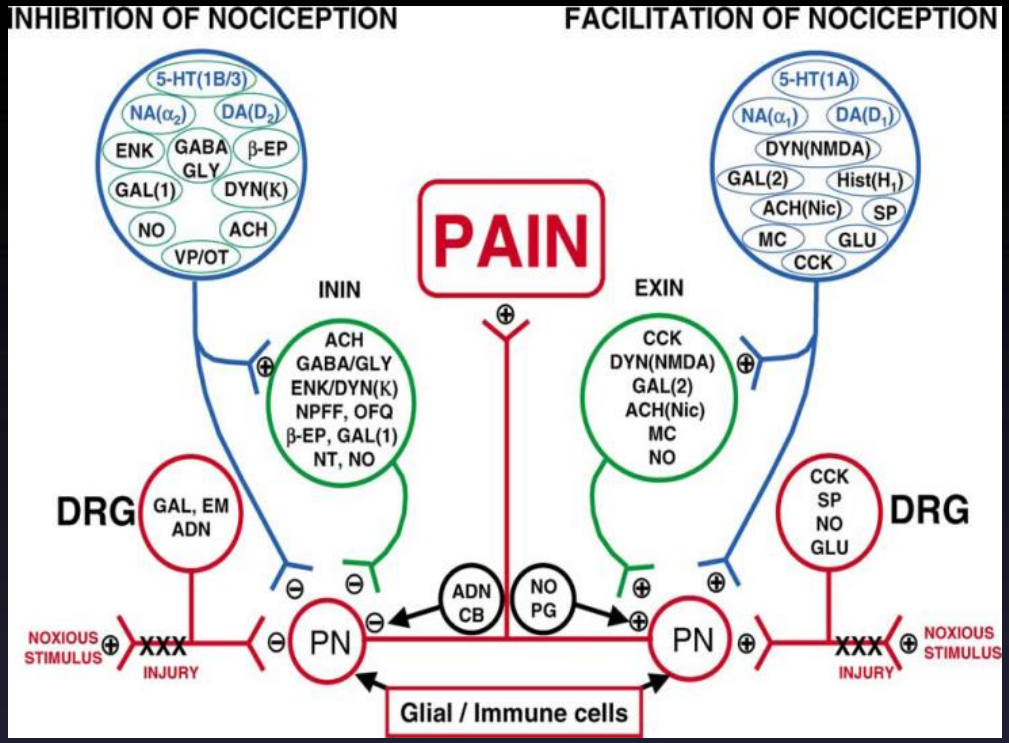
PHYSIOLOGY OF PAIN



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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**

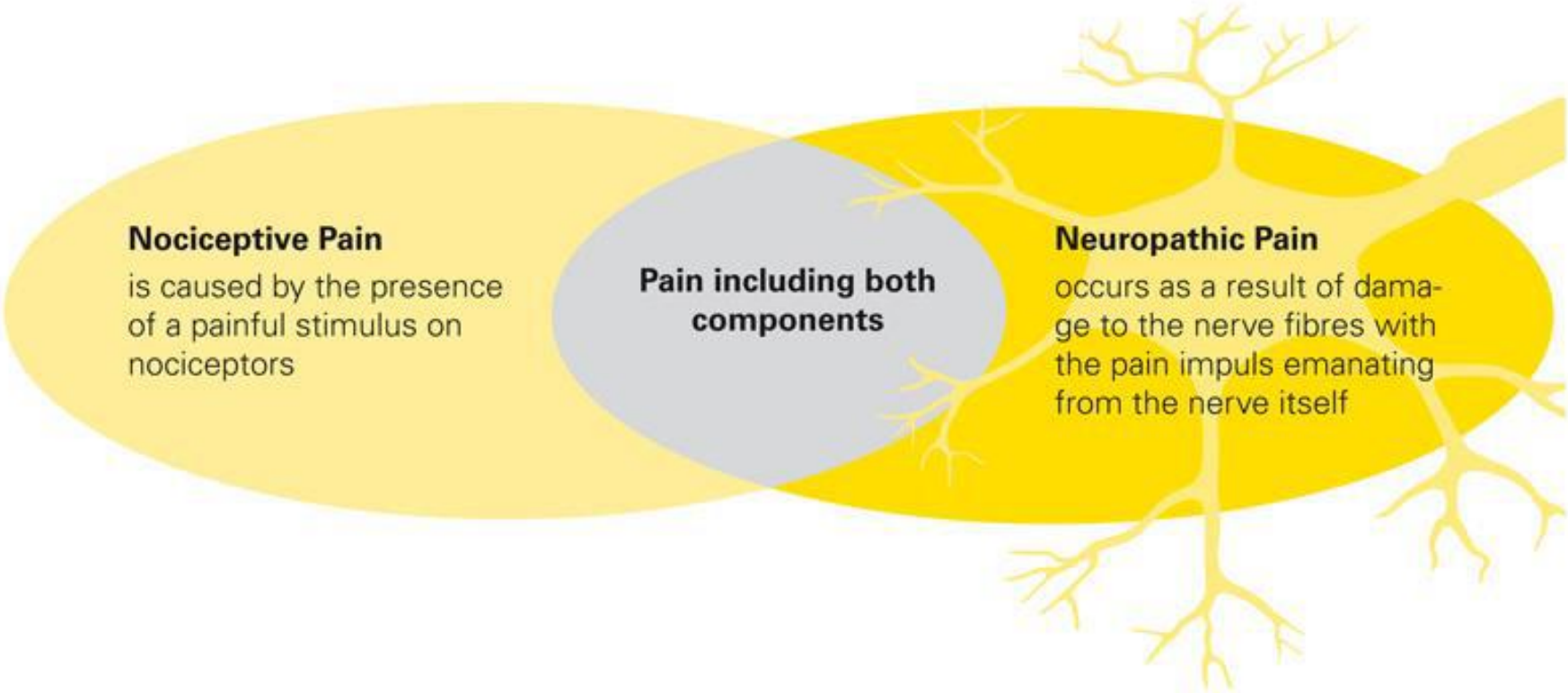
Pain & Nociception

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.

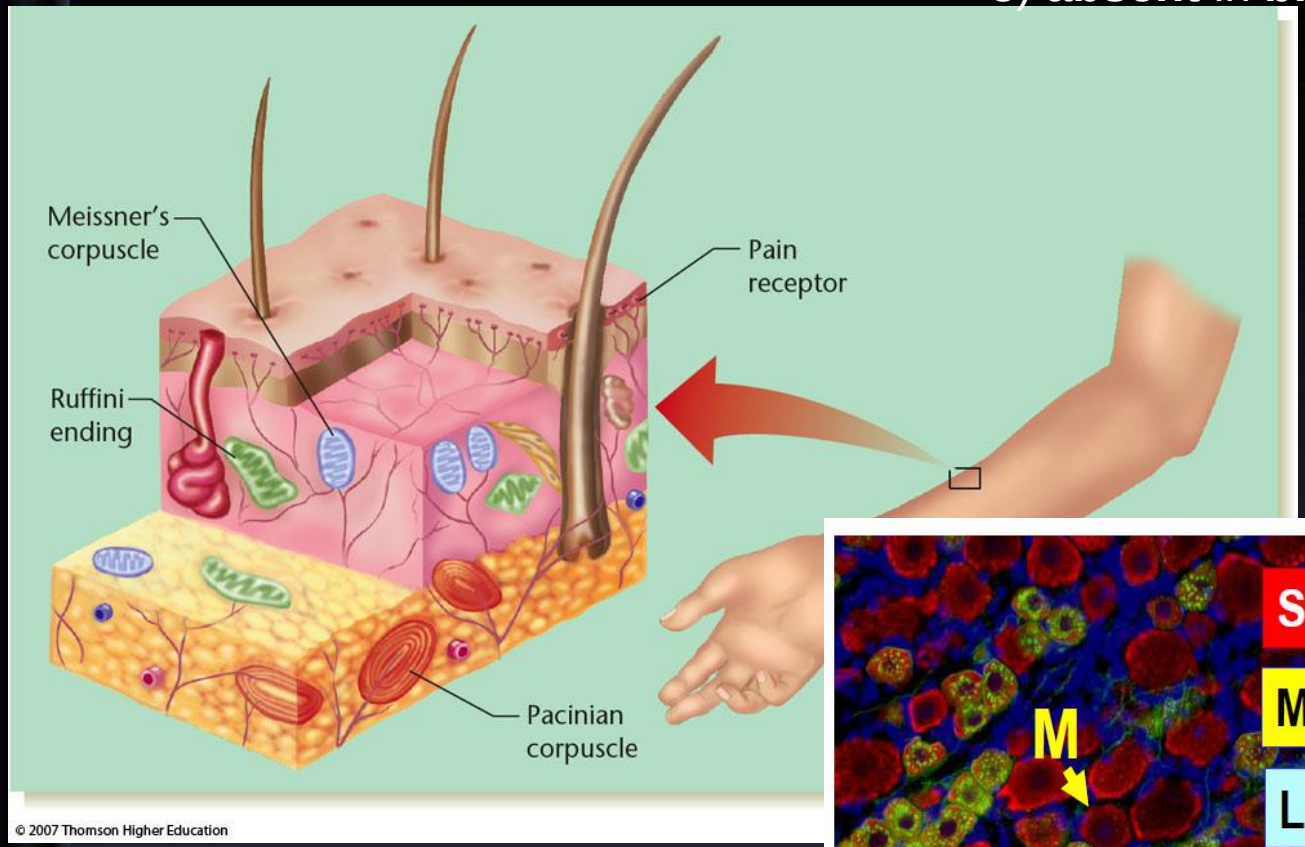
Pain receptors are Free nerve endings (Nociceptors)

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

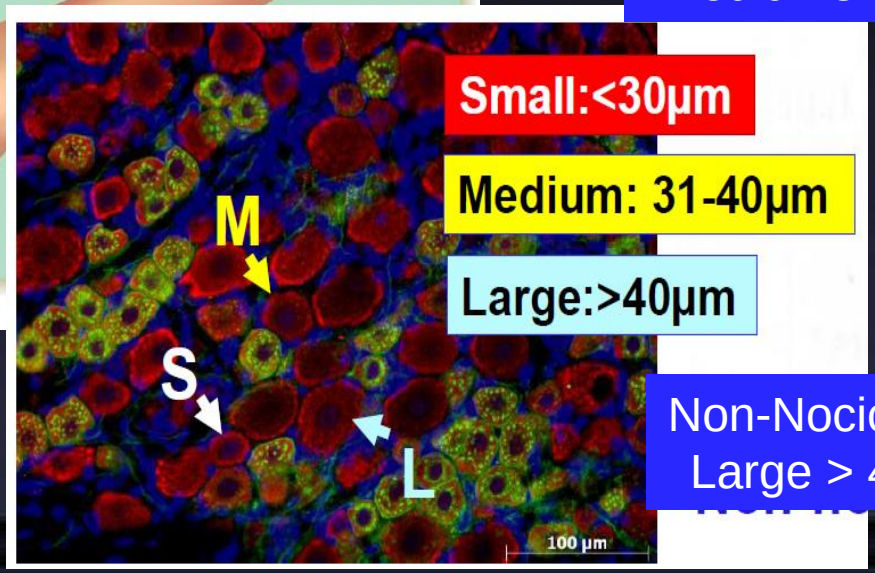
- **Pain receptors do not adapt at all or very slowly.**
- They are found in largest no. & density in skin, periostium joint surface, arterial wall & duramatar.
- pain receptors are activated by 3 types of stimuli;
  1. **Mechanical** - they elicit fast pain.
  2. **Thermal** - they elicit also fast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

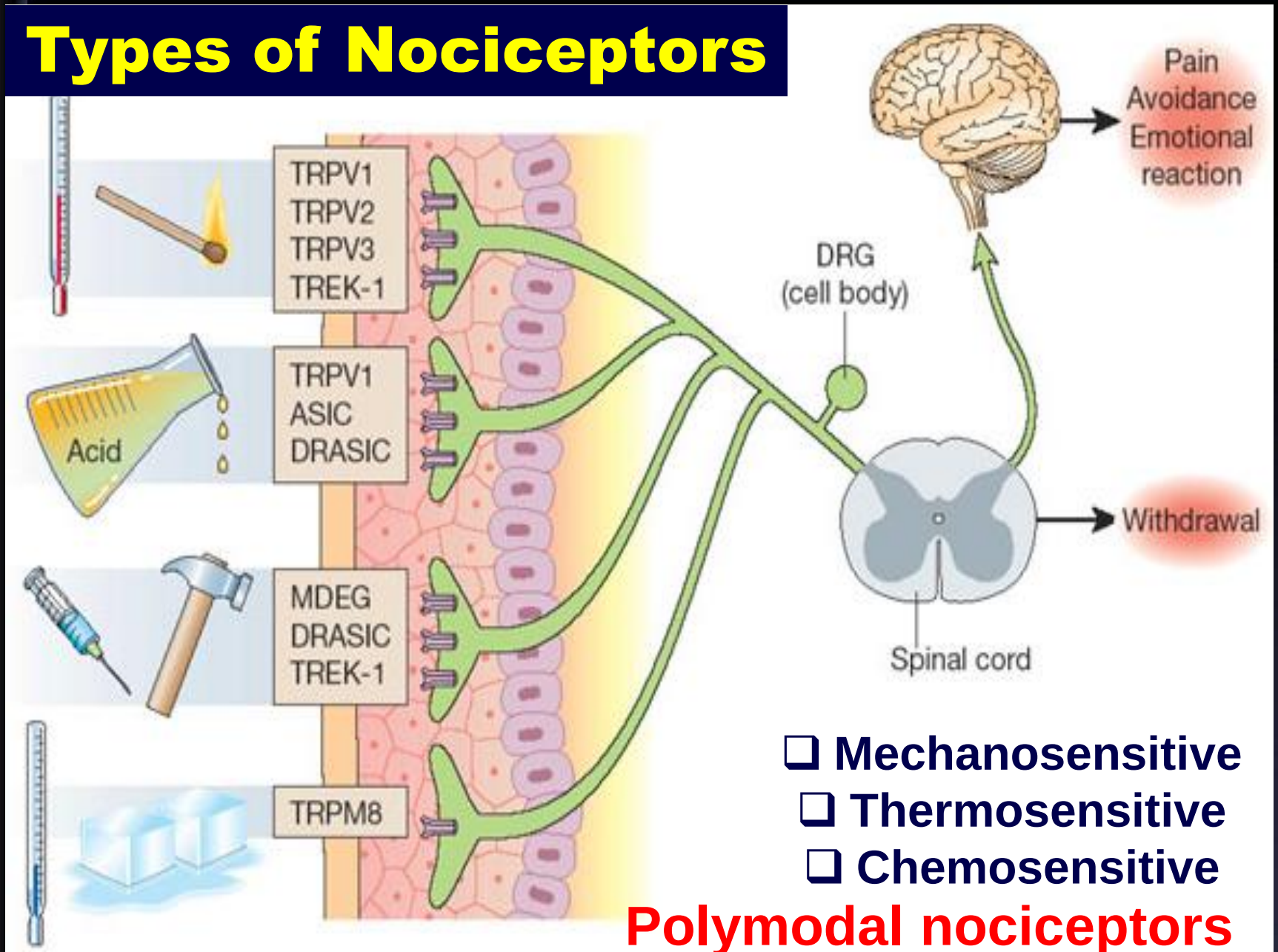


Nociceptors
Small < 30 µm
Medium31-40 µm



Non-Nociceptors
Large > 40 µm

Types of Nociceptors



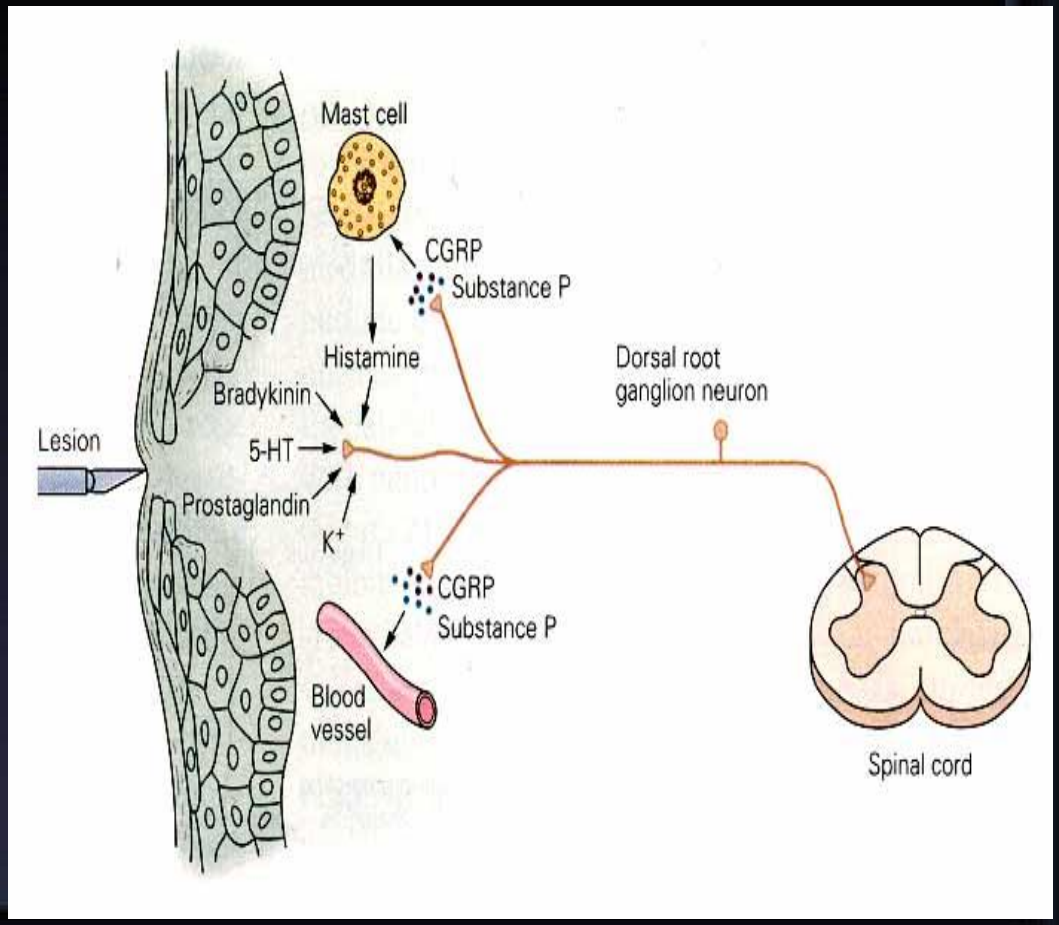
- ❑ Mechanosensitive
- ❑ Thermosensitive
- ❑ Chemosensitive

Polymodal nociceptors

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

- 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 Painlamina I (lamina marginalis)

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

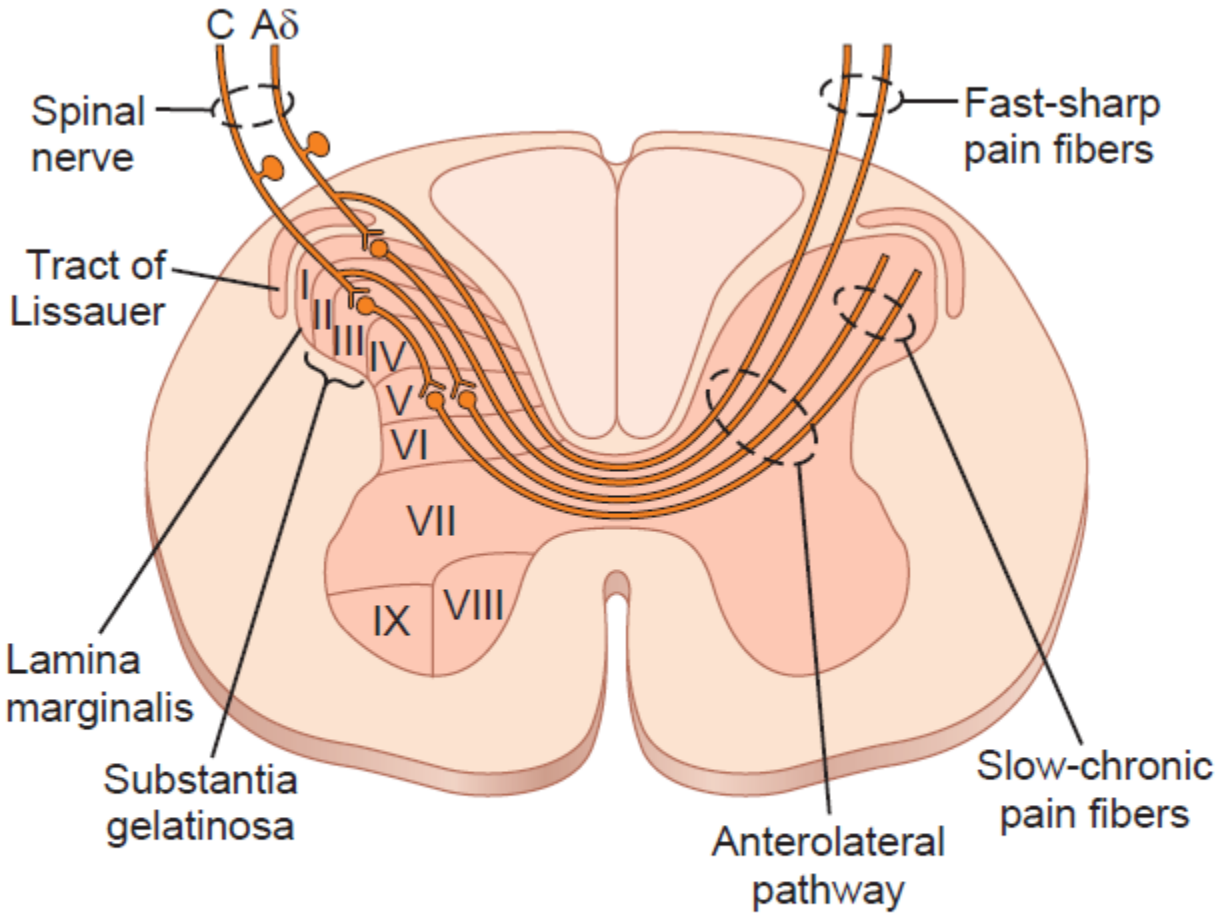


Figure 49-2. Transmission of both "fast-sharp" and "slow-chronic" pain signals into and through the spinal cord on their way to the brain. Aδ fibers transmit fast-sharp pain, and C fibers transmit slow-chronic pain.

Pain Pathways

- **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.**

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

Neospinothalamic Tract

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 feeling the suffering types of pain

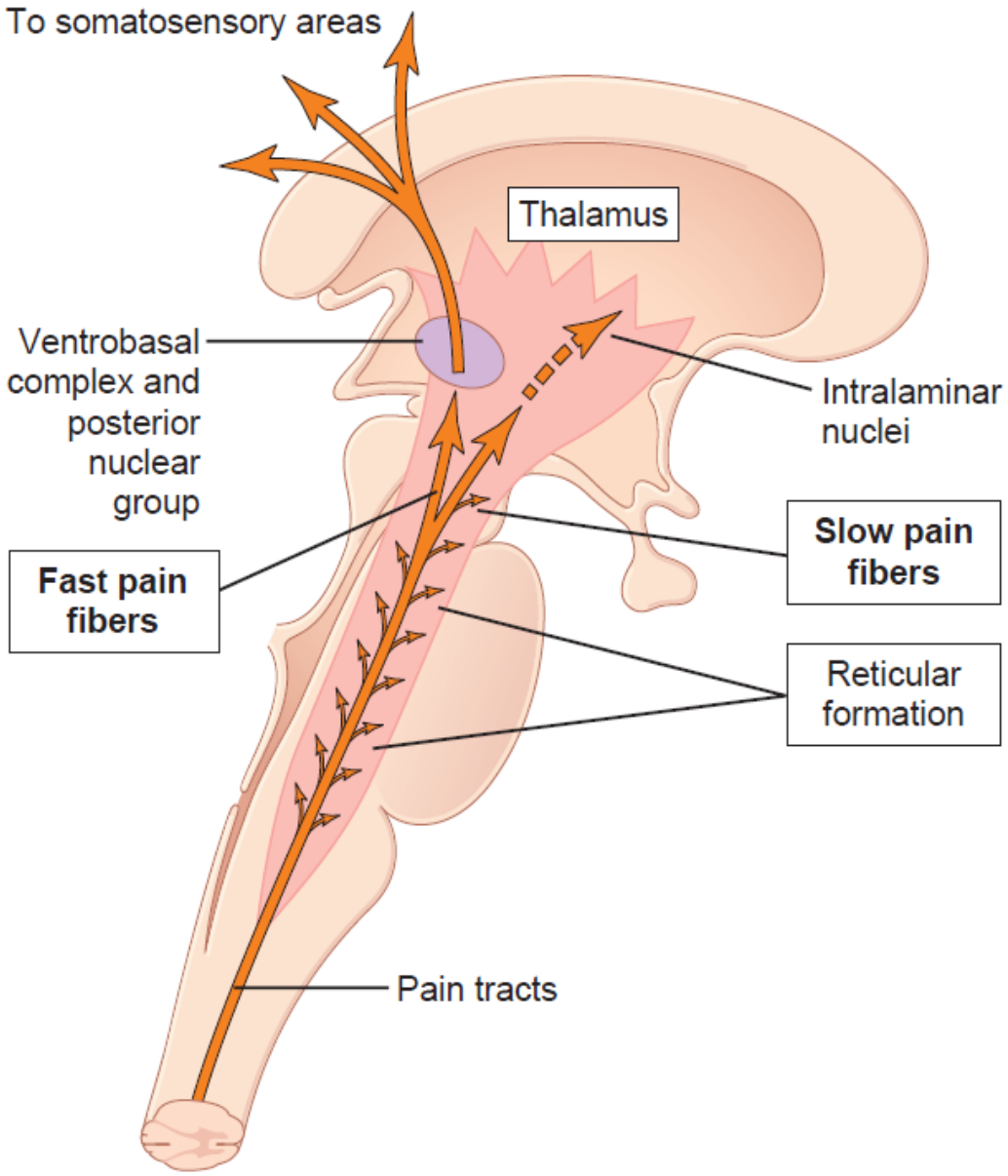
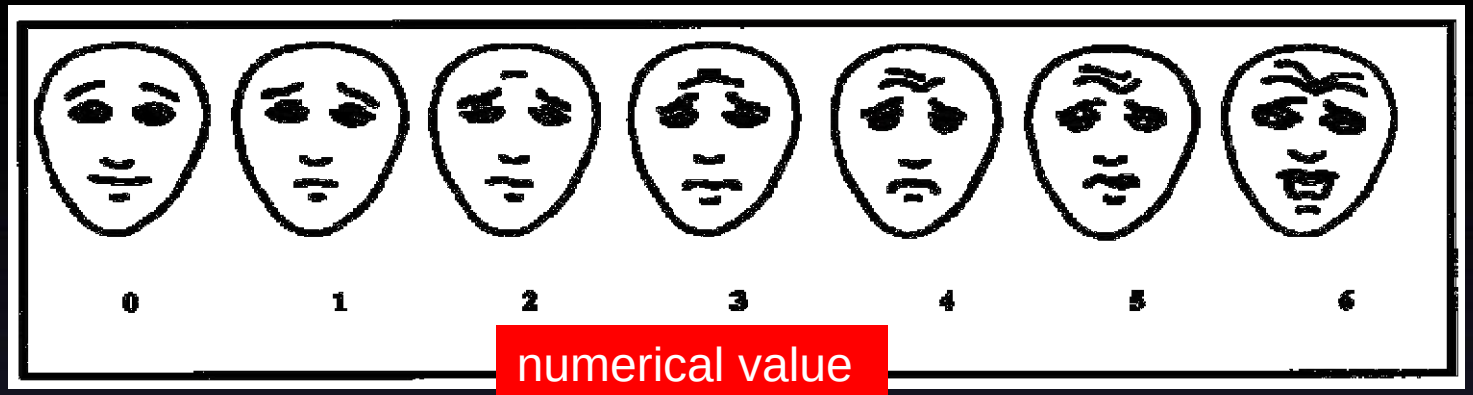
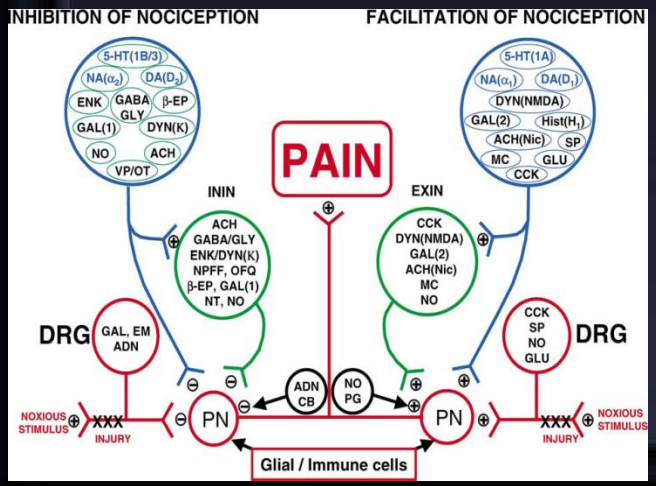


Figure 49-3. Transmission of pain signals into the brain stem, thalamus, and cerebral cortex by way of the *fast pricking pain pathway* and the *slow burning pain pathway.*


THANKS

PAIN MODULATION





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OBJECTIVES

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

- **Nociceptors, Referred Pain, radiating pain**
- **“Gating” of Pain**
- **Pain Suppression (“Analgesia”) System in the Brain and Spinal Cord**
- **Transcutaneous Electrical Nerve Stimulation (TENS)**
- **Transcranial Direct Current Stimulation (tDCS)**
- **Applied aspects of pain**

Nociceptive & Neuropathic Pain

- **Nociceptive pain** is detected by specialized transducers connected to A-delta and C-fibers (stimuli from somatic and visceral structures)

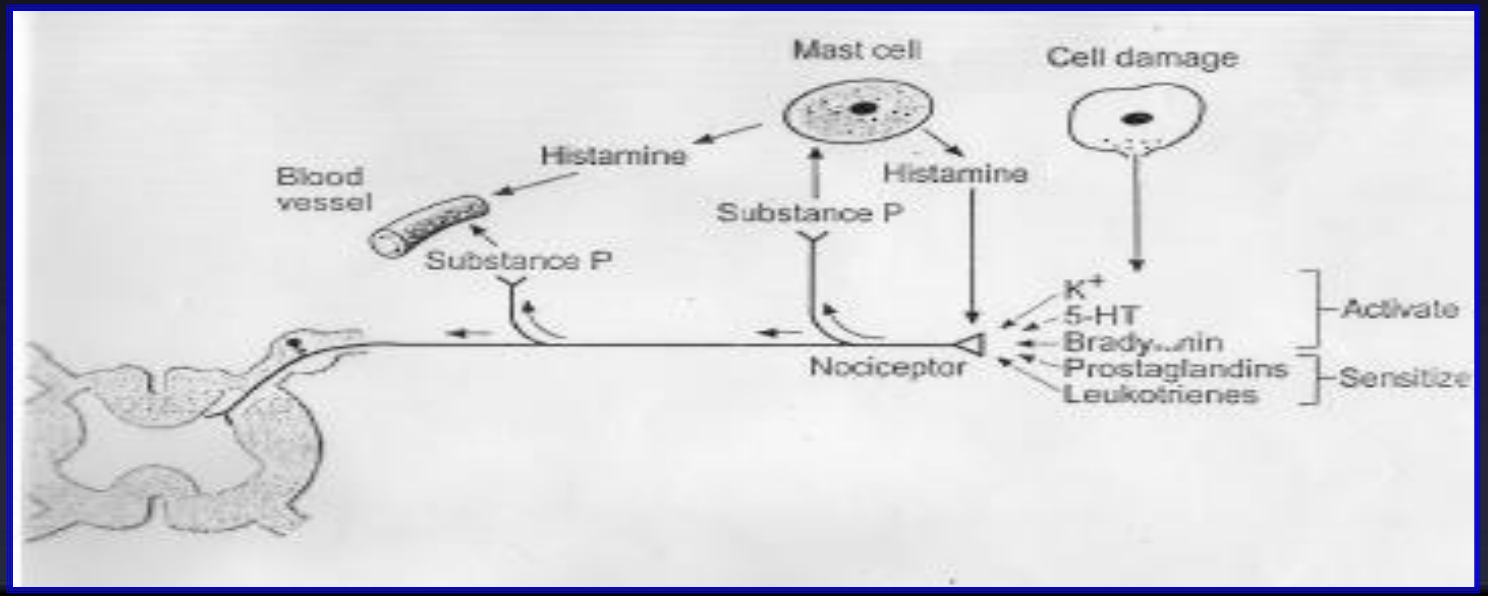
- **Neuropathic pain** damage to nerves (trigeminal neuralgia, postherpetic pain, diabetic neuropathy)

4 Basic Processes

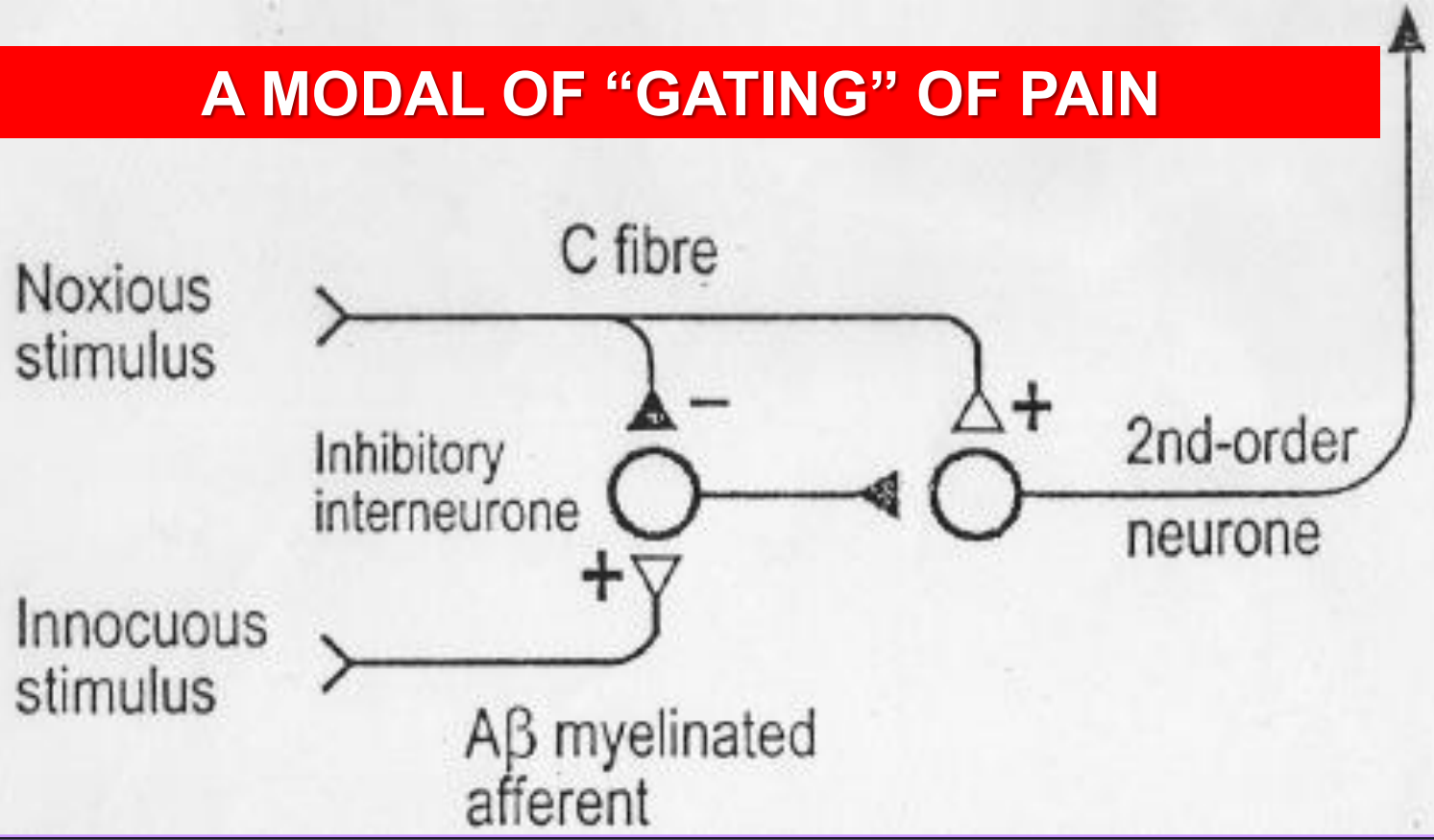
1. **Transduction**—nociceptors free nerve endings
2. **Transmission**
3. **Perception** of Pain-At cortical Level
4. **Modulation** of Pain, Changing or inhibiting pain impulses in the descending tract (brain→ spinal cord) [norepinephrine and serotonin]

Chemical agents that produce pain

- **Nociceptors are activated by**: Bradykinin, serotonin, Histamine, K^+ ion, Acids, acetyl choline, & proteolytic enzymes.
- **Nociceptors are sensitized by**: Prostaglandins & substance P

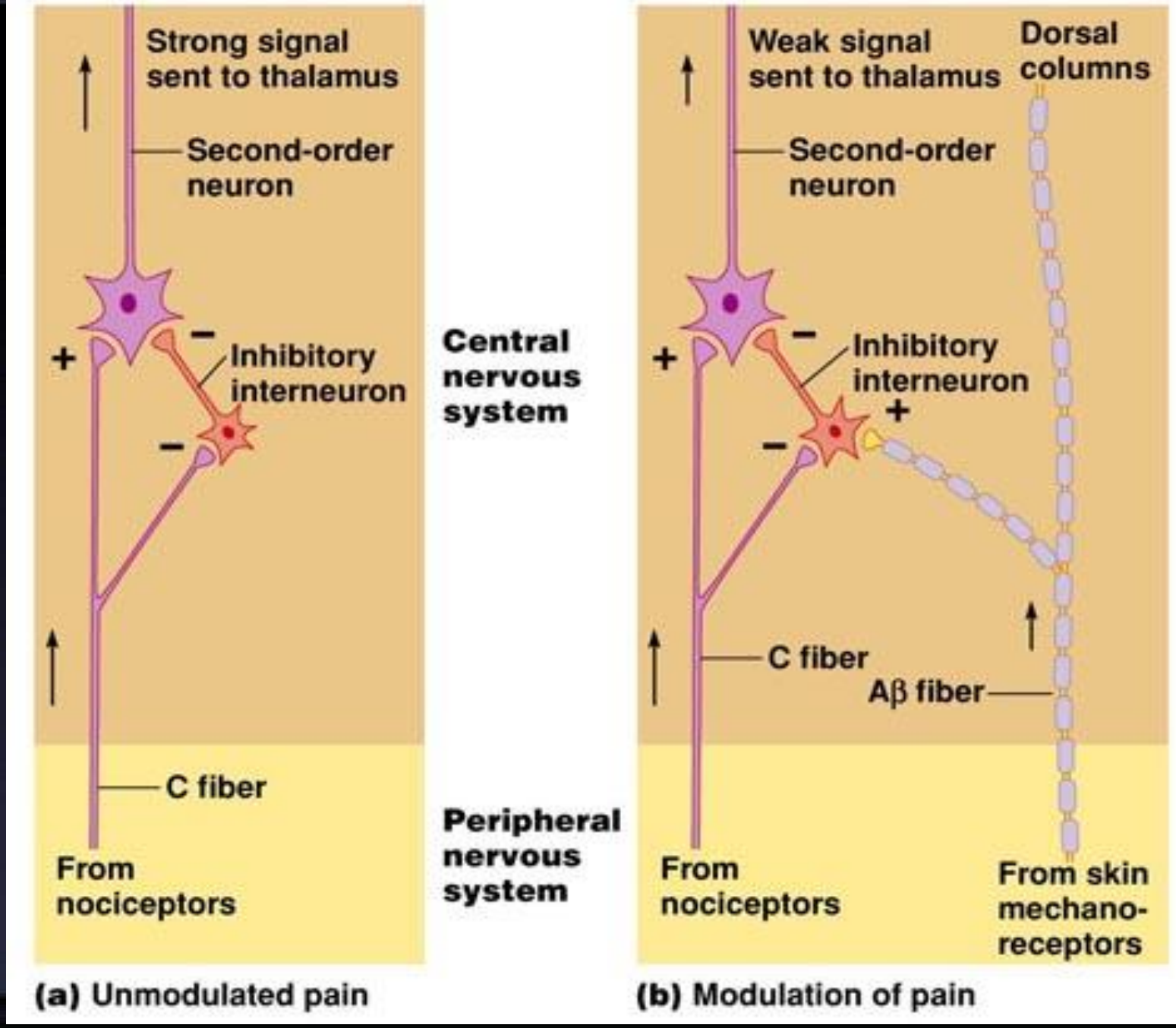


A MODAL OF "GATING" OF PAIN



Implies a non-painful stimulus can block the transmission of a noxious stimulus. Is based on the premise that the gate, located in the dorsal horn of the spinal cord, modulates the afferent nerve impulses.

1. **A-Delta fibres (sharp pain)**
2. **C fibres (dull pain)**
3. **A-Beta fibres that carry messages of light touch**


Strong signal sent to thalamus
Second-order neuron
Inhibitory interneuron
C fiber
From nociceptors
Central nervous system
Peripheral nervous system
Weak signal sent to thalamus
Dorsal columns
Second-order neuron
Inhibitory interneuron
C fiber
Aβ fiber
From nociceptors
From skin mechano-receptors
(a) Unmodulated pain
(b) Modulation of pain

Conditions that open or close the gate

	Conditions that open the gate	Conditions that close the gate
Physical conditions	Extent of the injury	Medication
	Inappropriate activity level	Counterstimulation, eg massage
Emotional Conditions	Anxiety or worry	Positive emotions
	Tension	Relaxation
	Depression	Rest
Mental conditions	Focusing on the pain	Intense concentration or distraction
	Boredom	Involvement and interest in life activities

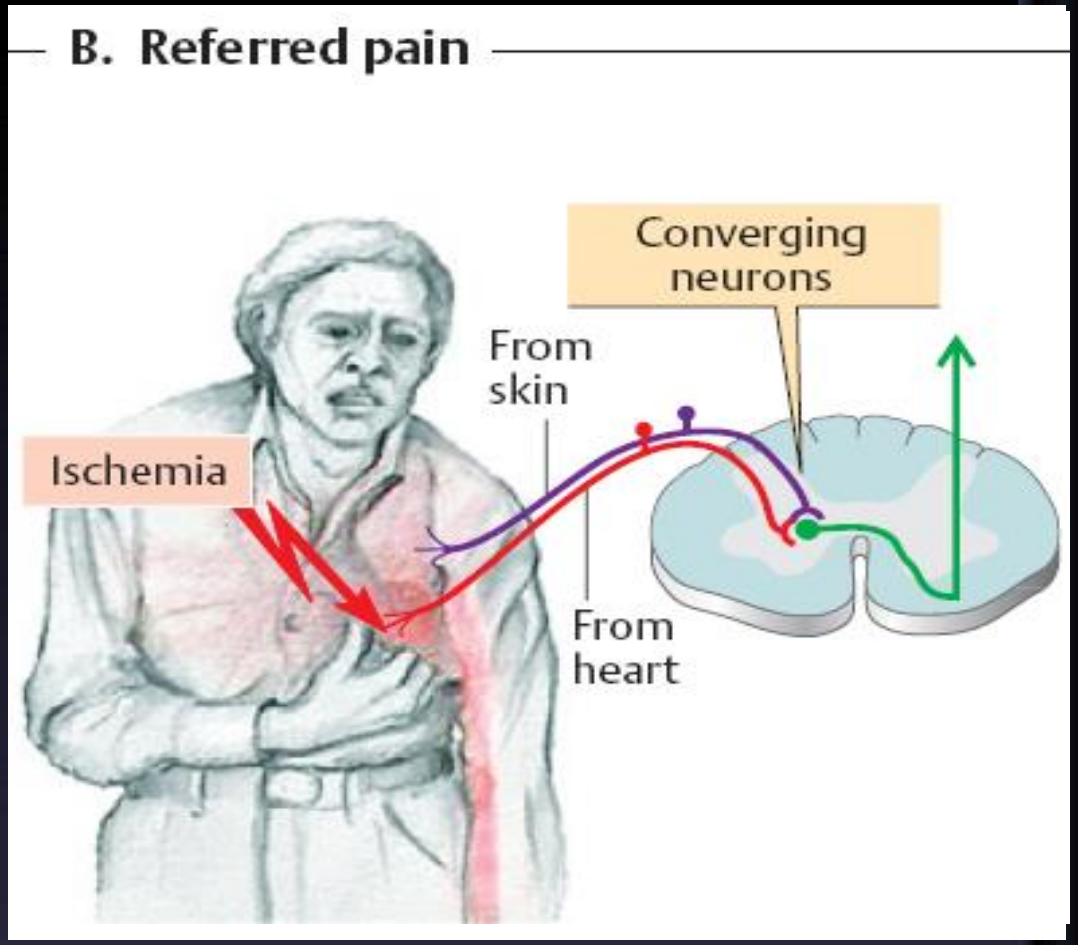
REFERRED PAIN

- Pain that is not felt in the diseased structure itself, but at another place in the body far away from the site of origin.
- Visceral and deep somatic pain are often referred, but superficial pain is not.
- Mechanism of referred pain
  - Convergence of peripheral & visceral pain on the same second order neuron that project to brain
  - Facilitation theory: Impulses from diseased viscus pass through afferents which give collaterals to ST neurons receiving pain fibers from skin dermatomes

REFERRED PAIN

Convergence

Branches of visceral pain fibers synapse in the spinal cord on the same second-order Neurons that receive pain signals from the skin



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.

Dermatomal rule

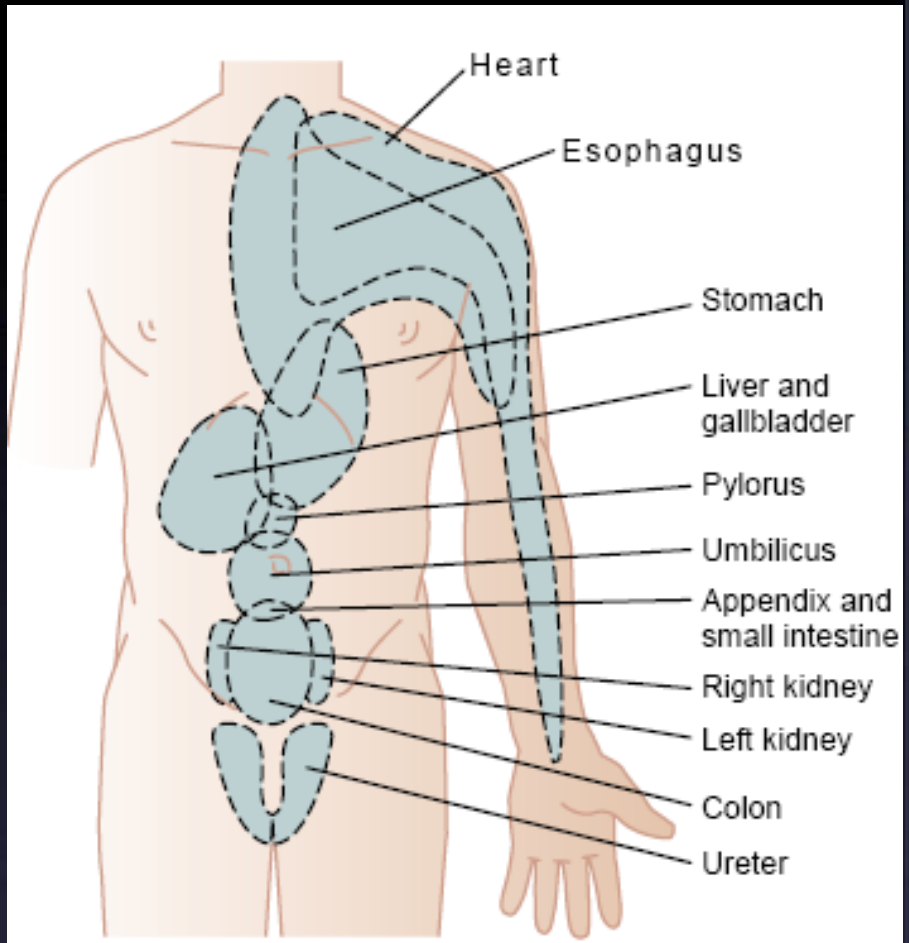


Figure 48–6

Surface areas of referred pain from different visceral organs.

REFERRED PAIN

Localization of Visceral Pain "Visceral" and the "Parietal" Pain Transmission Pathways

When pain is both localized and referred it is called radiating pain

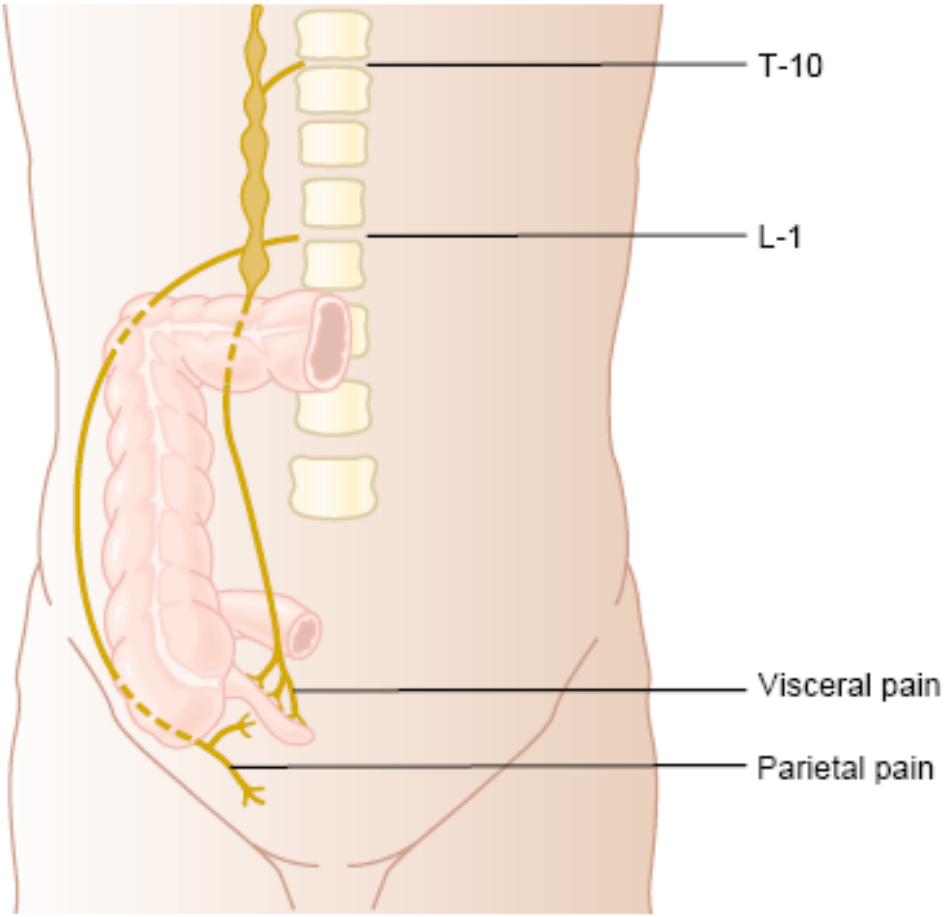


Figure 48–7

Visceral and parietal transmission of pain signals from the appendix.

The brain tissues themselves are almost totally insensitive to pain.

Tugging on the venous sinuses around the brain, damaging the tentorium, or stretching the dura at the base of the brain can cause intense pain that is recognized as headache. Also, almost any type of traumatizing, crushing, or stretching stimulus to the blood vessels of the meninges can cause headache.

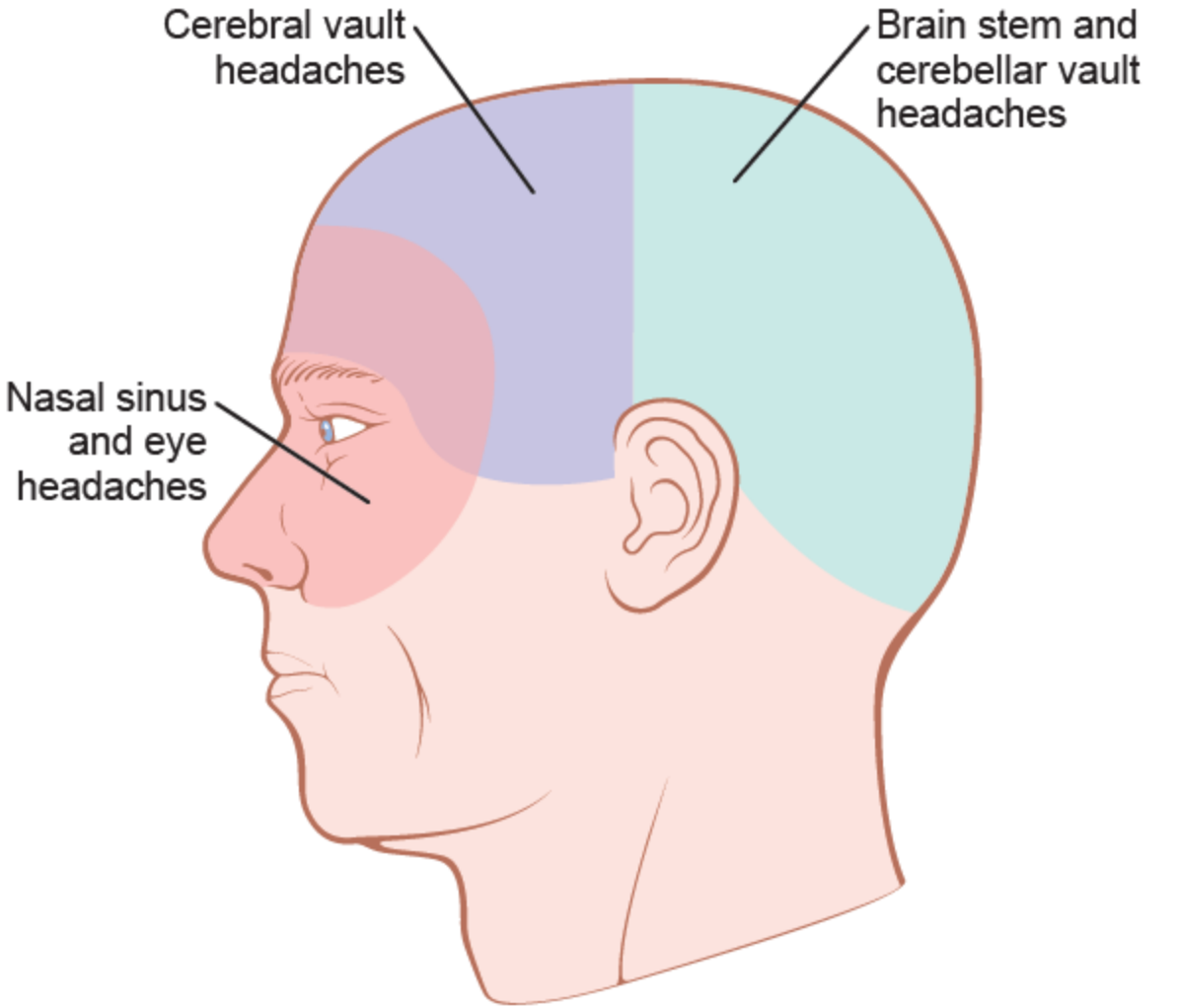
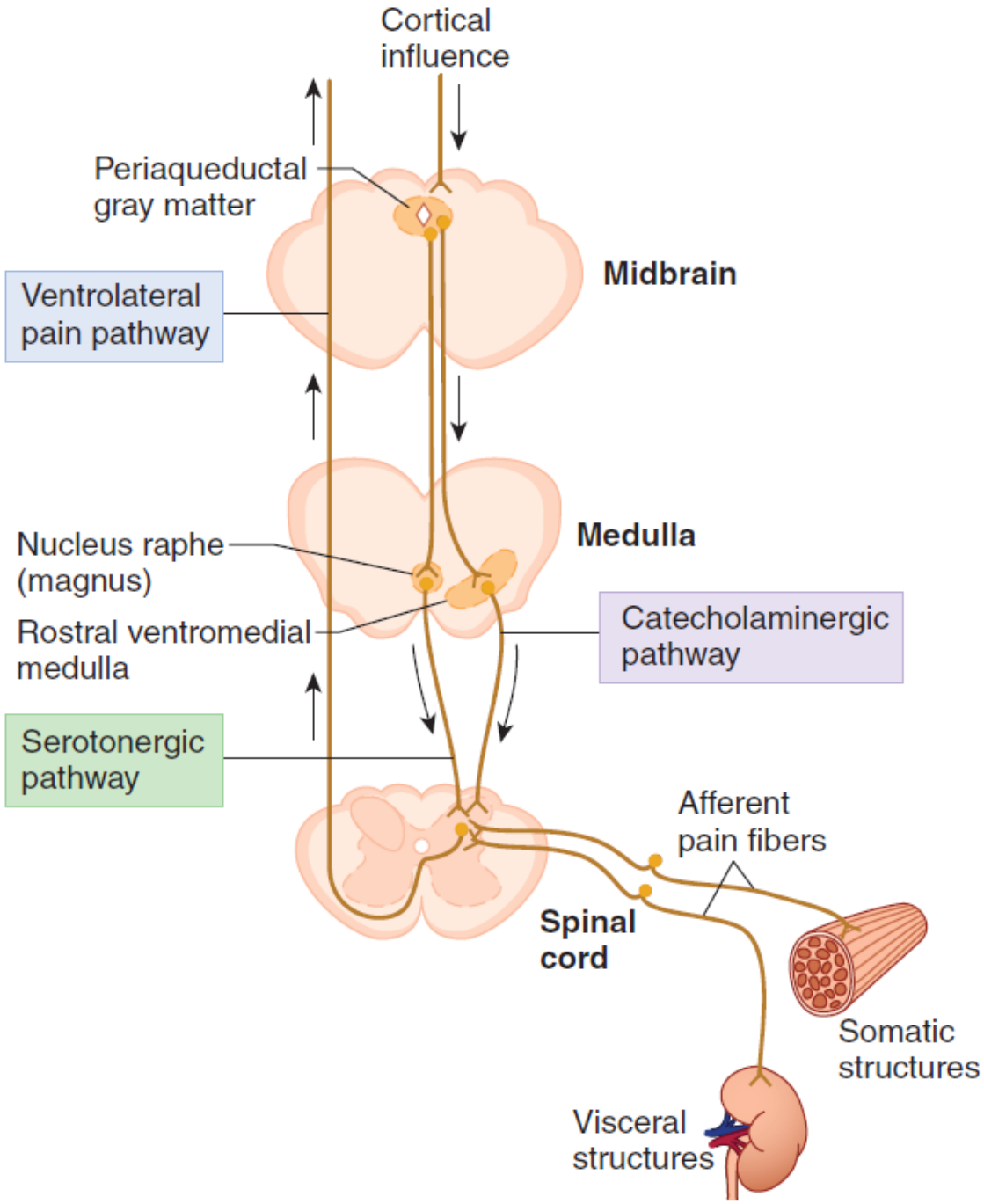


Figure 49-9. Areas of headache resulting from different causes.

Pain Suppression ("Analgesia") System in the Brain and Spinal Cord

Ascending Pain Pathway

Descending Analgesic Pathway



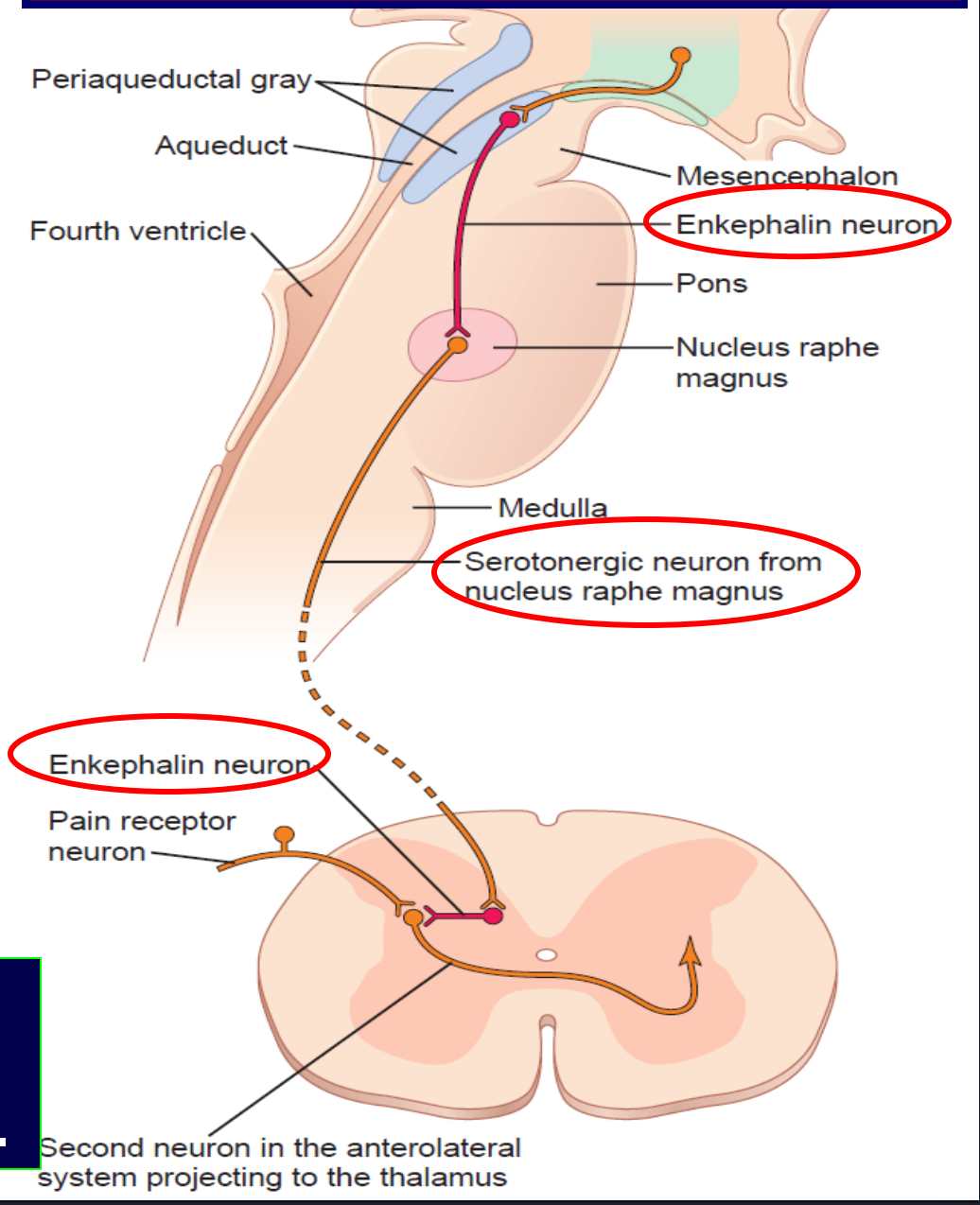
(1) Enkephalin Neurons from periaqueductal gray and periventricular areas of the mesencephalon and upper pons send signals to

(2) Raphe magnus nucleus, in the lower pons and upper medulla From these nuclei, second-order N go down the dorsolateral columns in the spinal cord & secrete Serotonin which act on local neurons to secrete Enkephalin

(3) a pain inhibitory complex in the dorsal of spinal cord

At this point, the analgesia signals can block the pain before it is relayed to the brain.

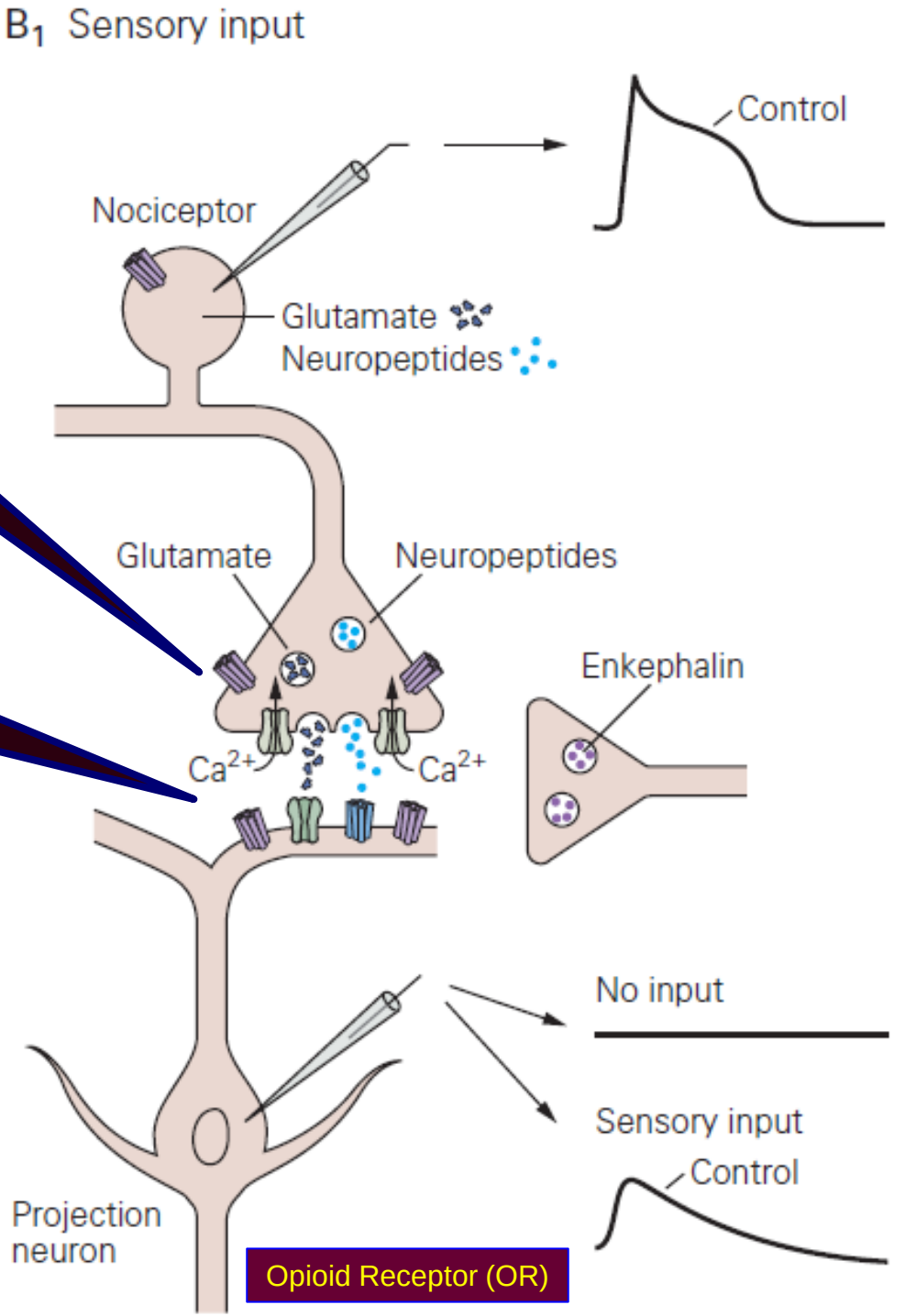
Pain Suppression ("Analgesia") System in the Brain and Spinal Cord

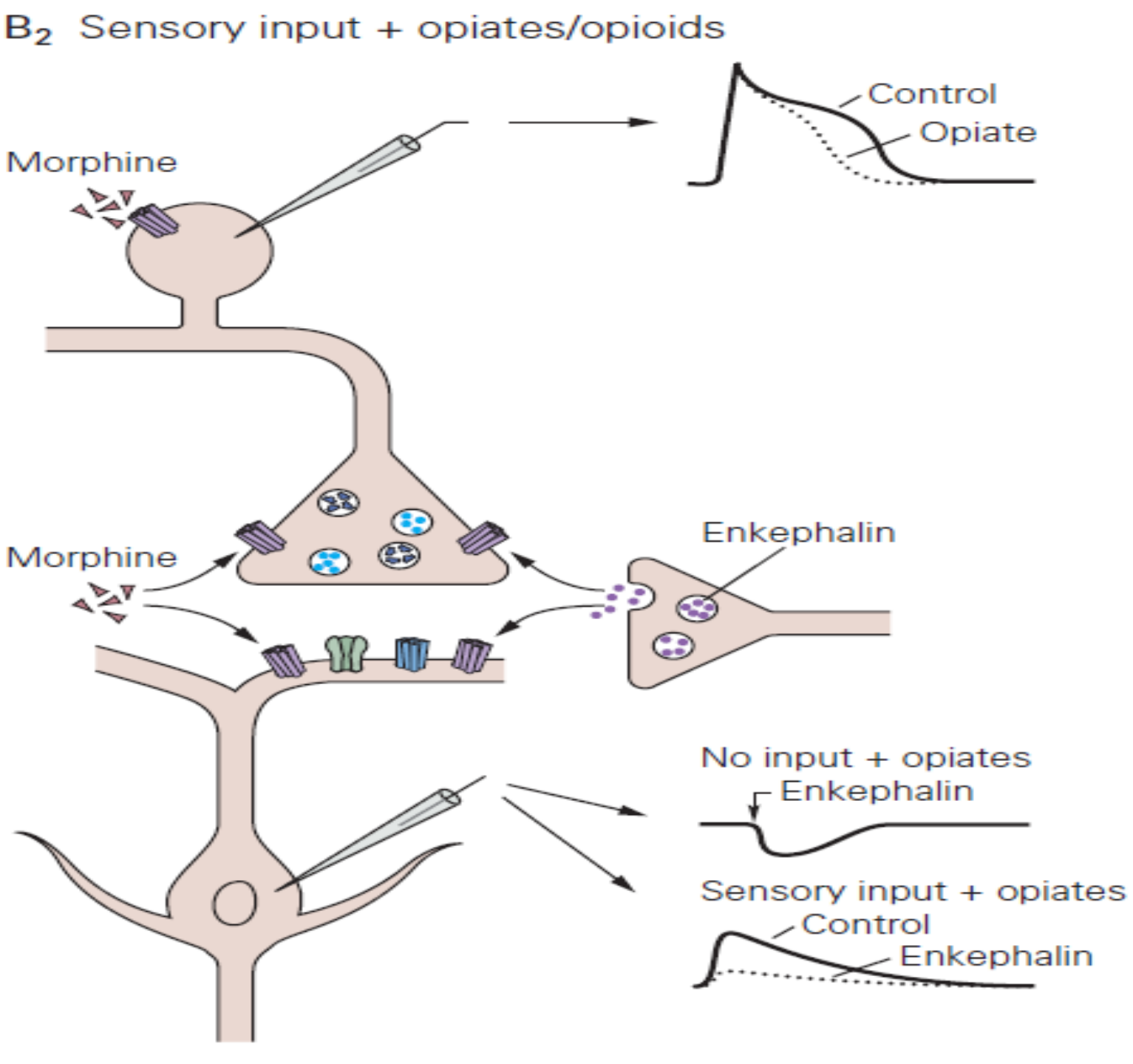


Activation of the presynaptic OR leads to a decrease in Ca^{++} influx, resulting in a decrease in release of glutamate and substance P.

Activation of the postsynaptic OR hyperpolarizes the dorsal horn interneuron by causing an increase in K^{+} conductance.

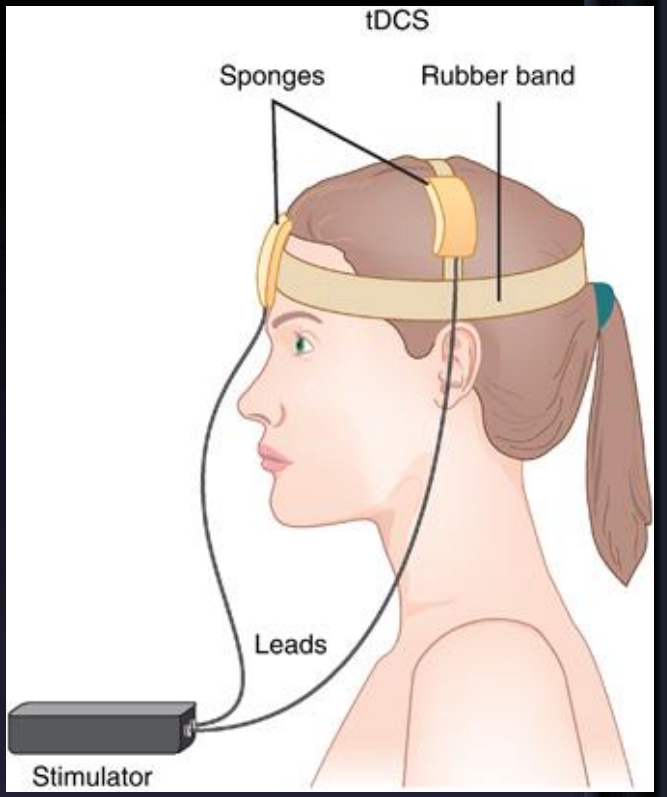
- ↓ duration of the EPSP in the dorsal horn neuron.
- Activation of OR on dorsal root ganglia cell bodies also contributes to reduced transmission from nociceptive afferents.




B2 Sensory input + opiates/opioids
Control
Opiate
Morphine
Morphine
Enkephalin
No input + opiates
Enkephalin
Sensory input + opiates
Control
Enkephalin

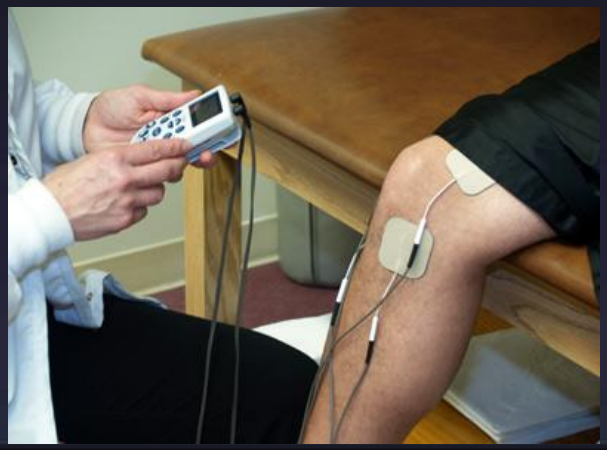
TRANSCRANIAL DIRECT CURRENT STIMULATION (TDCS)

- It is a non-invasive procedure in which a device sends a small Direct Current (DC) across electrodes in the areas of interest on the scalp to modulate brain function.
- This current flow can increases or decreases the neuronal excitability in the specific area being stimulated, based on which type of stimulation.
- When the current passes from the anode to the cathode, it may increase the activity of the brain at the anode site and decrease the activity of the brain near the cathode site.



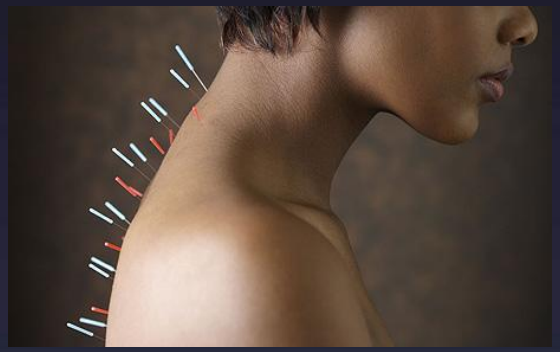
TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION (TENS)

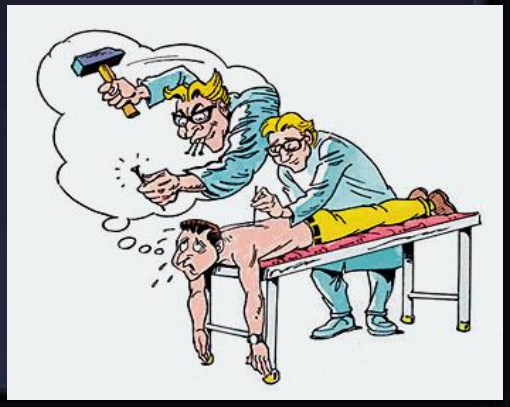
- The gate-control mechanism of pain modulation and serves as the rationale behind the use of transcutaneous electrical nerve stimulation (TENS) for pain relief.
- TENS uses electrodes to activate Aα and Aβ fibers in the vicinity of the injury.



Inhibition of Pain Transmission by Tactile Sensory Signals

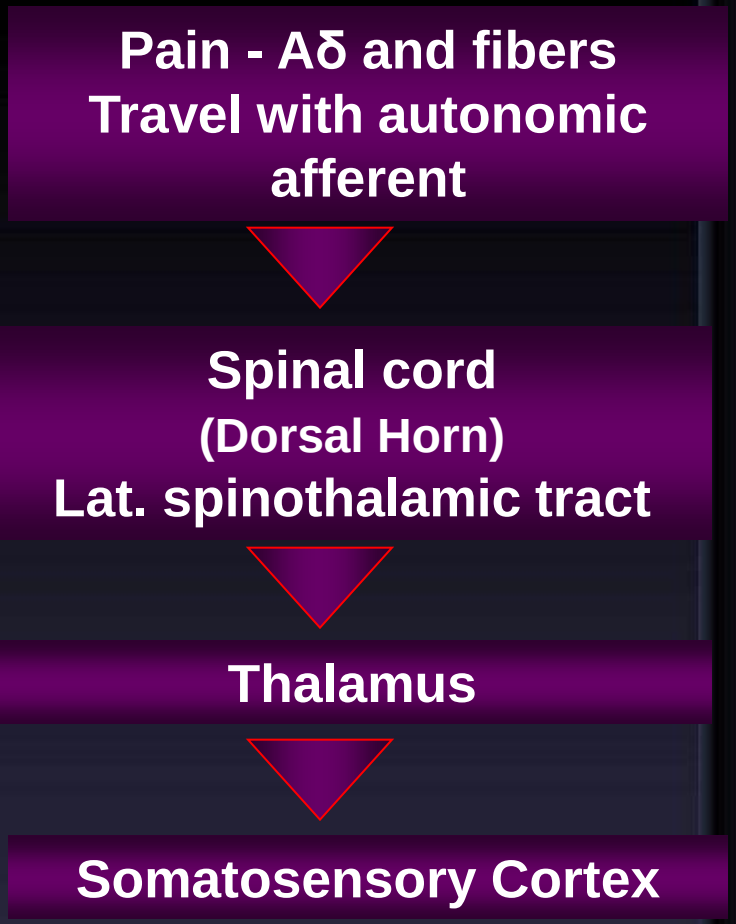
- Stimulation of large type Aβ sensory fibers from peripheral tactile receptors depress transmission of pain signals from the same body area by lateral inhibition in the spinal cord
- The simultaneous physical and psychogenic excitation of the central analgesia system is the basis of pain relief by ***ACUPUNCTURE.***





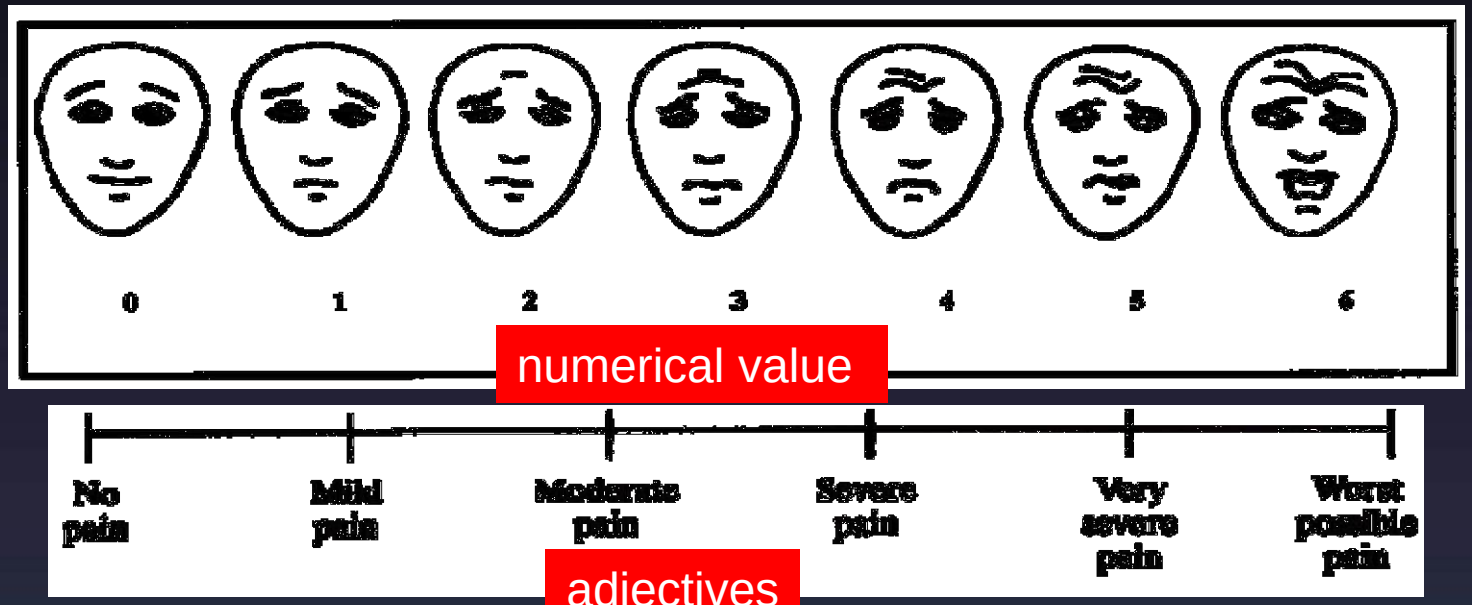
CHARACTERSITICS OF VISCERAL PAIN

- Poorly localized
- Associated with nausea and autonomic disturbance
- Often referred
- Cutting, crushing are not painful when applied to viscera
- Pain is caused by distension, ischemia and inflammation



PAIN SCALES

- Visual Analog Scale
- Locate area of pain on a picture
- McGill pain questionnaire
  - Evaluate sensory, evaluative, & affective components of pain
    - 20 subcategories, 78 words



Mc Gill-Melzack
PAIN QUESTIONNAIRE

Patient's name _____ Age _____
File No. _____ Date _____
Clinical category (e.g. cardiac, neurological, etc.):

Diagnosis: _____
_____
_____

Analgesic (if already administered):
1. Type _____
2. Dosage _____
3. Time given in relation to this test _____

Patient's intelligence: circle number that represents best estimate
1 (low) 2 3 4 5 high

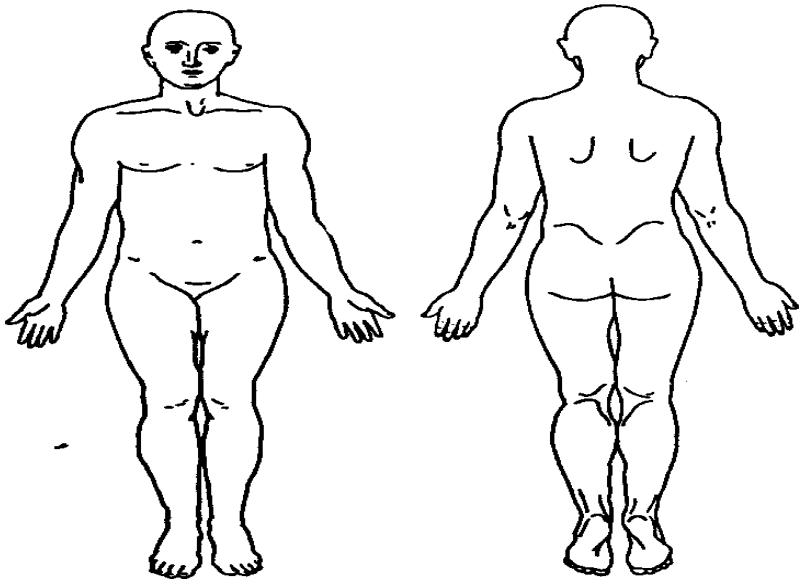
****

This questionnaire has been designed to tell us more about your pain. Four major questions we ask are:
1. Where is your pain?
2. What does it feel like?
3. How does it change with time?
4. How strong is it?

It is important that you tell us how your pain feels now. Please follow the instructions at the beginning of each part.

Part 1. Where is your Pain?

Please mark, on the drawings below, the areas where you feel pain. Put E if external, or I if internal, near the areas which you mark. Put EI if both external and internal.



Part 2. What Does Your Pain Feel Like?

Some of the words below describe your present pain. Circle ONLY those words that best describe it. Leave out any category that is not suitable. Use only a single word in each appropriate category–the one that applies best.

1	2	3	4
Flickering	Jumping	Pricking	Sharp
Quivering	Flashing	Boring	Cutting
Pulsing	Shooting	Drilling	Lacerating
Throbbing		Stabbing	
Beating		Lancinating	
Pounding			
5	**6**	**7**	**8**
Pinching	Tugging	Hot	Tingling
Pressing	Pulling	Burning	Itchy
Gnawing	Wrenching	Scalding	Smarting
Cramping		Searing	Stinging
Crushing			
9	**10**	**11**	**12**
Dull	Tender	Tiring	Sickening
Sore	Taut	Exhausting	Suffocating
Hurting	Rasping		
Aching	Splitting		
Heavy			
13	**14**	**15**	**16**
Fearful	Punishing	Wretched	Annoying
Frightful	Cruel	Blinding	Troublesome
Terrifying	Vicious		Miserable
	Killing		Intense
			Unbearable
17	**18**	**19**	**20**
Spreading	Tight	Cool	Nagging
Radiating	Numb	Cold	Nauseating
Penetrating	Drawing	Freezing	Agonizing
Piercing	Squeezing		Dreadful
	Tearing		Torturing

Part 3. How Does Your Pain Change With Time?

1. Which word or words would you use to describe the pattern of your pain?

1	2	3
Continuous	Rhythmic	Brief
Steady	Periodic	Momentary
Constant	Intermittent	Transient

2. What kind of things relieve your pain?

3. What kind of things increase your pain?

Part 4. How Strong Is Your Pain?

People agree that the following 5 word represent pain in increasing intensity. They are:

1	2	3	4	5
Mild	Discomforting	Distressing	Horrible	Excruciating

To answer each question below, write the number of the most appropriate word in the space beside the question.

1. Which word describes your pain right now? _____
2. Which word describes it at its worst? _____
3. Which word describes it when it is least? _____
4. Which word describes the worst toothache you ever had? _____
5. Which word describes the worst headache you ever had? _____
6. Which word describes the worst stomach-ache you ever had? _____

Applied

1. **What will happen if sensory area SI is removed?**

Ans. persons ability to interpret the quality of pain & precise location of pain will be affected.

2. **Why patient with chronic pain syndrome have difficulty in sleeping?**

Ans. Paleospinothalamic pathway sends information to reticular formation and thalamic nuclei which are part of brain activating / alerting system, therefore chronic pain syndrome causes difficulty in sleep.

Placebo Effect

- **Placebo** stems from the Latin word for **"I shall please"**
  - Used to describe pain reduction obtained from a mechanism other than those related to the physiological effects of the tx.
  - Linked to psychological mechanisms
- All Treatments ™ have some degree of placebo effect
  - Most studies involving TM involving the use of a sham TM (ultrasound set at the intensity of 0) and an actual treatment have shown ↓ levels of pain in each group.

Congenital Analgesia

Congenital insensitivity to pain (CIP), also known as congenital analgesia, is one or more rare conditions in which a person cannot feel (and has never felt) physical pain

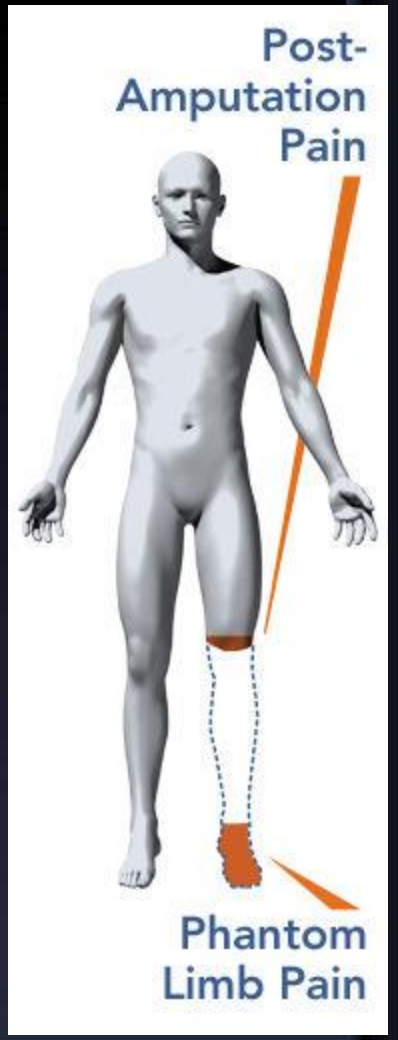
- A well-known case of congenital insensitivity to pain is a girl referred to as **'Miss C'** who was a student at McGill university in Montreal in the 1950s.
- She was normal in every way, except that she could not feel pain. When she was a child she had bitten off the tip of her tongue and had suffered third-degree burns by kneeling on a radiator.
- She did not feel any pain when she was given strong electric shocks or when exposed to very hot and very cold water. When these stimuli were presented to her she showed no change in heart rate, blood pressure or respiration.
- She died at the age of 29 as a result of her condition, because she damaged her knees, hips and spine.

Fibromyalgia: Pain Without Injury

- The occurrence of body-wide pain in the absence of tissue damage, as in fibromyalgia, interferes with all aspects of a person's life and undermines their credibility.
- The problem is that normal activities can be exhausting, sleep is disturbed, the ability to concentrate is impaired, gastrointestinal function is often abnormal, persistent headaches are common, and the unrelenting pain that no one can see is often detrimental to their personal and professional lives--as it creates a "credibility gap."

Phantom limb pain

- Phantom limbs give impression of pressure and pain
- Even if phantom limb is experienced as spatially detached from the body, it is still felt to belong to the patient.
- Paraplegic people experience phantom limbs. They can even experience continually cycling legs.
- It is the emotional and motivational systems that cause the phantom limb experience.



Our brain can reorganize if sensory input is cut off at the ventral posterior thalamic nucleus even after that part is amputated

The acquired tolerance is different from addiction

Opiate Tolerance

- receptor desensitization
- compensatory adaptations in neuronal circuit
- learning mechanisms

Physical Dependence

compensatory adaptations in neuronal circuit

Drug Withdrawal

removal of opiate unmasks compensatory adaptations

Drug Addiction Psychological addiction is extremely rare during treatment of pain

- The acquired tolerance is different from addiction, which refers to a psychological craving.
- Psychological addiction rarely occurs when morphine is used to treat chronic pain, provided the patient does not have a history of drug abuse.

TERMS FREQUENTLY USED

- **Hyperalgesia:** Increased sensitivity to Pain
- **Allodynia:** clinical feature of many painful conditions, such as neuropathies, complex regional pain syndrome, postherpetic neuralgia, fibromyalgia, and migraine Muscular Pain: Less blood flow in the muscles (ischemia). you feel pain from stimuli that don't normally cause pain. For example, lightly touching your skin or brushing your hair might feel painful.
- **Stress analgesia:** Mild degree of pain is not felt if the other part of the body has excessive pain.
- **Causalgia:** It is chronic burning pain condition seen after the section (damage, cutting) of a nerve Triggered by a simple stimulus e.g. breeze or vibration.
- **Neuralgia** - sharp pain along a nerve pathway.
- **Thalamic Syndrome:** Obstruction of the thalmogeniculate branch of the posterior cerebral artery Affects posterior thalamic nuclei Patient suffers from prolonged severe pain


THANKS