اللهم صل على محمد وآل محمد

السلام عليكم ورحمة الله وبركاته

جامعة الملك سعود
King Saud University
1957

Physiology of Pain

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Learning Objectives

- *What is pain and its significance*
- *Pain reception and perception*
- *Pain receptors (nociceptors)*
- *Mechanism of stimulation of pain receptors*
- *Qualities of pain*
- *Types of pain*
  - *Somatic pain (superficial & deep pain).*
  - *Visceral pain.*
- *Referred pain*
- *Pathway of pain*
  - *The neospinothalamic pathway*
  - *The paleospinothalamic pathway*
- *Role of thalamus and cerebral cortex in pain perception*

Pain & Nociception 

What is nociception?

Refers to the transmission of signals evoked by activation of nociceptors (pain receptors) from periphery to the CNS.

What is pain?

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

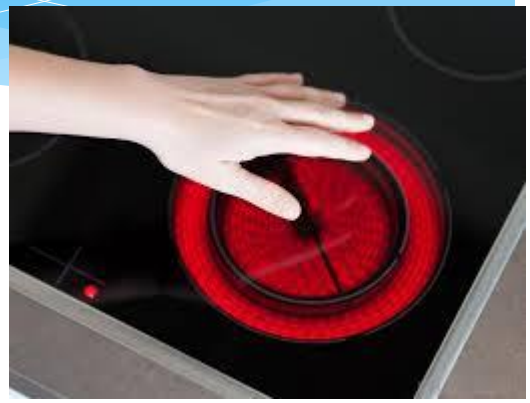
Is an unpleasant sensory and emotional experience associated with actual or potential tissue damage.

Definitions

- *Sensory receptors: are specialized peripheral endings of primary afferent neurons.*
- *Nociceptors (pain receptors): primary afferent receptors that respond selectively to noxious stimuli.*
- *Noxious stimulus: any stimulus (mechanical, chemical or thermal) that produces tissue damage or threatens to do so (≠ innocuous).*
- *Polymodal nociceptors: respond to various noxious stimuli.*

Significance of Pain: Why do we feel pain?

- *It is a protective mechanism meant to make us aware that tissue damage is occurring or is about to occur:-*
  - *Avoid noxious stimuli*
  - *Remove body parts from danger*
  - *Promote healing by preventing further damage*
  - *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, anxiety or fear).*
- *Pain is perceived at both the cortical & thalamic levels.*

Pain Reception and Perception

Reception ***(الإستقبال):*** *Response of nerve receptors in the skin and tissues to stimuli resulting from actual or potential tissue damage.*

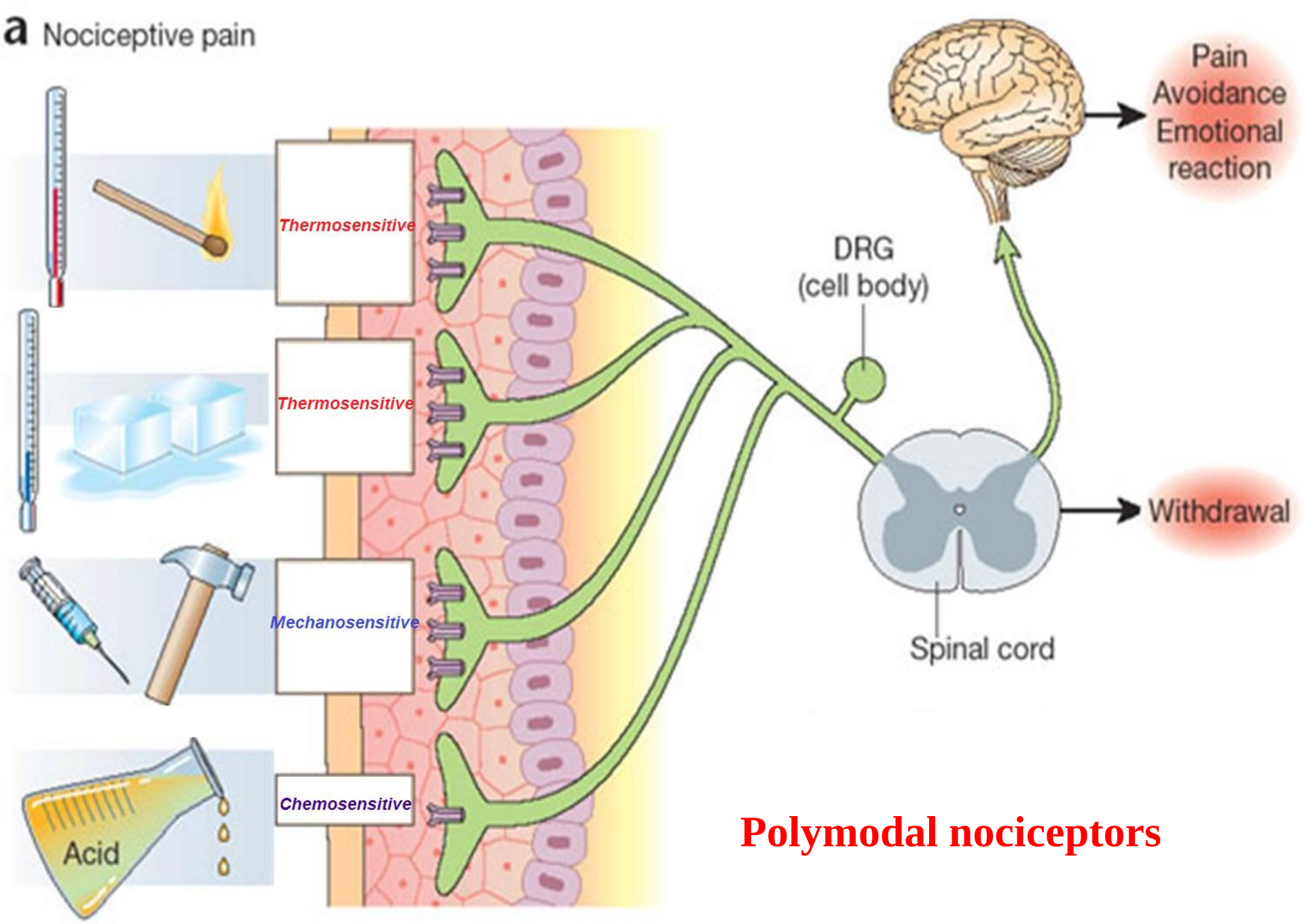
Perception ***(الإدراك):*** *The process by which pain is recognized and interpreted by the brain.*

Pain Receptors `Nociceptors`?

Sir Charles Scott Sherrington

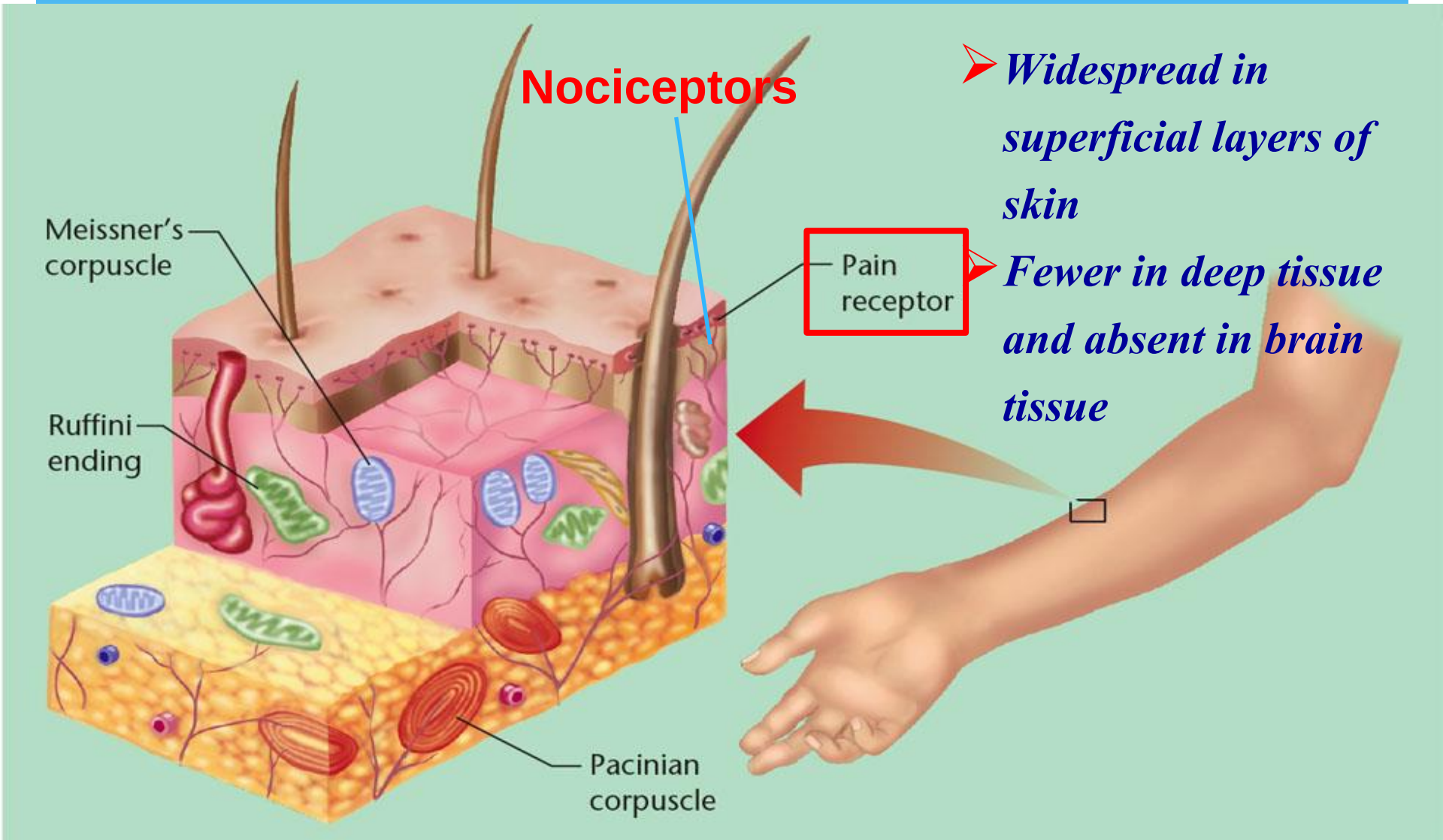
" Are special receptors that respond only to ***noxious*** *stimuli and generate nerve impulses which the brain interprets as "pain".*
(Sherrington 1906)

- *They are the most widely distributed.*
- *They are specific (have adequate stimulus) in that pain is not produced by overstimulation of other receptors.*
- *They are high threshold receptors i.e. painful stimuli must be strong & noxious to produce tissue damage.*
- *Do not adapt (or very little) to repetitive stimulation (it allows the pain to keep the person apprised of a tissue-damaging stimulus as long as it persists.)*



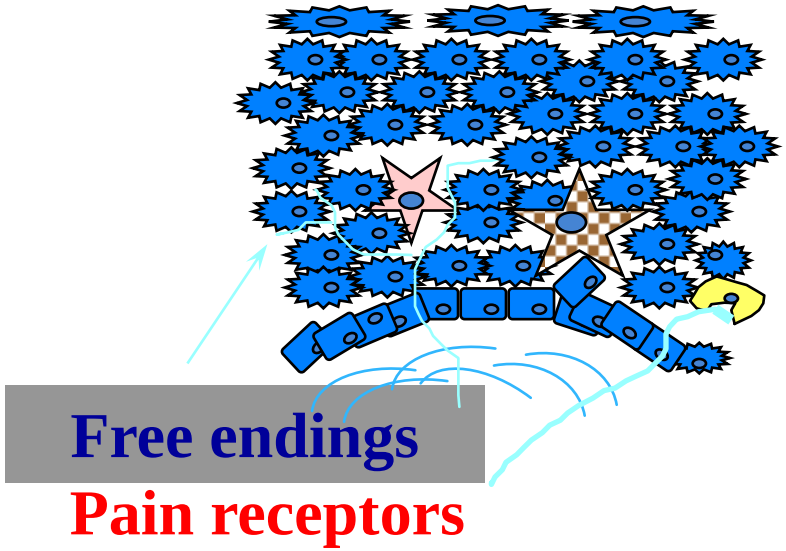
Polymodal nociceptors

Distribution of Pain Receptor(Nociceptors)



- *Widespread in superficial layers of skin*
- *Fewer in deep tissue and absent in brain tissue*

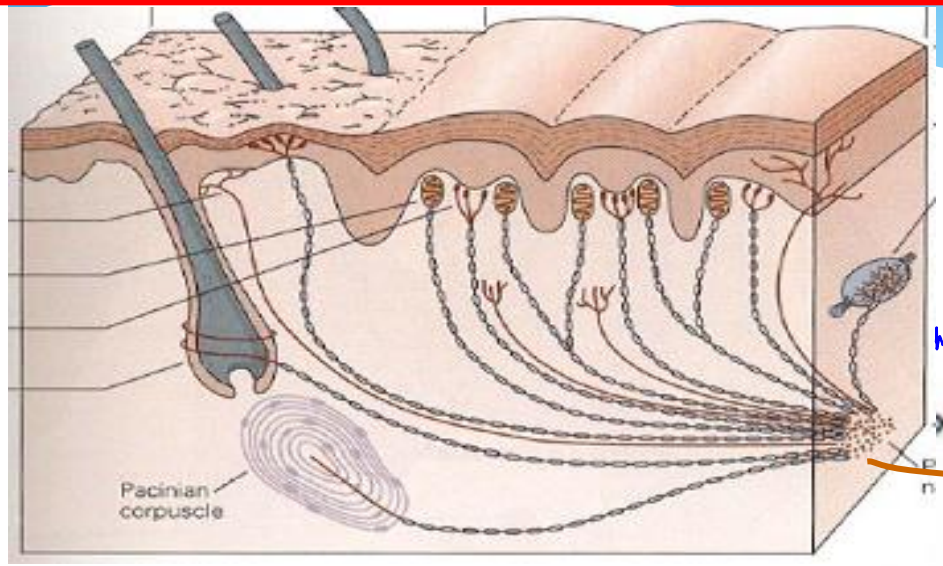
- *All pain receptors are **free nerve endings** of unmyelinated **C fibers** & small diameter myelinated **Aδ fibers**.*

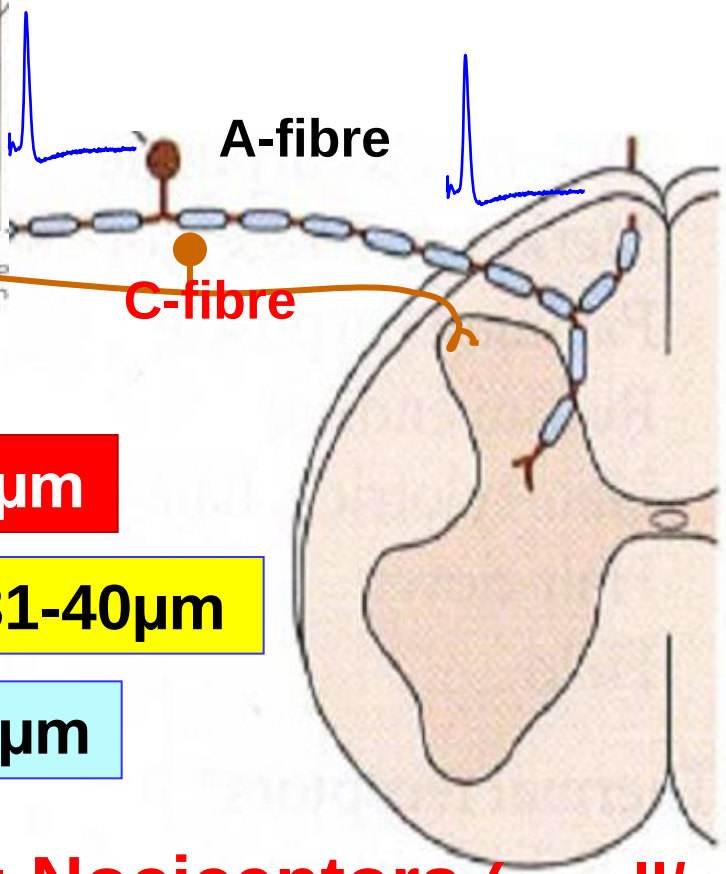


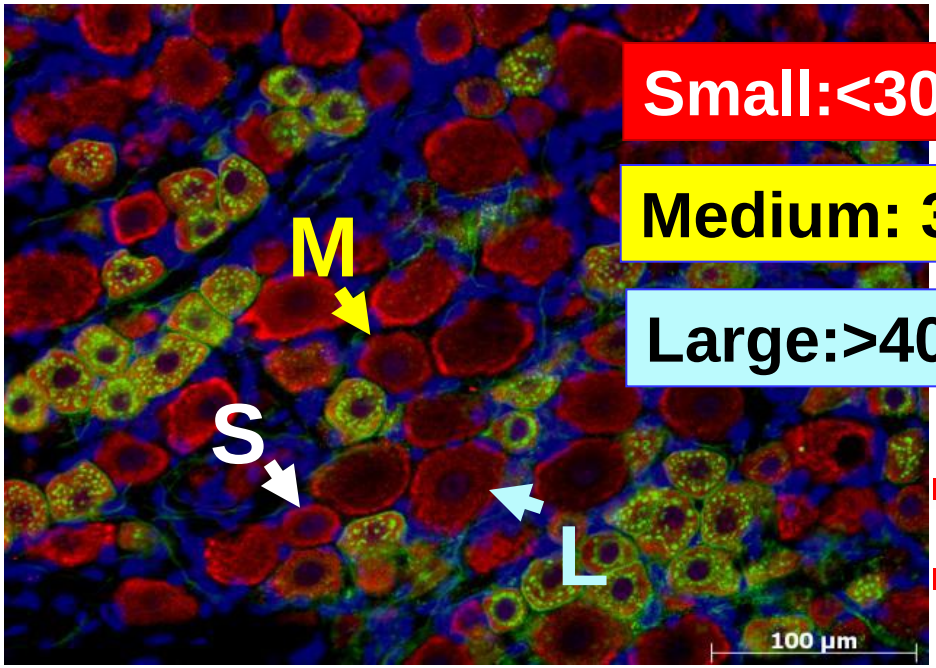
Free endings

Pain receptors

Type-A & Type-C Fibers







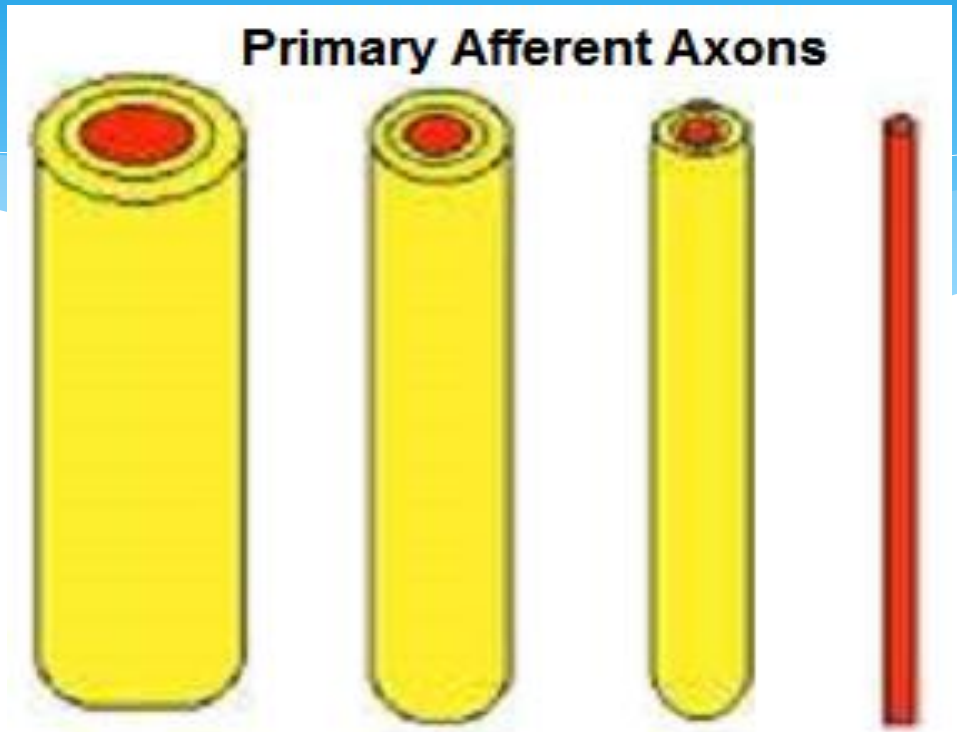
Small:<30µm

Medium: 31-40µm

Large:>40µm

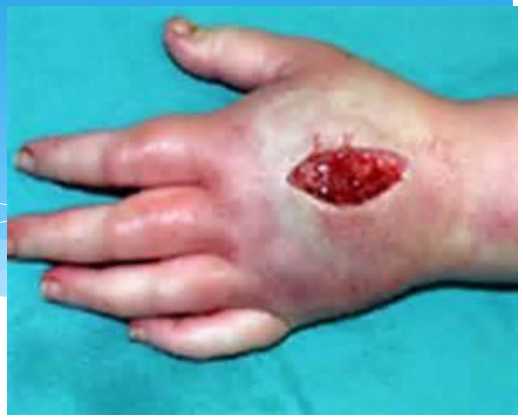
- **Nociceptors (small/medium)**
- **Non-nociceptors (large)**

Classification of Nerve fibres

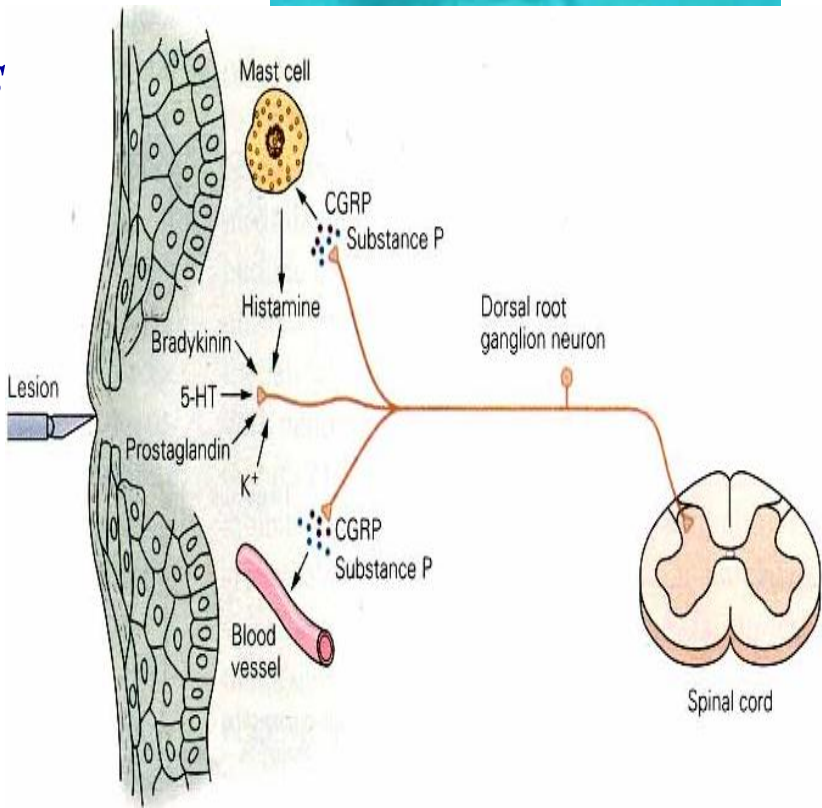


Type	I	II	III	IV
Type	Aα	Aβ	Aδ	C
Diameter (μm)	10-20	5-10	2-5	0.5-2
Conduction Velocity (m/s)	70-120	30-70	5-30	0.5-2

Mechanism of stimulation of nociceptors



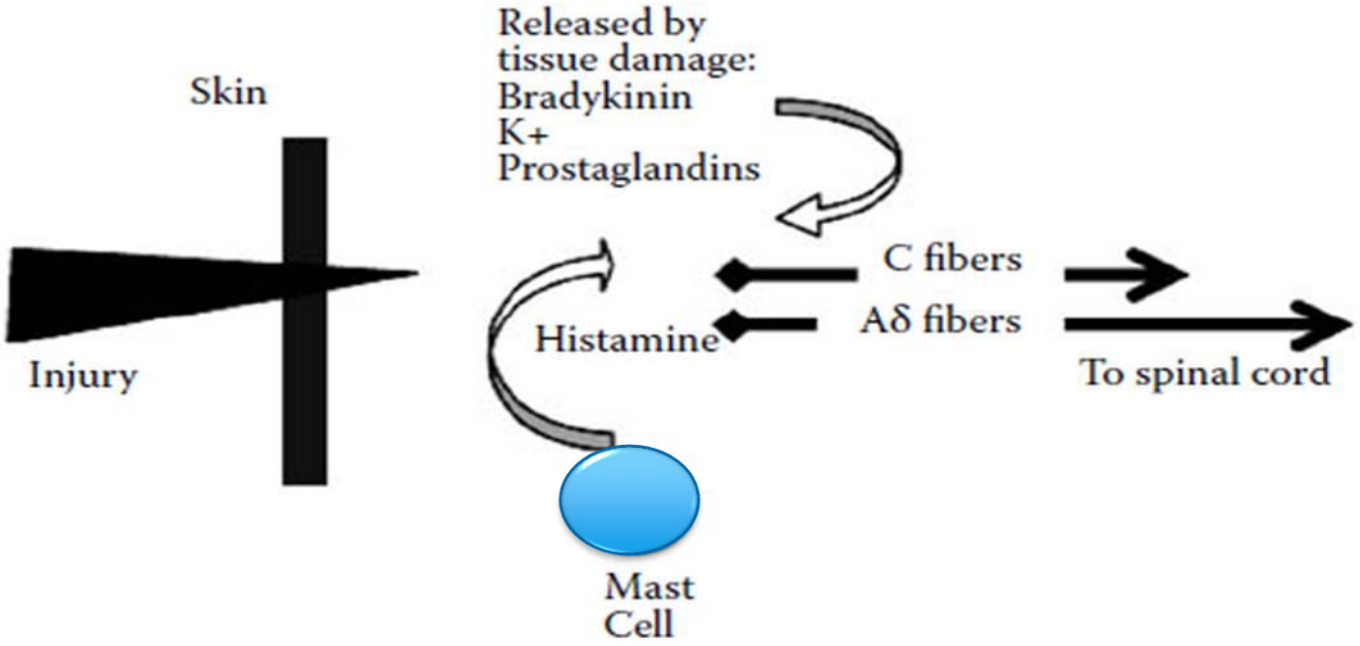
* *Pain receptors are depolarized either directly or through the production of pain producing substances from damaged tissues as a result of inflammation (also called inflammatory mediators)*
* *e.g. bradykinin, histamine, substance P, calcitonin gene-related peptide (CGRP), interleukins, prostaglandins, K^+, Ach, proteolytic enzymes.*



Chemical substances released during tissue damage

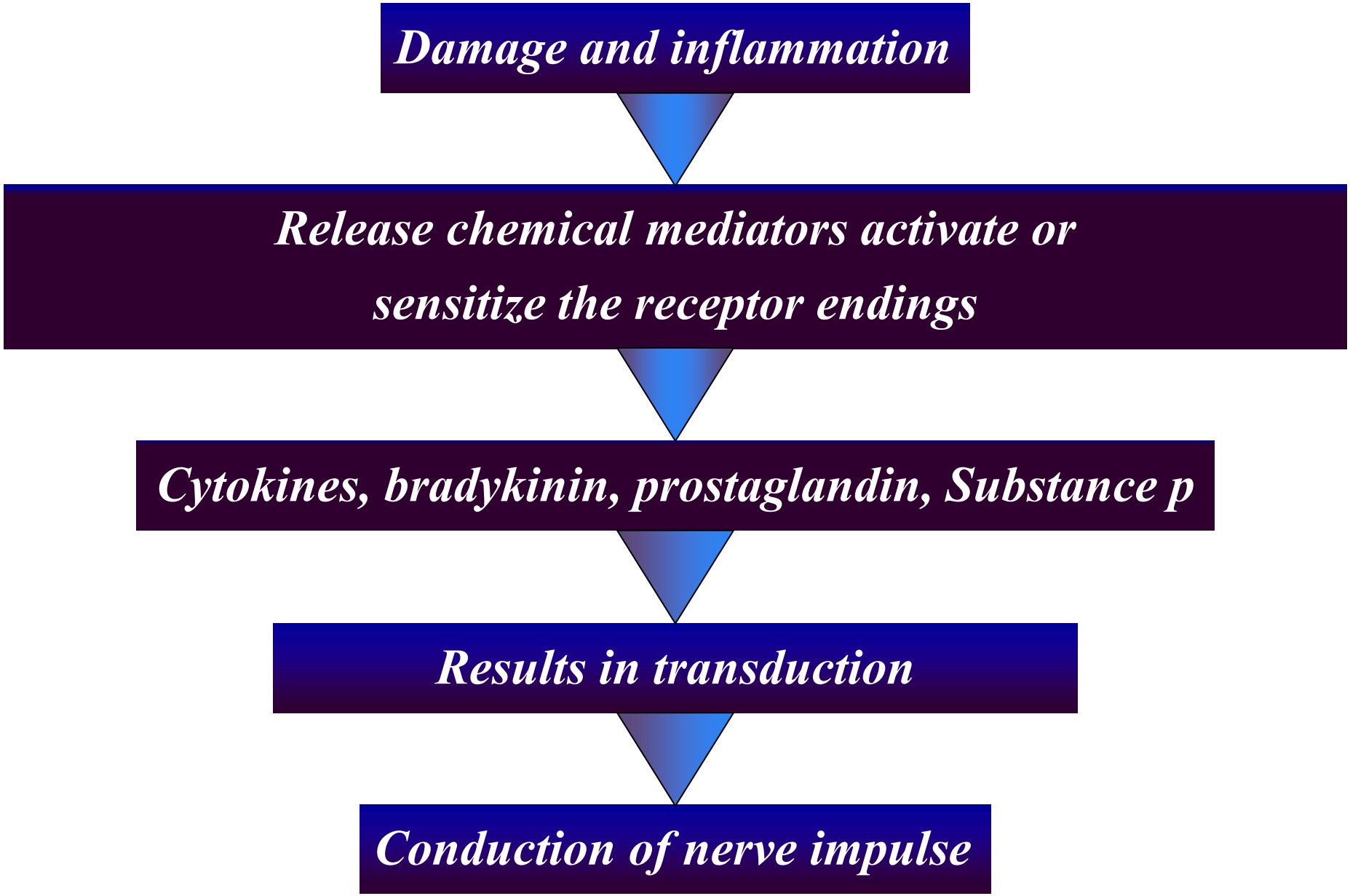
Substance	Source
Potassium	Damaged cells
Serotonin	Platelets
Bradykinin	Plasma
Histamine	Mast cells
Prostaglandins	Damaged cells
Leukotrienes	Damaged cells
Substance P	Primary nerve afferents

Pain Mechanism

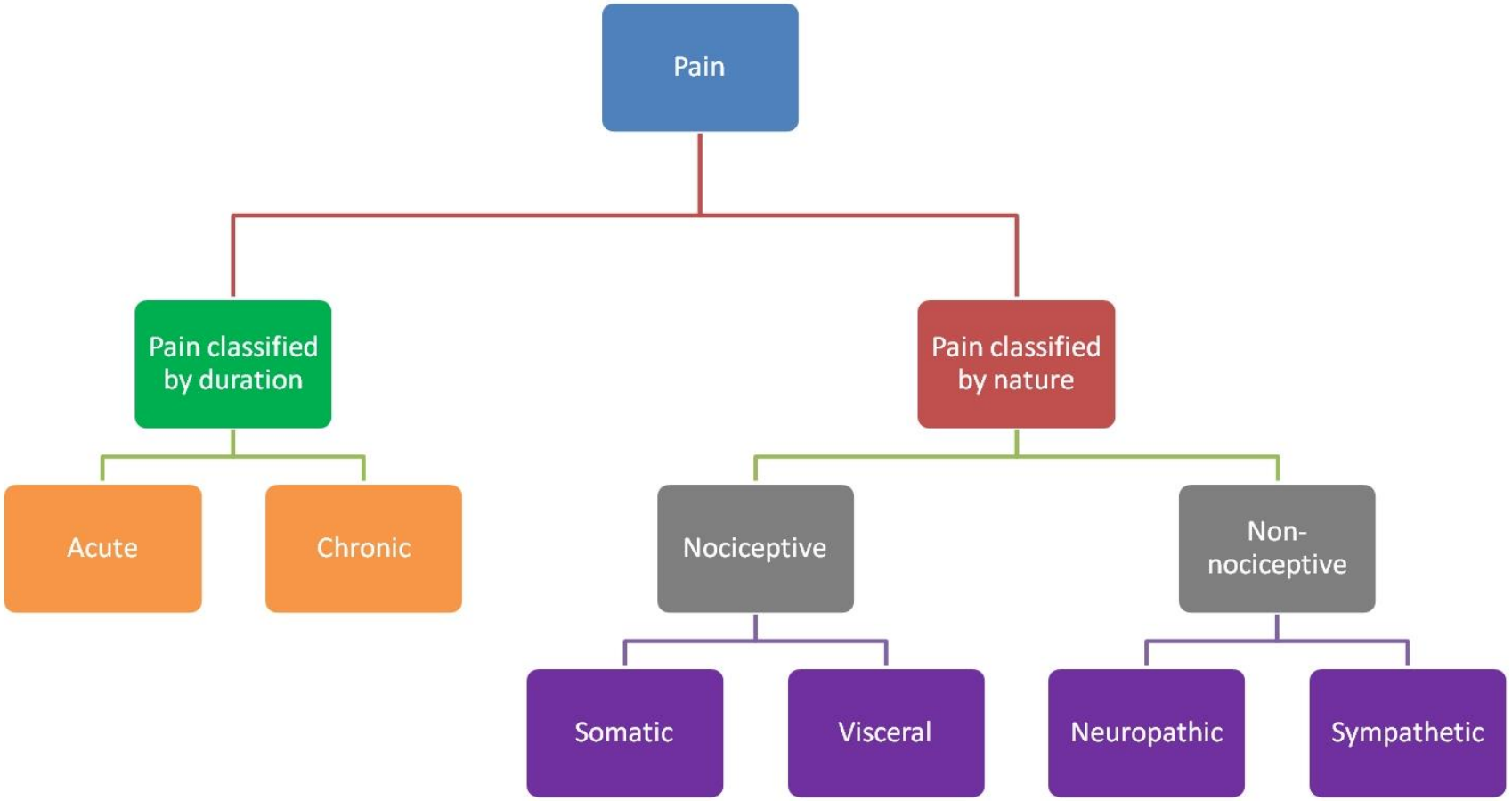


Some chemicals released by tissue damage that stimulates nociceptors. In addition release of substance-P, along with histamine, produce vasodilation and swelling.

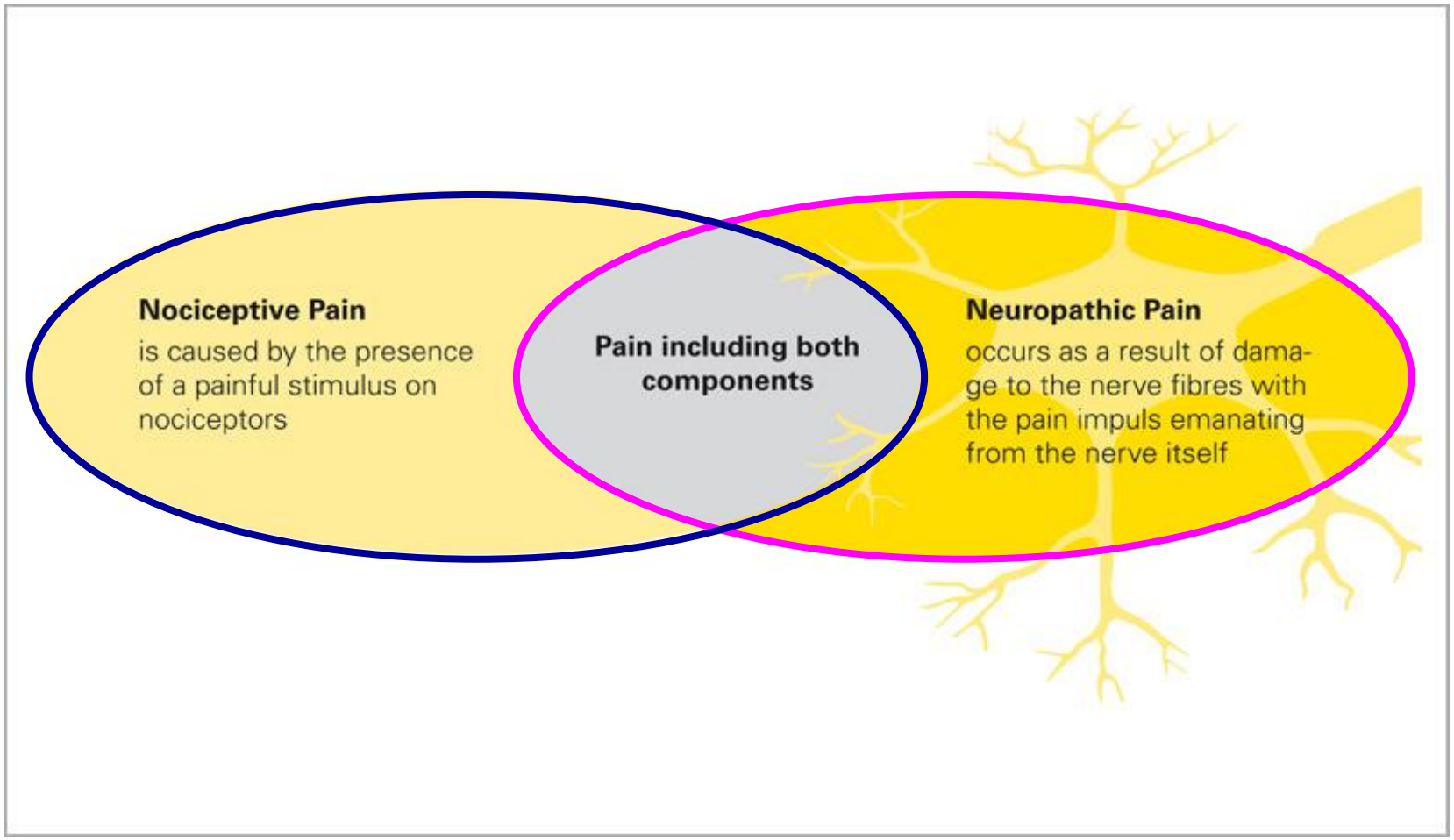
Pain Mechanism



Classification of Pain



Nociceptive & Neuropathic Pain



Qualities of pain

(Phenomenon of double-pain)

Fast/Sharp/immediate (1st) pain vs slow/diffuse/delayed (2nd) pain

Fast pain	Slow pain (or second)
▪ *Sharp, intense, pricking*	▪ *Burning, aching, throbbing "unbearable" diffuse, dull, or chronic pain*
▪ *Felt within **0.1 sec***	▪ *Felt after **1 sec** or more*
▪ *Associated with reflex withdrawal*	▪ *Associated with destruction of tissue*
▪ *Usually somatic not visceral*	▪ *Can occur in skin or any internal organ/tissue*
▪ *Well localized and is mediated by **Aδ-fiber nociceptors***	▪ *Poorly localized and is mediated by **C-fiber nociceptors**: → misery (responsible for emotional aspect of pain)*
▪ *Terminate at I and V laminas*	▪ *Terminate at II and III laminas*
▪ *Neurotransmitter – glutamate*	▪ *Neurotransmitter – Substance- P*

Types of pain

Pain can be classified according to the site of stimulation into:-

- ***Somatic pain*** *(superficial & deep pain).*
- ***Visceral 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** (i.e. 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

- *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.***

Characters of visceral pain

- *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.*

Causes of visceral pain

- *Distension of a hollow organs*
- *Inflammation of an organ.*
- *Ischemia e.g. pain due to myocardial ischemia.*

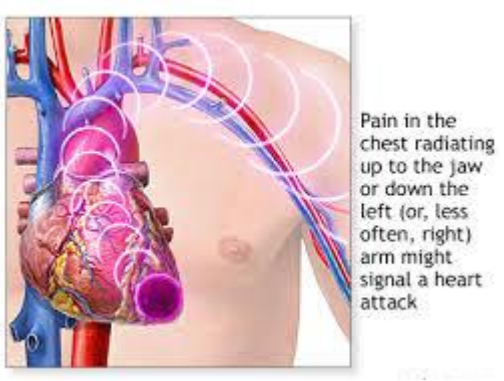
N.B: Cutting, crushing are not painful when applied to viscera.

Referred pain

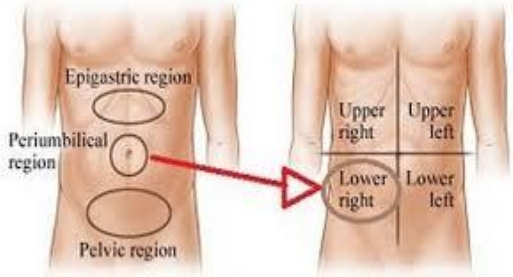
- *This is pain that is felt away from its original site.*
- *It is most frequent with visceral pain & deep somatic pain but **cutaneous pain is not referred.***
- *Pain is referred according to dermatomal rule.*

Examples of referred pain:

- ***Cardiac pain*** *is referred to the jaw, left shoulder & inner side of left arm.*

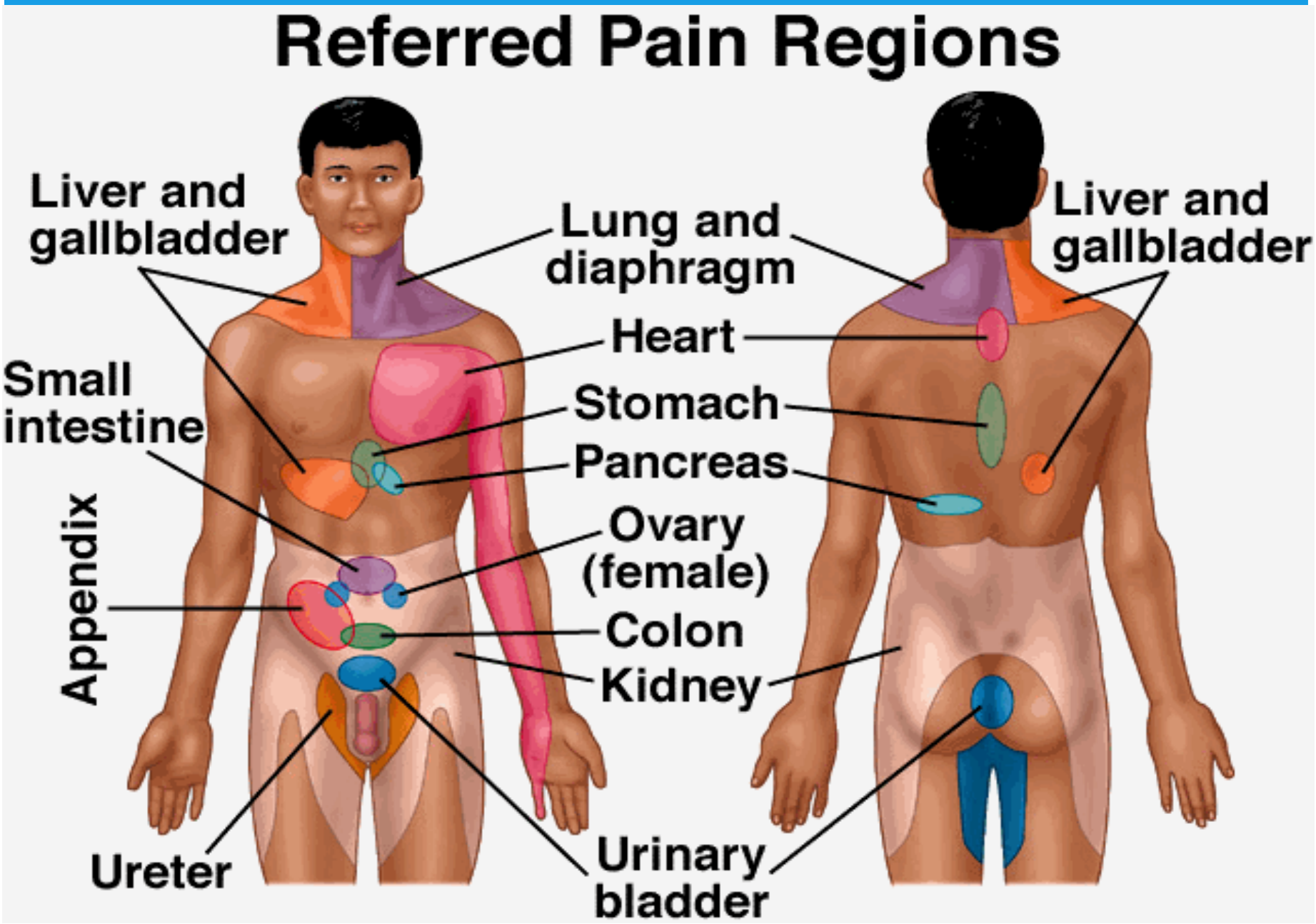


- *Pain of* ***appendicitis*** *is referred to periumbilical region.*



- *Pain from the* ***ureter*** *is referred to testicular region.*

Referred Pain Regions

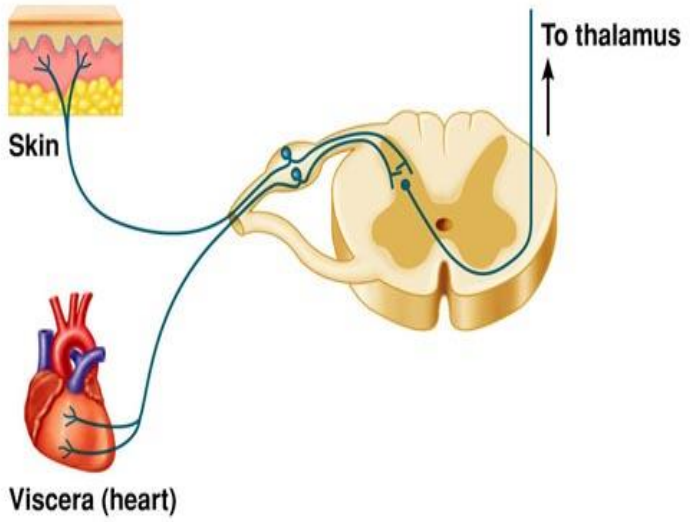


Organ	*Site of referred pain*
Meninges	*Back of head &neck*
Heart	*Central chest, left arm*
Diaphragm	*Shoulder tip*
Esophagus	*Behind sternum*
Stomach, duodenum	*Epigastrium*
Small bowel, pancreas	*Around umbilicus*
Large bowel, bladder	*Lower abdomen*
Kidney	*Loin*
Ureter	*Testicles*
Trigon of bladder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

Mechanism of referred pain

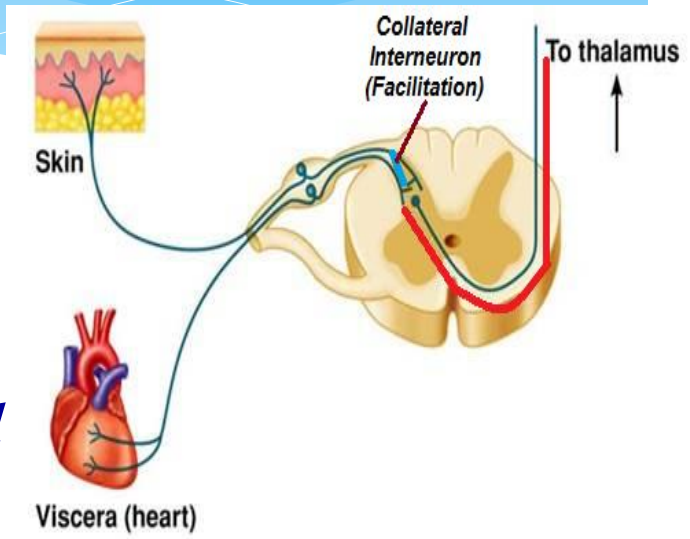
Convergence theory

- *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*

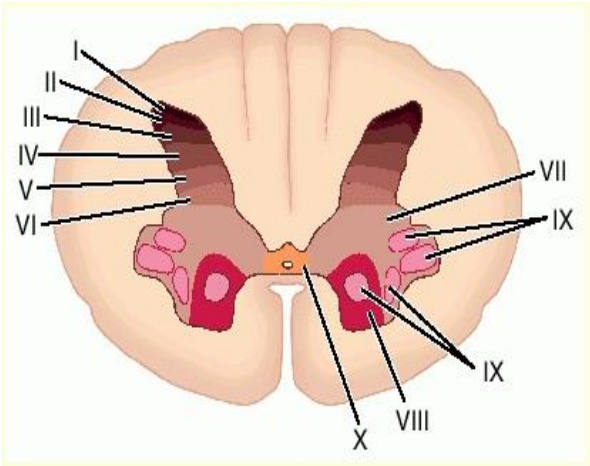


Facilitation theory

- *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*



Pathway of Pain



*Pain sensation is carried by **lateral spinothalamic tracts** which includes*

2 separate pathways:-

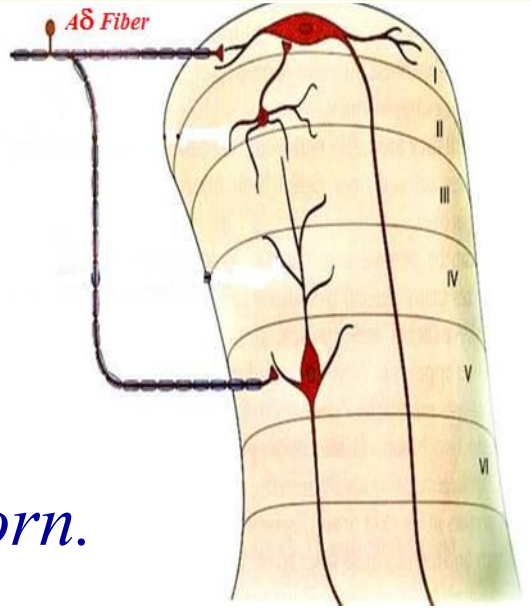
A) The neospinothalamic pathway:

This transmits fast pain.

- ***First order neurons***

Are mainly Aδ afferent nerves.

They terminate at lamina I & V of dorsal horn.

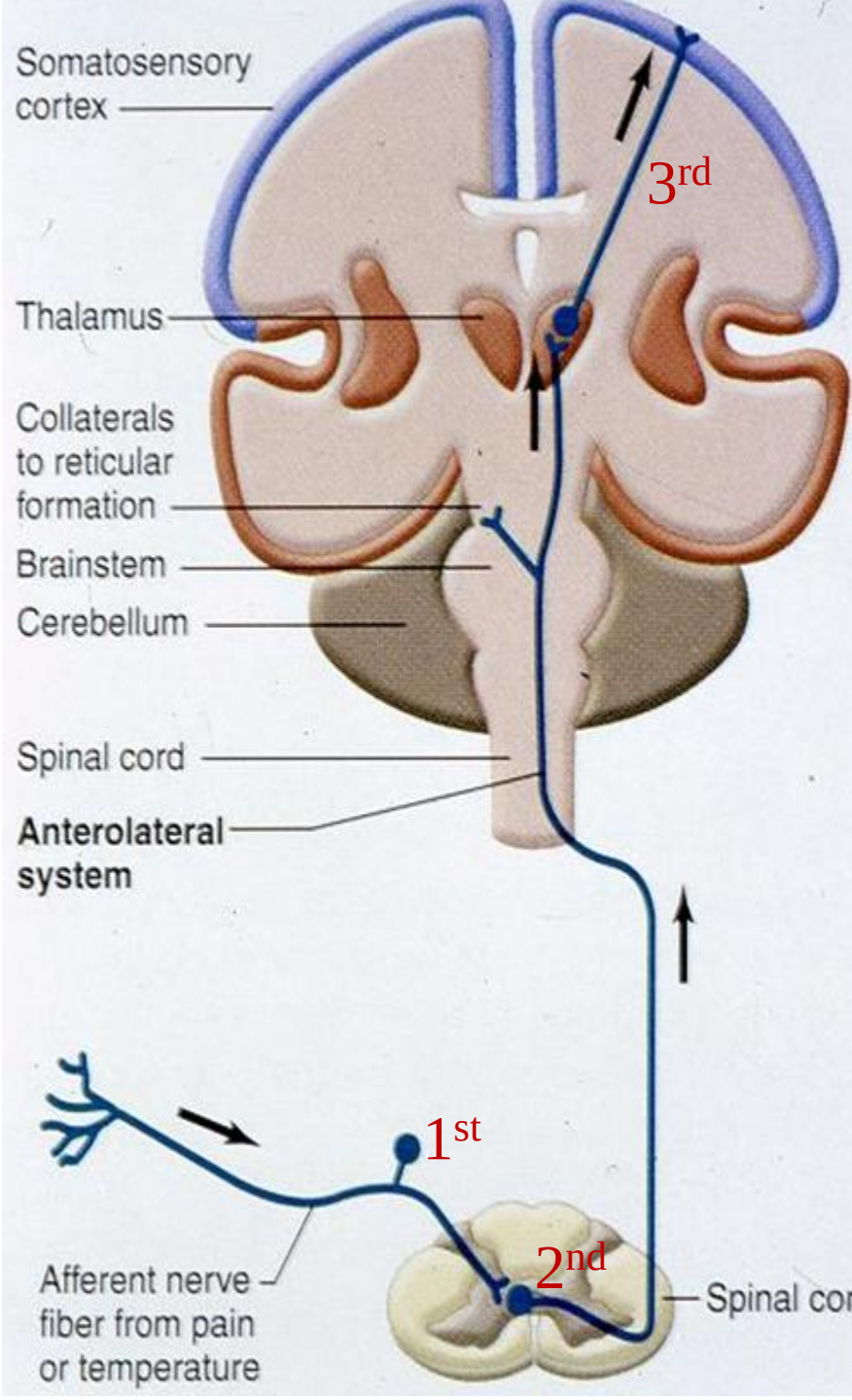


- ***Second order neurons***

  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.



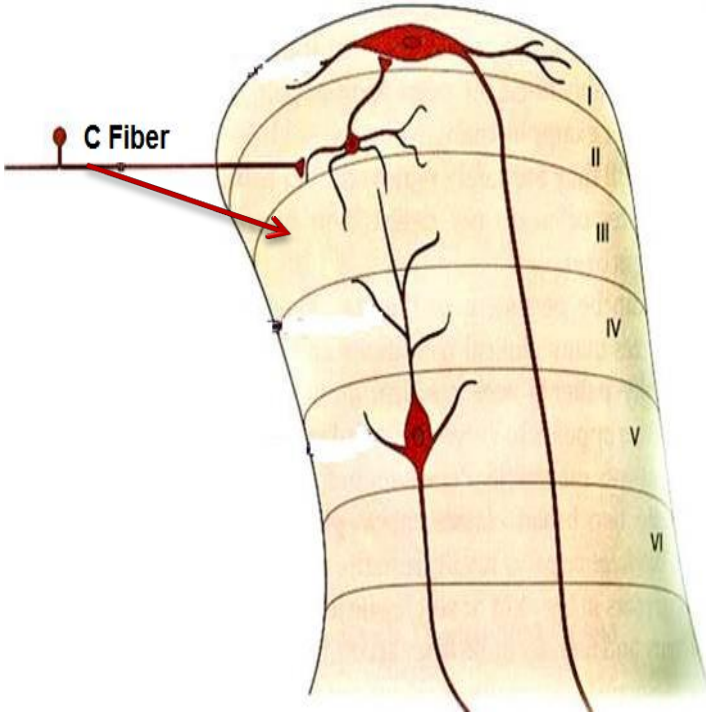
B) The paleospinothalamic pathway:

This transmit slow pain sensation.

- ***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(substantia gelatinosa).



○ Second order neurons

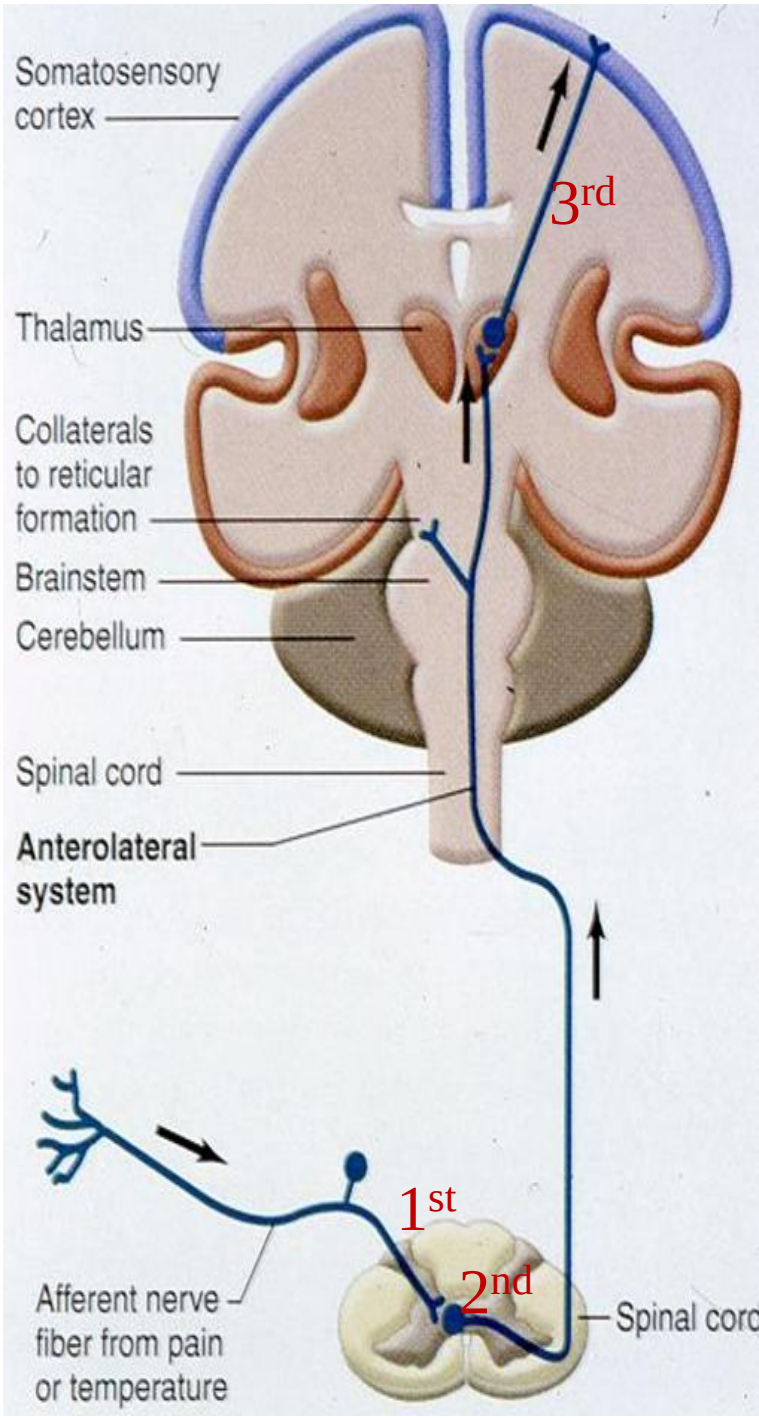
They start at SGR, cross to opposite side in front of central canal, ascend in lateral column of SC & terminate at:-

- *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.

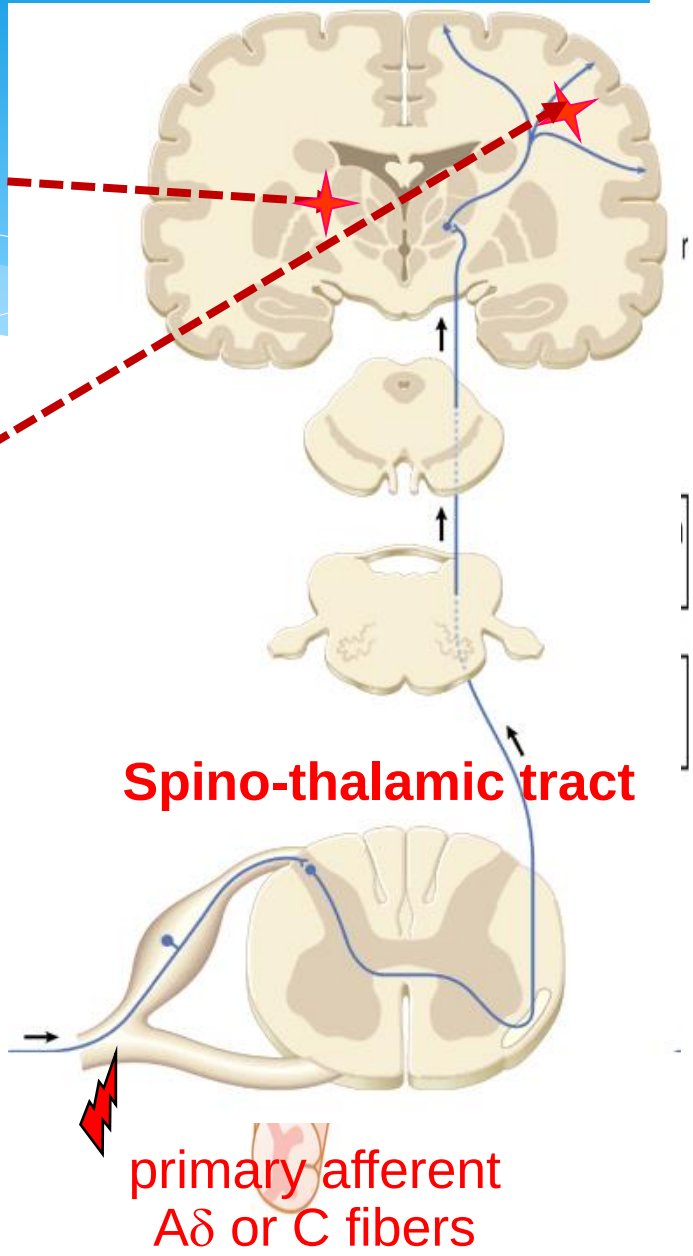
○ Third order neurons

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



Role of thalamus & cerebral cortex in pain perception

- *Full perception of pain occurs when signals enter RF of brain stem, thalamus & 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.*

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