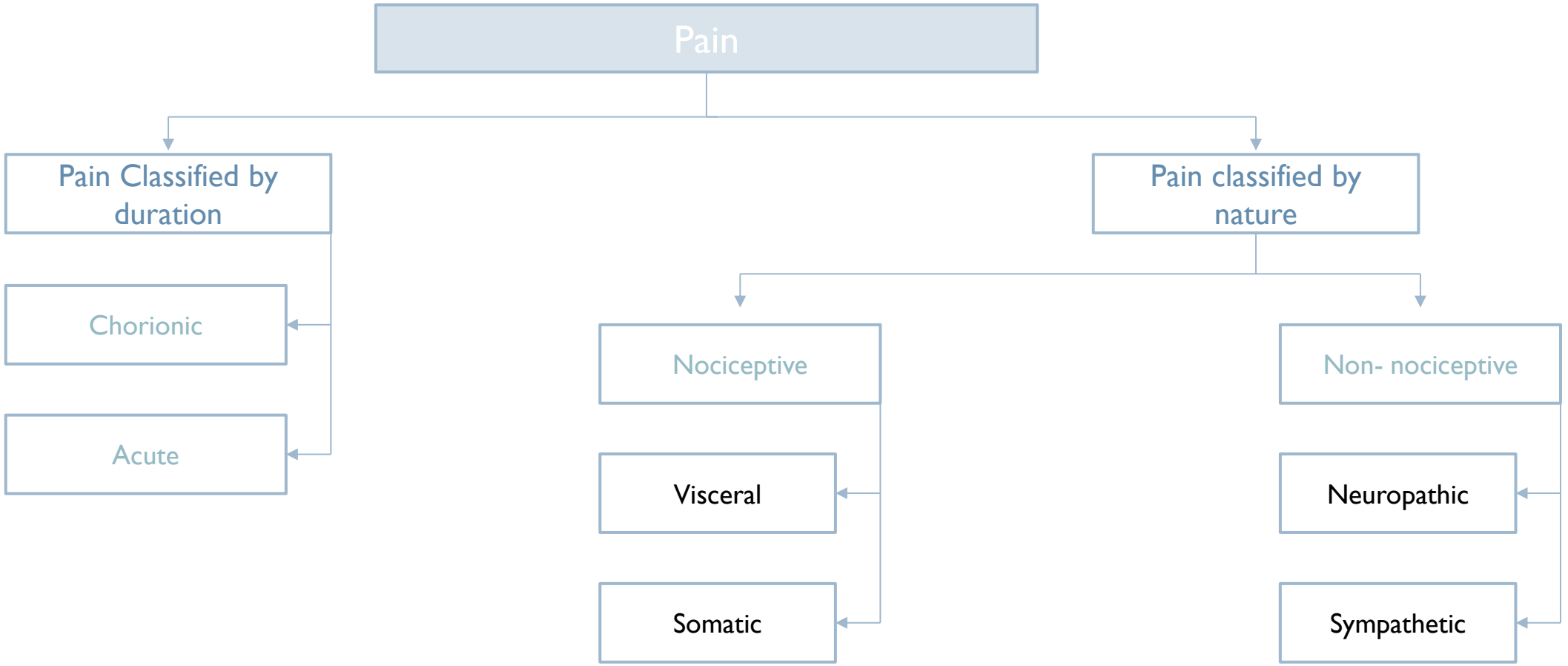
Fast pain

- Sharp, intense, pricking.
- It is felt within 0.1 sec. after stimulation. Ex: pricking, cut with knife.
- Associated with reflex withdrawal.
- Usually somatic not visceral.
- Well localized and is mediated by Aδ- fiber nociceptors in the peripheral nerves & centrally by Neospinothalamic Tract.
- Neurotransmitter – glutamate.
- Occurs FIRST upon stimulation of Mechanical and Thermal nociceptors.
- 20% pain conduction.
- Characteristics of Aδ fiber:
  - Myelinated.
  - Diameter fine 2 - 5 µm.
  - 12 - 30 m/sec. conduction velocity.
  - Terminate at I and V laminas.

Slow pain (or second)

- Burning, aching, throbbing "unbearable" diffuse, dull, or chronic pain.
- Felt after 1 sec or more.
- Associated with destruction of tissue.
- Can occur in skin or any internal organ / tissue.
- Poorly localized and is mediated by C-fiber nociceptors: misery (responsible for emotional aspect of pain).
- The noxious stimuli activates 10-20% of the A-delta fibers and 50-80% of the C-fibers.
- Occurs SECOND upon stimulation of Polymodal receptors.
- Chronic type of pain, transmitted by C fibers peripherally & centrally by paleospinothalamic Tract.
- 80% of pain conduction.
- Characteristics of C fibers:
  - Non-Myelinated.
  - Diameter fine 0.4 – 1.2 µm.
  - 0.5 – 2 m/sec. conduction velocity.
  - Terminate at II and III laminas, Neurotransmitter – Substance- P.

Classification of pain



Classification of pain

Nociception

- Sustained primarily by the nociceptive system.
- Proportionate to the stimulation of the nociceptor.
- When acute:
  - Serves a protective function.
  - Normal pain.
- Pathologic when chronic.
- Responds to common analgesics.
- Eg: acute burns, bone fracture, and other somatic and visceral pains

Neuropathic Pain

- Sustained by aberrant processes in PNS or CNS.
- Disproportionate to the stimulation of nociceptor.
- Serves no protective function.
- Pathologic pain.
- Resistant to common analgesics.
- Eg: painful diabetic & peripheral neuropathies, deafferentation and sympathetically-maintained pains, nerve inflammation, compression.

Idiopathic pain: no underlying lesion found

Yet, disproportionate to the degree of clinically discernible tissue injury.

Mixed Pain: Eg; Failed low-back-surgery syndrome.

Complex regional pain syndrome.

Significance

- Pain is mainly a protective mechanism of the body, as it is not a pure sensation but a response to tissue injury.

  The response may be Motor, e.g. withdrawal.

- Emotional, e.g. anxiety, crying, depression.

- Autonomic reaction, e.g. tachycardia, rise in B.P., sweating.

Types of pain

Pain can be classified according to the **site** of stimulation into

Somatic pain

Superficial pain

- It arises from skin or other superficial structures.
- It occurs in 2 phase of fast pricking followed by slow burning pain.
- It can be well localized.
- It may be associated with motor, autonomic, emotional reactions.

Deep pain

- It originates from muscles, joints, periosteum, tendons &ligaments.
- It is slow prolonged conducted by type C fibers.
- It is diffuse (poorly localized).
- It can initiate reflex contraction of nearby muscles.
- It may be referred to other sites.
- It is caused by: trauma, bone fracture & inflammation, arthritis, muscle spasm & ischemia.

Visceral pain

➢ Characters:

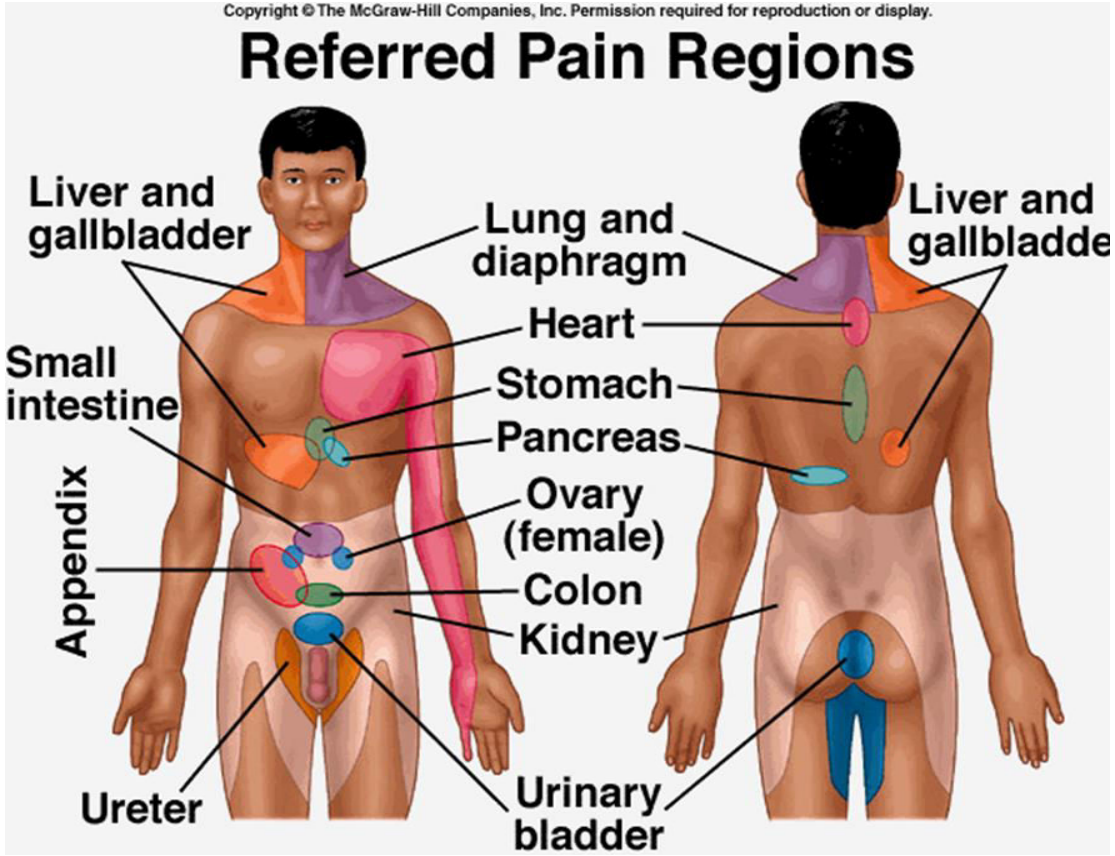
- It is slow pain conducted by C fibers (pain arising from parietal peritoneum, pleura and pericardium is sharp, pricking type).
- It is diffuse, poorly localized, the patient feels pain arising from inside but he cannot pinpoint it exactly.
- It is often associated with nausea and autonomic reactions.
- It can be associated with rigidity of nearby muscles.
- It often referred to other sites.
- There are few pain receptors in most viscera.
- Some viscera are pain insensitive e.G. Liver parenchyma, lung alveoli, brain tissue, visceral layer of peritoneum, pleura and pericardium.

➢ Causes:

- Distension of a hollow organs
- Inflammation of an organ.
- Ischemia e.G. Pain due to myocardial ischemia.
- Cutting, crushing are not painful when applied to viscera.

Referred Pain

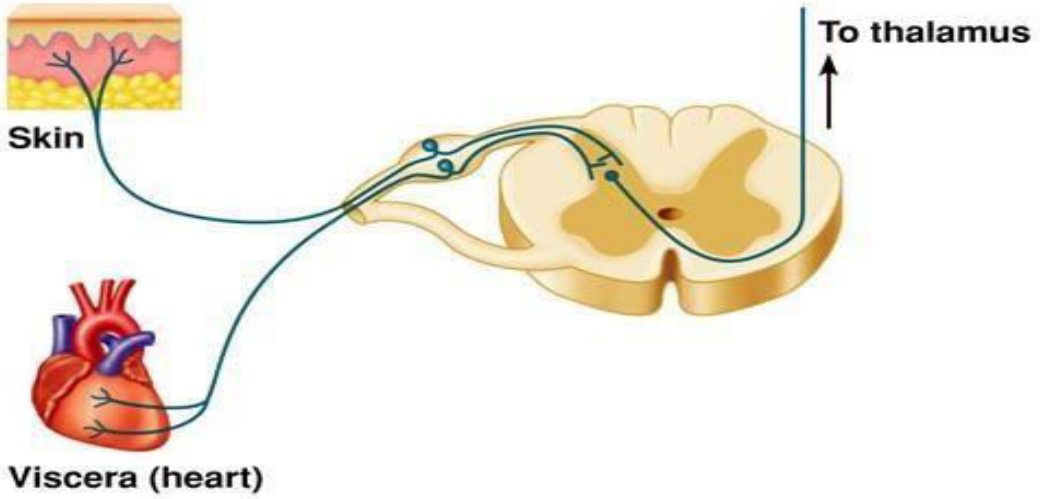
- Visceral pain that is felt at a somatic structure that can be far away from the origin site.
- Poorly localized and is not identical in all people.
- In some people heart pain can be referred to right (not left) arm or neck.
- This is pain that is felt away from its original site.
- It is most frequent with visceral pain & deep somatic pain but cutaneous pain is not referred.
- Pain is referred according to dermatomal rule.



Mechanism of referred pain

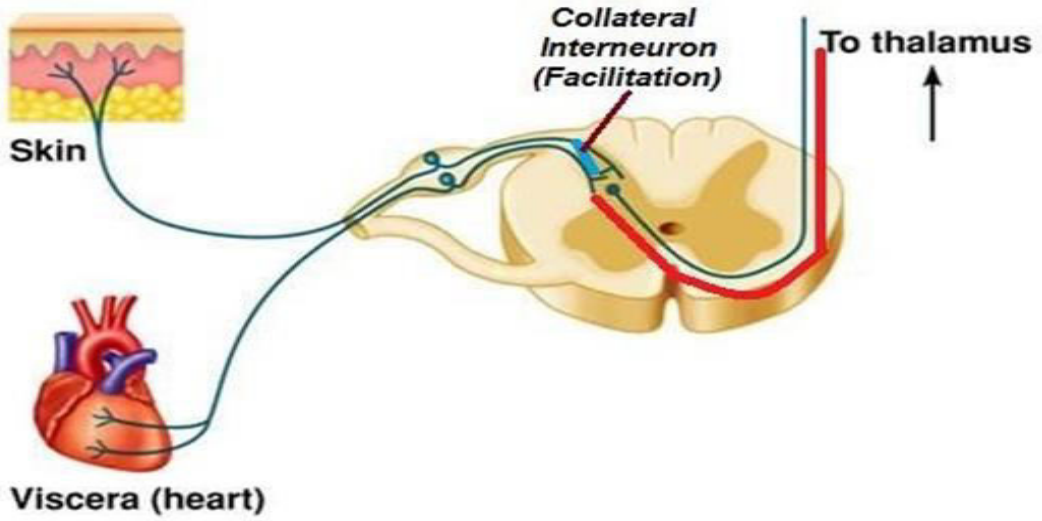
1. Convergence theory:

- Afferent pain fibers from skin area & diseased viscera that develop from same embryonic segment converge on same 2nd order neuron and finally stimulate the same cortical neuron.
- The brain interprets the information coming from visceral nociceptors as having arisen from cutaneous nociceptors, because this is where nociceptive stimuli originate more frequently



2. Facilitation theory:

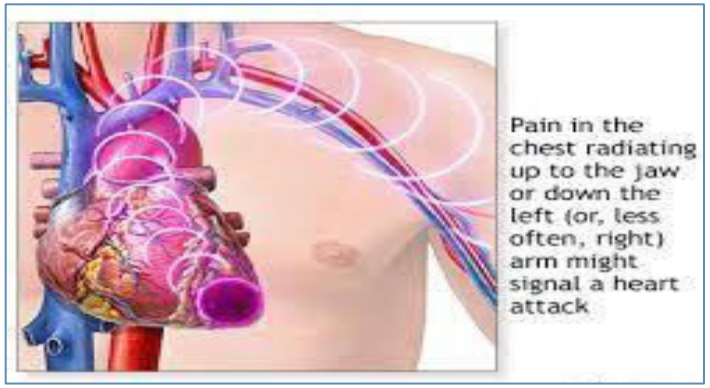
- Pain fibers from skin are always carrying impulses, not enough to produce pain.
- Impulses from diseased viscus pass through afferents which give collaterals to st neurons receiving pain fibers from skin.
- As a result, st neurons' excitability is raised (they are facilitated) to reach a threshold level.
- The signals reaching the brain are projected to skin area and pain is felt in skin dermatome.

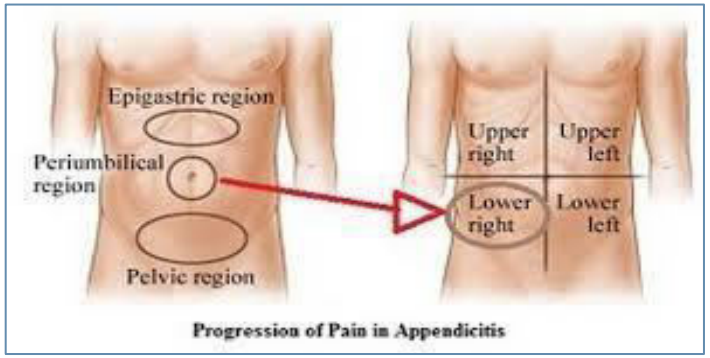


Examples of referred pain

- Cardiac pain is referred to the jaw, left shoulder & inner side of left arm.
- Pain of appendicitis is referred to periumbilical region.
- Pain from the ureter is referred to testicular region.

Organ	Site of referred pain
Meninges	Back of head &neck
Heart	Central chest, left arm
Diaphragm	Shoulder tip
Esophagus	Behind sternum
Stomach, duodenum	Epigastrium
Small bowel, pancreas	Around umbilicus
Large bowel, bladder	Lower abdomen
Kidney	Loin
Ureter	Testicles
Trigon of bladder	Tip of penis
Hip	Knee
Appendix	Umbilicus
Uterus	Low back





Pathway of pain

Pain sensation is carried by lateral spinothalamic tracts which includes 2 separate pathways

The neospinothalamic pathway
Transmit fast pain

First order neurons

- Are mainly Aδ afferent nerves.
- They terminate at lamina I & V of dorsal horn.

Second order neurons

These constitute the tract. They start at dorsal horn, cross to opposite side and ascend in lateral column of spinal cord. The fibers ascend in brain stem to terminate in ventrobasal complex of thalamus.

Third order neurons

These start at thalamus & most fibers project to somatosensory cortex.

The paleospinothalamic pathway
Transmit slow pain

First order neurons

- They are mainly type C fibers.
- They enter spinal cord via dorsal roots, terminate at substantia gelatinosa in laminae II & III of dorsal horn (subtantia gelatinosa).

Second order neurons

- They start at SGR, cross to opposite side in front of central canal, ascend in lateral column of SC & terminate at:
- Reticular formation of brain stem.
- Intralaminar nuclei of thalamus.
- Hypothalamus & adjacent region of basal brain.
- Impulses arriving these regions have strong arousal effects and can be perceived.

Third order neurons

These start at thalamus, Few fibers project to cerebral cortex.

Cont.

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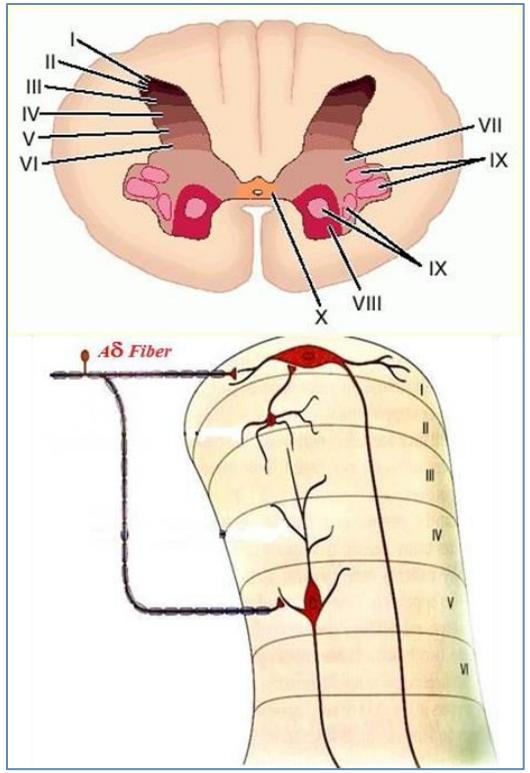
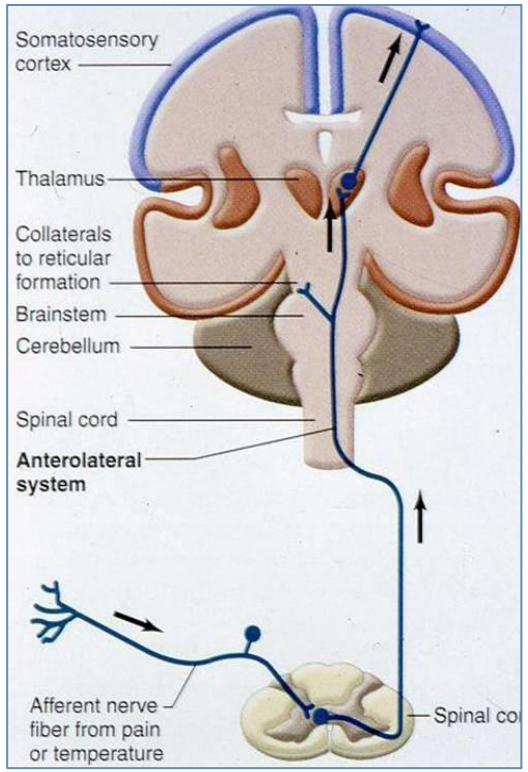
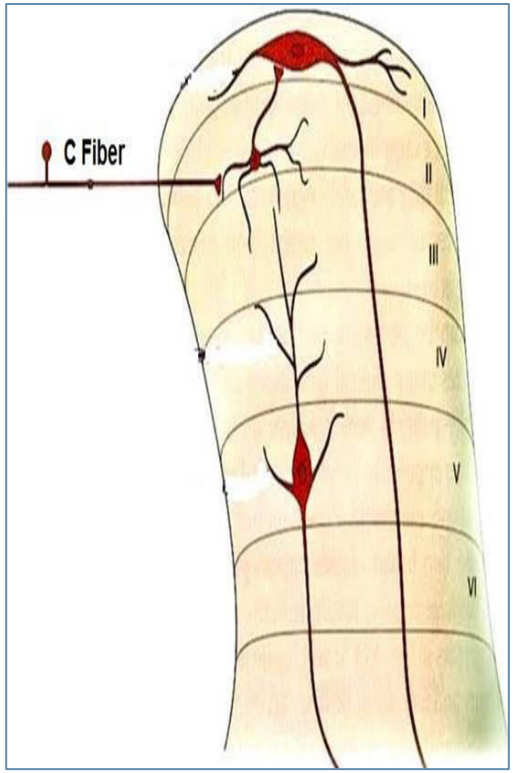
- Most of the slow pain fibers project to reticular formation & then proceed to thalamus (posterior nuclei).
- Reticular system project to all parts of brain but specially to cerebral cortex therefore they cause arousal from sleep.

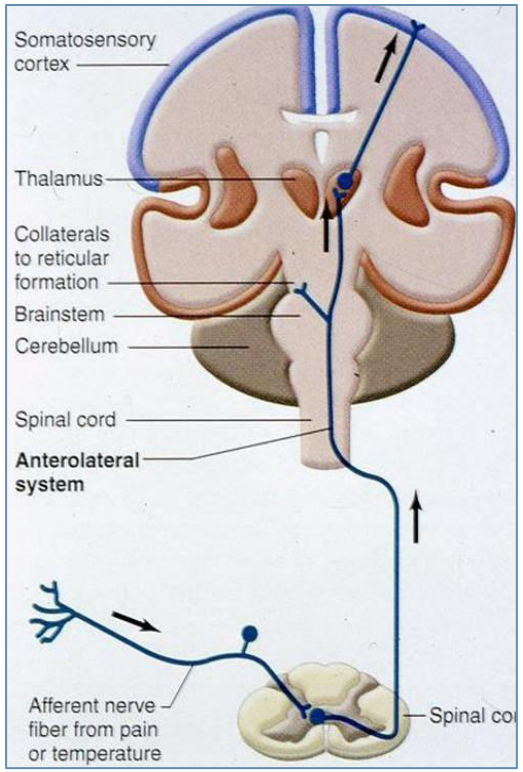
The neospinothalamic pathway:





The paleospinothalamic pathway:



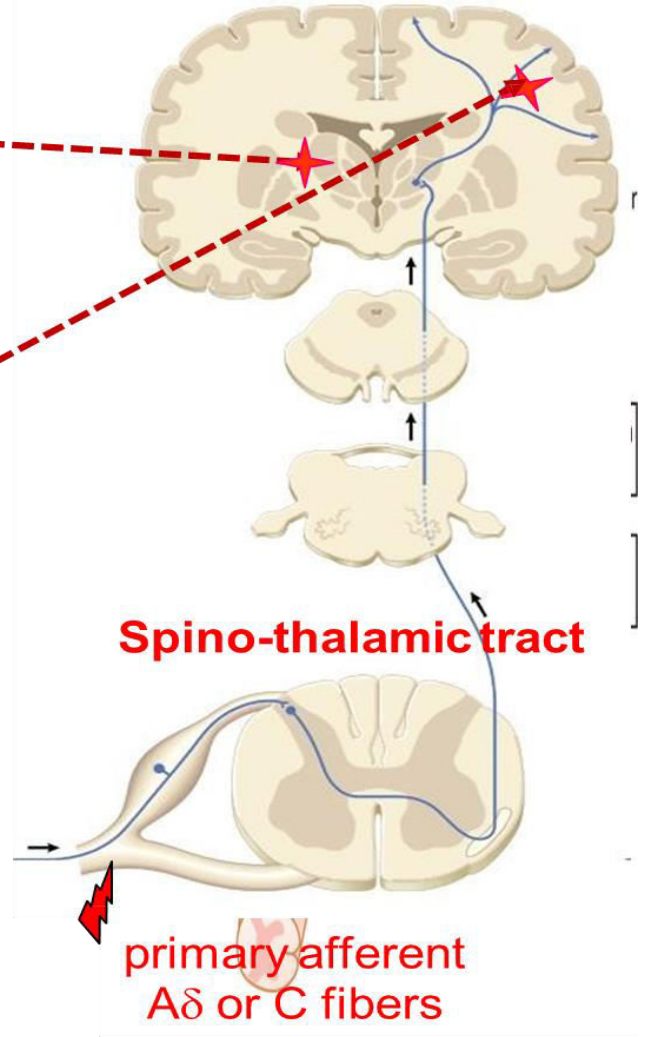


Role of thalamus and cerebral cortex in pain perception

Full perception of pain occurs when signals enter RF of brain stem, thalamus and basal regions

Somatosensory cortex plays important role in topognosis i.e. localization & interpretation of pain quality.

Fast pain is localized better than slow pain because signals carried in neospinothalamic tract reach somatosensory cortex, while a small propotion of paleospinothalamic pathway reach there.



Thank you!

اعمل لترسم بسمة، اعمل لتمسح دمعة، اعمل و أنت تعلم أن الله لا يضيع أجر من أحسن عملا.

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QUIZ

اقتراحات وشكاوي

References:

- Females' and Males' slides.
- Guyton and Hall Textbook of Medical Physiology (Thirteenth Edition.)