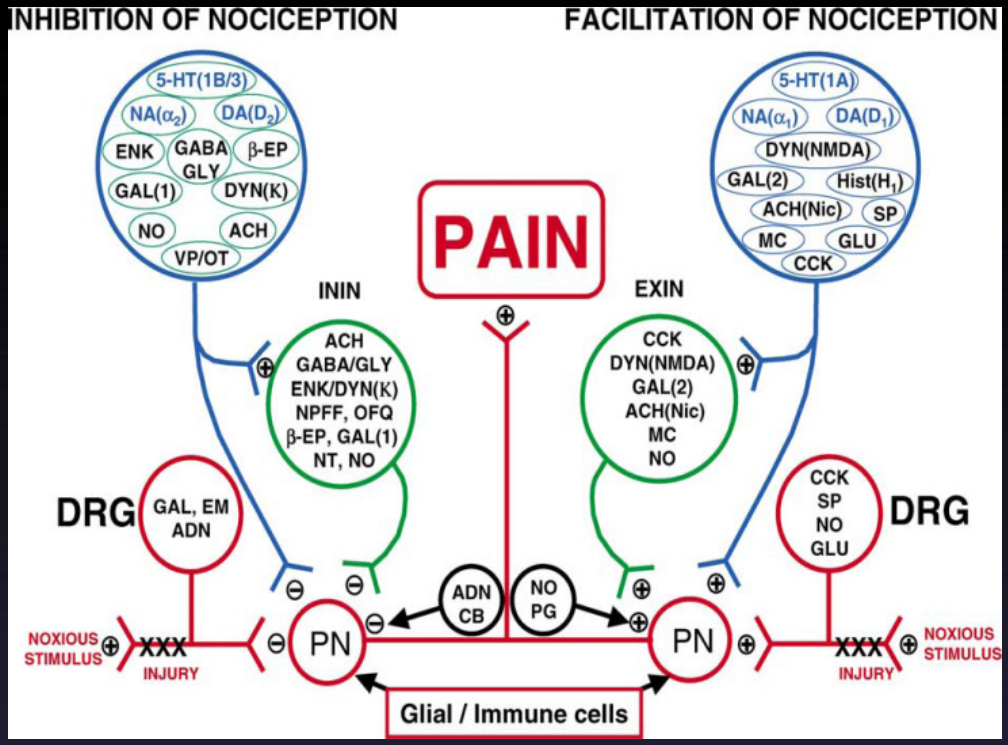
PHYSIOLOGY OF PAIN



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Objectives

At the end of this lecture you should be able to describe:

- **Differentiate between pain & nociception**
- **Describe the types of nerve fibres and receptor types that mediate pain**
- **Describe different types of pain and pain pathways**
- **Describe the role of thalamus and cerebral cortex in pain perception**

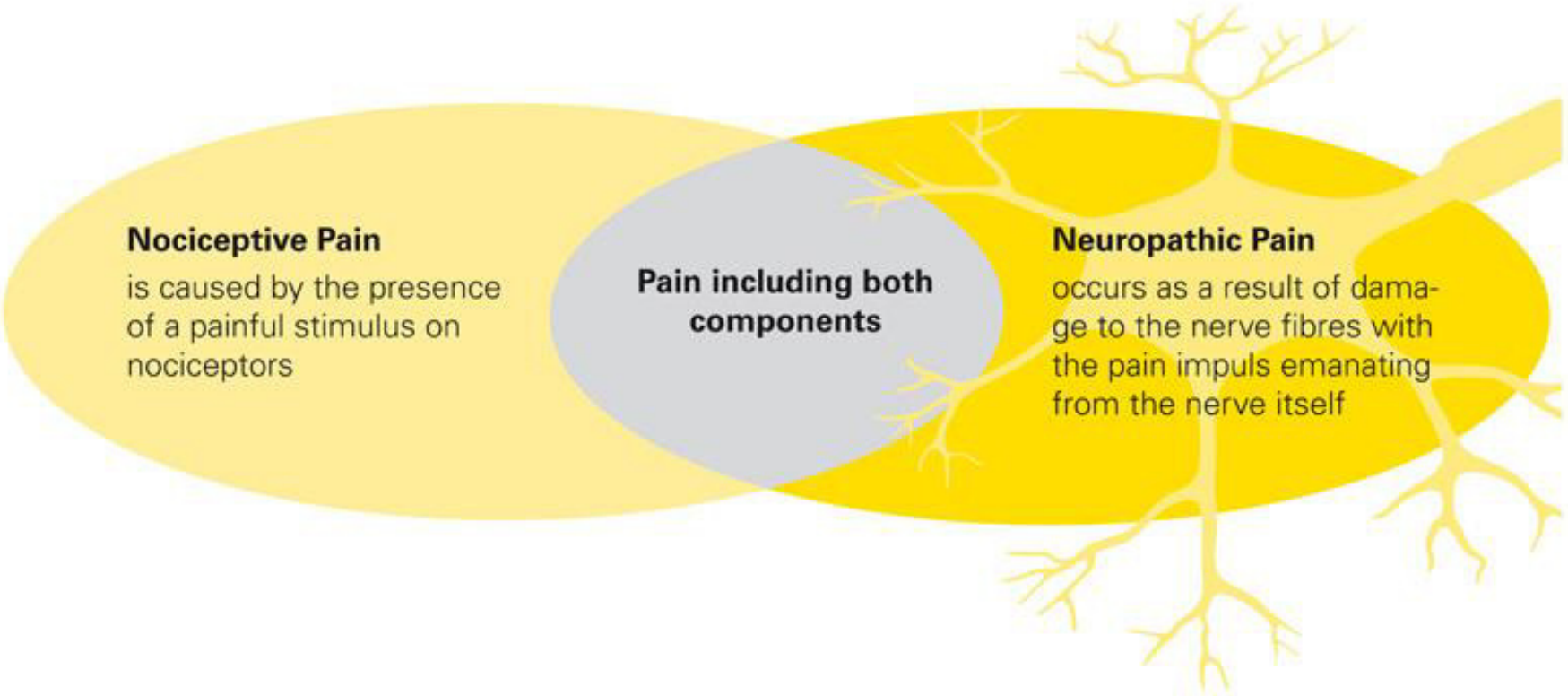
Pain & Nociception

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

International association for the study of pain (IASP)


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

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,

- 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

Pain is perceived at both the cortical & thalamic levels.

CLASSIFICATION OF PAIN

1. **Fast pain**
   - It is felt within 0.1 sec. after stimulation.
     - e.g. pricking, cut with knife.
2. **slow pain**
   - Felt in 1 sec. or more following painful stimulus.
   - It is associated with tissue damage & can be reffered to as burning pain, aching pain or chronic pain

The noxious stimuli activates 10-20% of the A-delta fibers and 50-80% of the C-fibers.

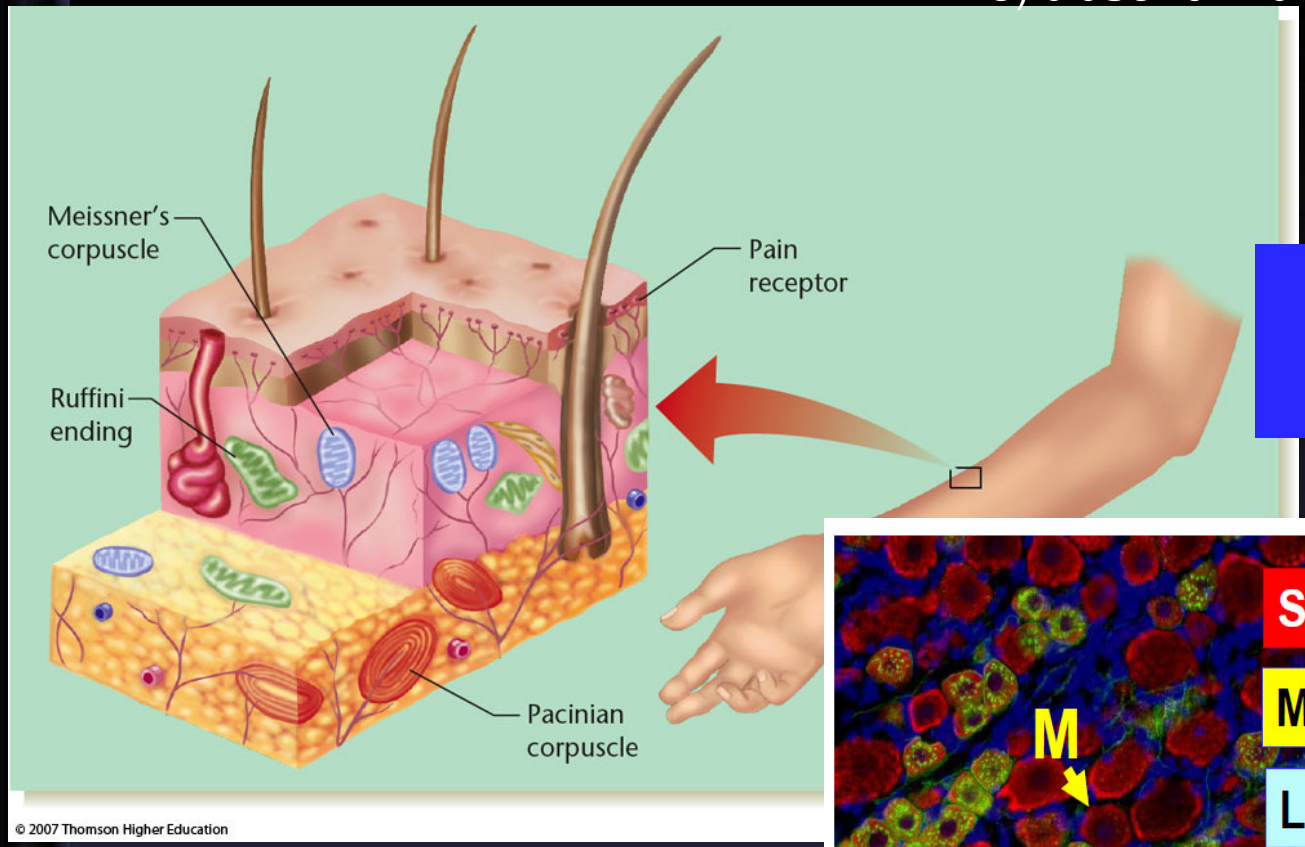
Pain receptors are Free nerve endings (Nociceptors)

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

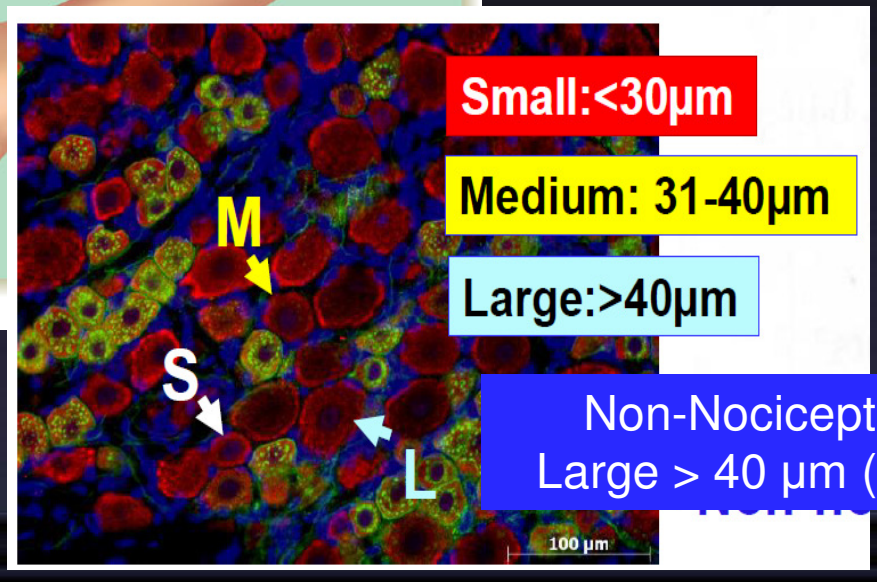
- **Pain receptors do not adapt at all or very slowly.**
- They are found in largest no. & density in skin, periostium joint surface, arterial wall & duramatar.
- pain receptors are activated by 3 types of stimuli;
  1. **Mechanical** - they elicit fast pain.
  2. **Thermal** - they elicit also fast pain.
  3. **Chemical** - they produce slow pain.

Distribution of Pain Receptors (Nociceptors)

1) **Widespread** in **superficial** layers of **skin**
2) **Fewer** in **deep tissue**
3) **absent** in **brain** tissue

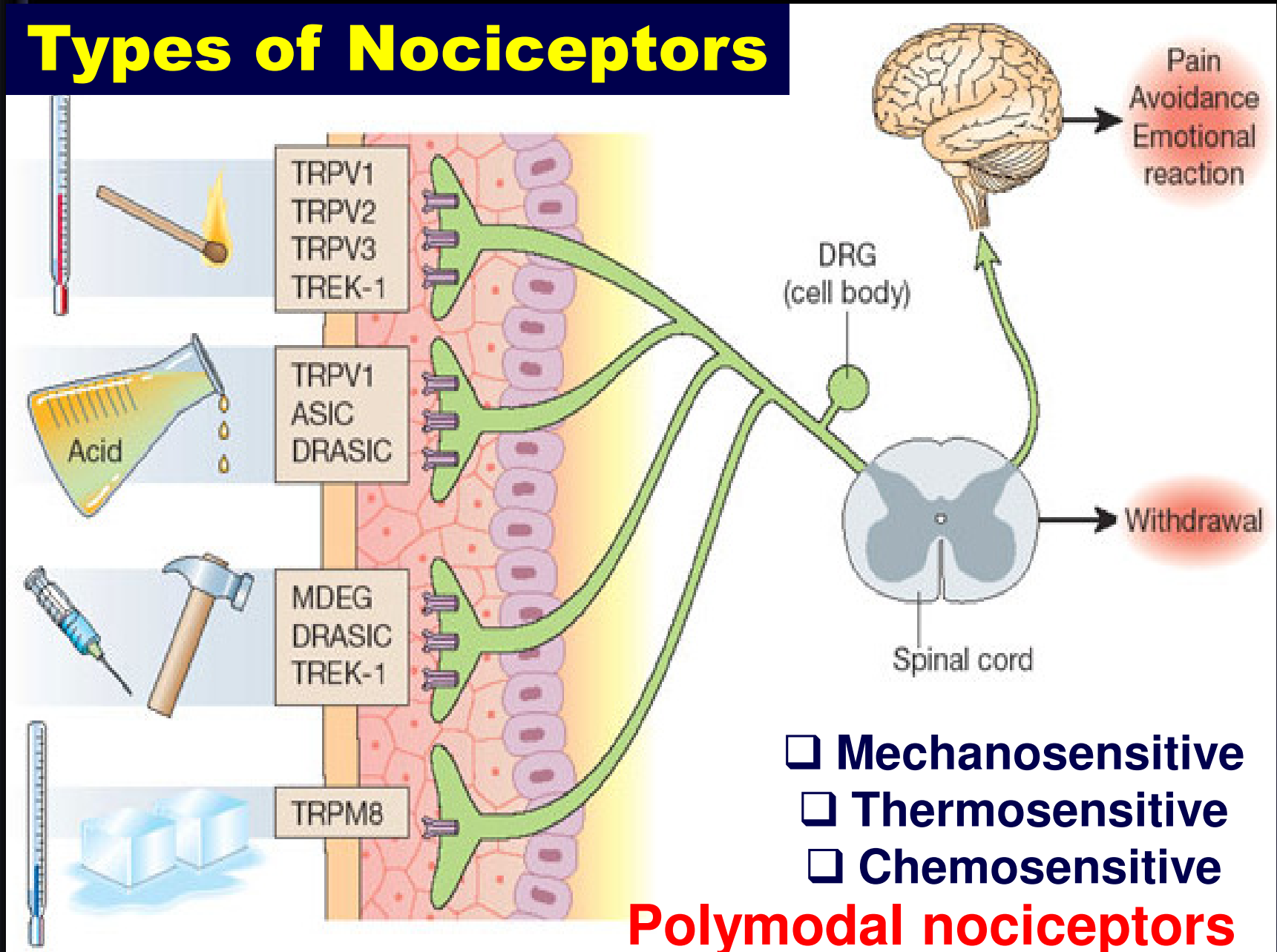


Nociceptors
Small < 30 µm (30%)
Medium31-40 µm (30%)



Non-Nociceptors
Large > 40 µm (40%)

Types of Nociceptors



- ❑ Mechanosensitive
- ❑ Thermosensitive
- ❑ Chemosensitive

Polymodal nociceptors

Types of Nociceptors

- **Mechanical nociceptors** respond to strong pressure (eg, from a sharp object).
- **Thermal nociceptors** are activated by skin temperatures above 42℃ or by severe cold.
- **Chemically sensitive nociceptors** respond to various chemicals like bradykinin, histamine, high acidity, and environmental irritants .
- **Polymodal nociceptors** respond to combinations of these stimuli.

THERMORECEPTORS

Innocuous **cold receptors** or **cool receptors** are on dendritic endings of Aδ fibers and C fibers, whereas innocuous **warmth receptors** are on C fibers. Mapping experiments show that the skin has discrete cold-sensitive and heat-sensitive spots. There are 4–10 times as many cold-sensitive as heat-sensitive spots.

The receptor that is activated by moderate cold is **TRPM8.** The M refers to **menthol,** the ingredient in mint that gives it its "cool" taste. **TRPV4** receptors are activated by warm temperatures up to 34°C; **TRPV3** receptors respond to slightly higher temperatures of 35–39°C.

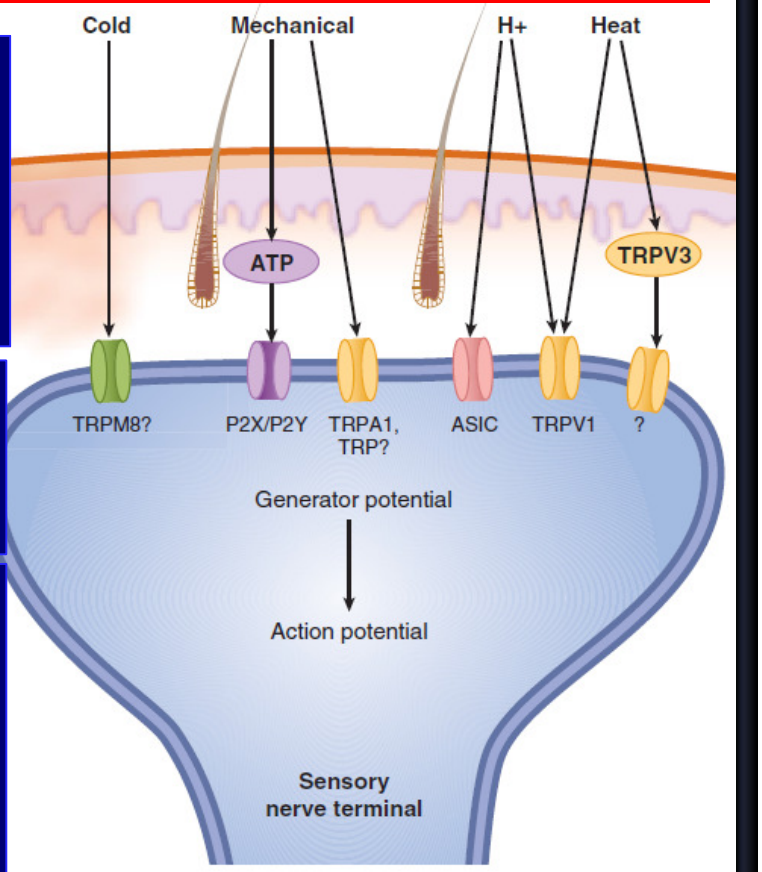
There are a variety of receptors located on the endings of nociceptive sensory nerves that respond to noxious thermal, mechanical, or chemical stimuli

Many of these are part of a family of nonselective cation channels called **transient receptor potential** (TRP) channels.

TRPV1: receptors (the V refers to a group of chemicals called **vanilloids**) that are activated by intense heat, acids, and chemicals such as **capsaicin** (the active principle of hot peppers and an example of a vanilloid).

TRPA1: Noxious mechanical, cold, and chemical stimuli may activate **TRPA1** receptors (A, for **ankyrin**) on sensory nerve terminals.

ASIC: Sensory nerve endings also have **acid sensing ion channel (ASIC) receptors** that are activated by pH changes within a physiological range and may be the dominant receptors mediating acid-induced pain.

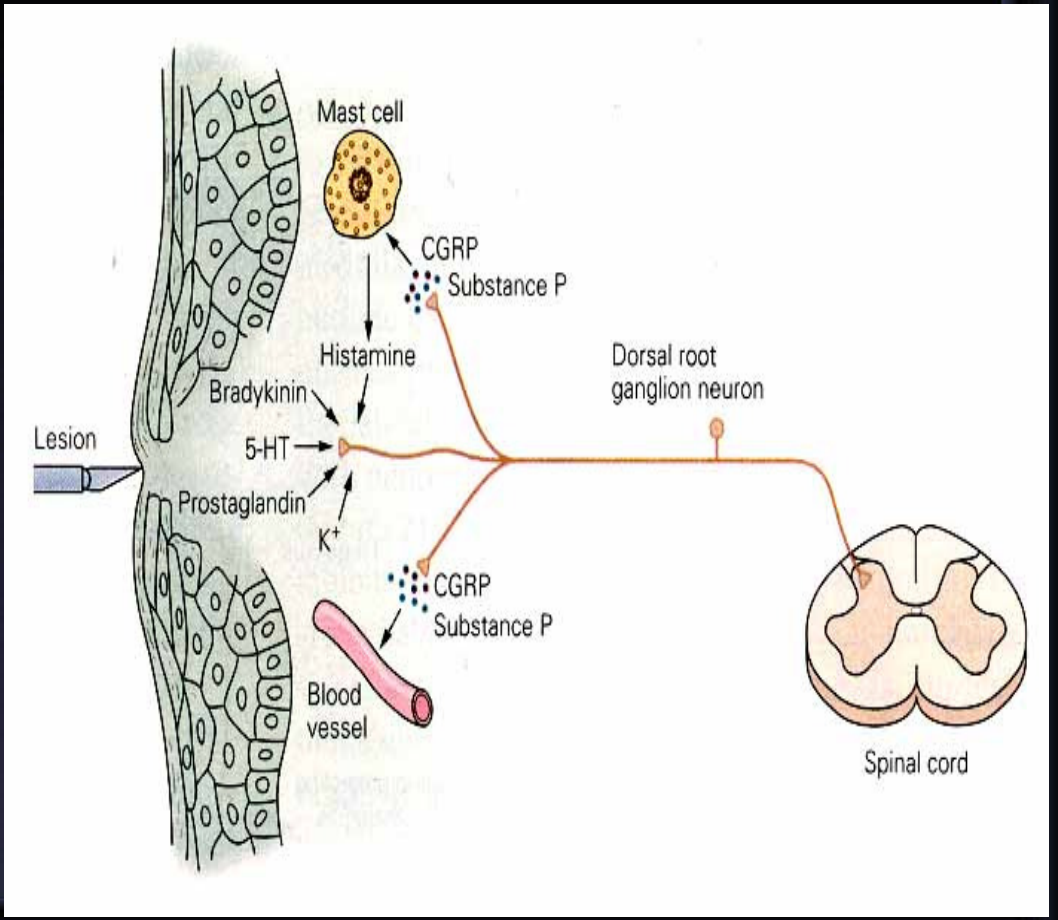


P2X & P2Y: For example, nociceptive mechanical stimuli cause the release of ATP that acts on **purinergic receptors** (eg, P2X, an ionotropic receptor and P2Y, a G protein-coupled receptor).

Nociceptors Stimulation

Pain receptors are depolarized either directly or through the production of pain producing substances from damaged tissues or as a result of inflammation

- Bradykinin, serotonin, Histamine, K^+ ion, Acids, proteolytic enzymes. calcitonin gene-related peptide (CGRP), interleukins, PGs, Ach,
- PGs & substance – P enhance the sensitivity of pain receptors.



Chemicals released with 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

Characteristics of Pain

- **FAST PAIN (epicritic Pain)**

- Occurs **FIRST** upon stimulation of Mechanical and Thermal nociceptors
- Transmitted by **Aδ(delta)** fibers in the peripheral nerves & centrally by **Neospinothalamic Tract**
- Characteristics of Aδ fibers
  - Myelinated -
  - Diameter fine 2 - 5 µm
  - 12 - 30 m/sec. conduction velocity
  - Terminated at I and V layer
- Fast pain, rapid, pricking and well localized
- **Neurotransmitter - Glutamate**
- 20% pain conduction

Characteristics of Pain

SLOW PAIN

- Occurs **SECOND** upon stimulation of Polymodal receptors
- Chronic type of pain, transmitted by **C fibers peripherally** & centrally by **paleospinothalamic Tract**
- Characteristics of C fibers
  - Non-Myelinated
  - Diameter 0.4 – 1.2 µm
  - conduction velocity 0.5 - 2 m/s
  - Terminate in layer II and III of dorsal horn (substantia gelatinosa)
- Slow, diffuse, dull, aching
- **Neurotransmitter - P-Substance**
- 80% of pain conduction

Neospinothalamic Tract for Fast Pain. terminate mainly in lamina I (lamina marginalis) of the dorsal horns

Paleo**spinothalamic** almost entirely in laminae II and III of the dorsal horns, which together are called the *substantia gelatinosa*

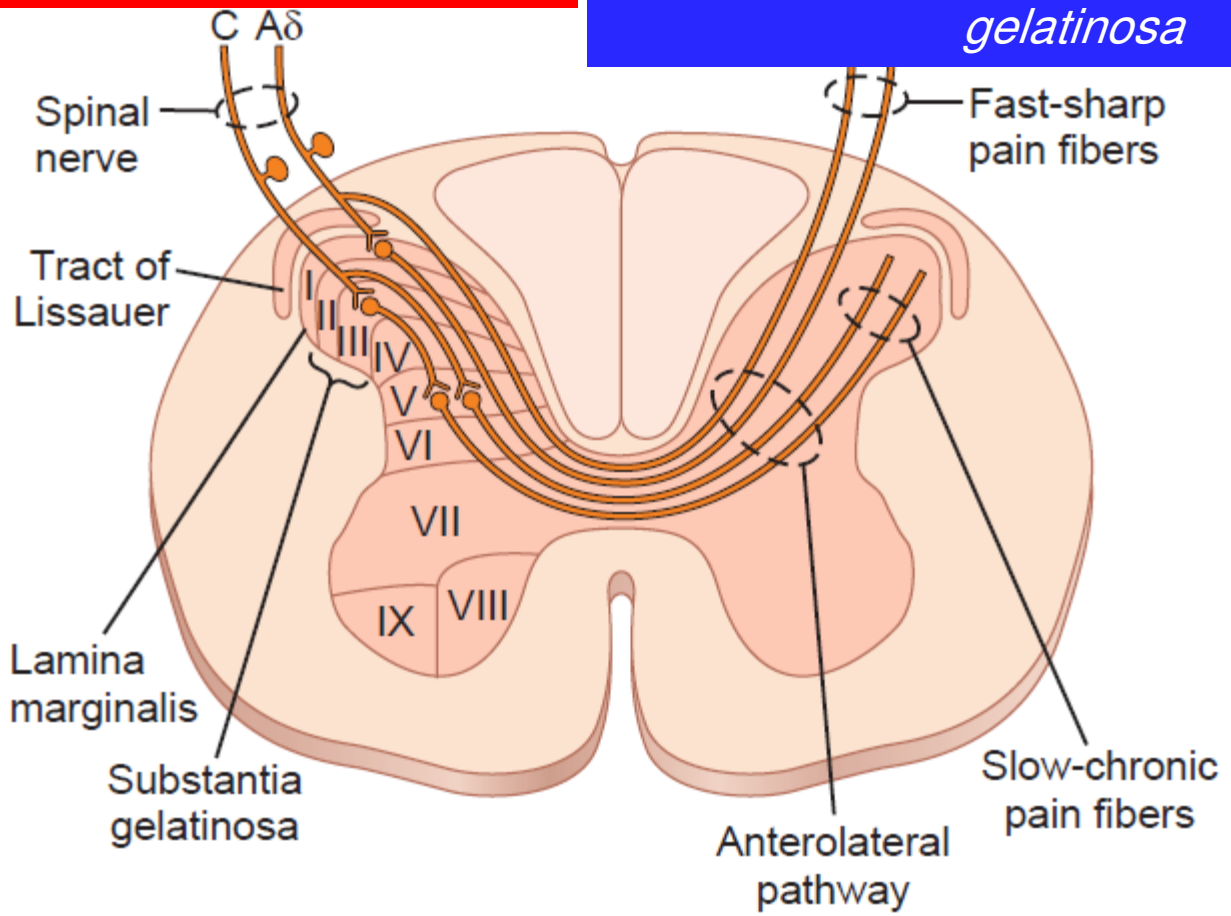


Figure 49-2. Transmission of both "fast-sharp" and "slow-chronic" pain signals into and through the spinal cord on their way to the brain. Aδ fibers transmit fast-sharp pain, and C fibers transmit slow-chronic pain.

Dual Pathways for Transmission of Pain Signals into the Central Nervous System

Neospinothalamic Tract

- Most pass all the way to the thalamus without interruption
- Rest to basal areas of the brain & somatosensory cortex

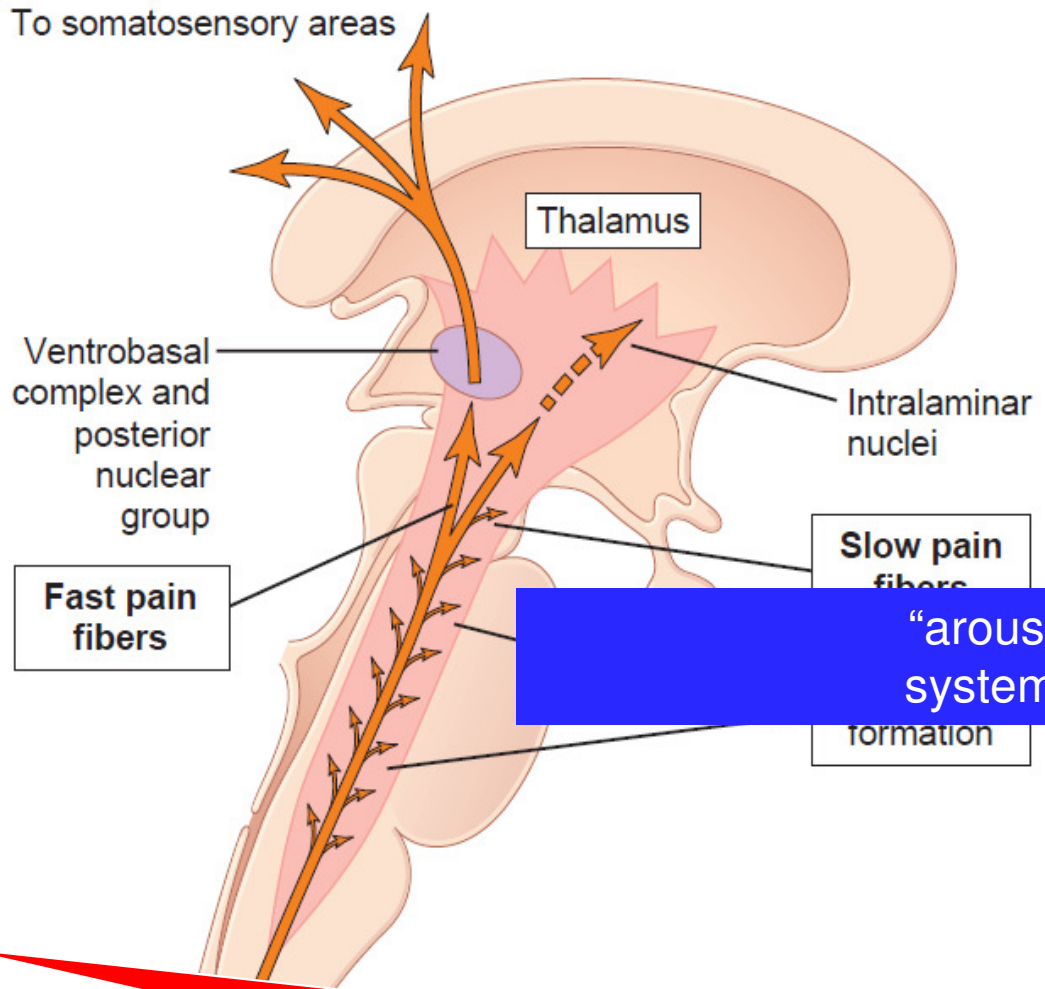
Paleospinothalamic Tract

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 for feeling the suffering types of pain

(Poor Localization)



"AROUSAL SYSTEM"
Reticular areas of the brain stem and in the intralaminar nuclei of the thalamus

Figure 49-3. Transmission of pain signals into the brain stem, thalamus, and cerebral cortex by way of the *fast pricking pain pathway* and the *slow burning pain pathway.*

Silent Nociceptors.

- In the skin and deep tissues there are additional nociceptors called "silent" or "sleep" nociceptors.
- These receptors are normally unresponsive to noxious mechanical stimulation, but become “awakened” (responsive) to mechanical stimulation during inflammation and after tissue injury. One possible explanation of the "awakening" phenomenon is that continuous stimulation from the damaged tissue reduces the threshold of these nociceptors and causes them to begin to respond.
- This activation of silent nociceptors may contribute to the induction of hyperalgesia, central sensitization, and allodynia. Many visceral nociceptors are silent nociceptors.


THANKS