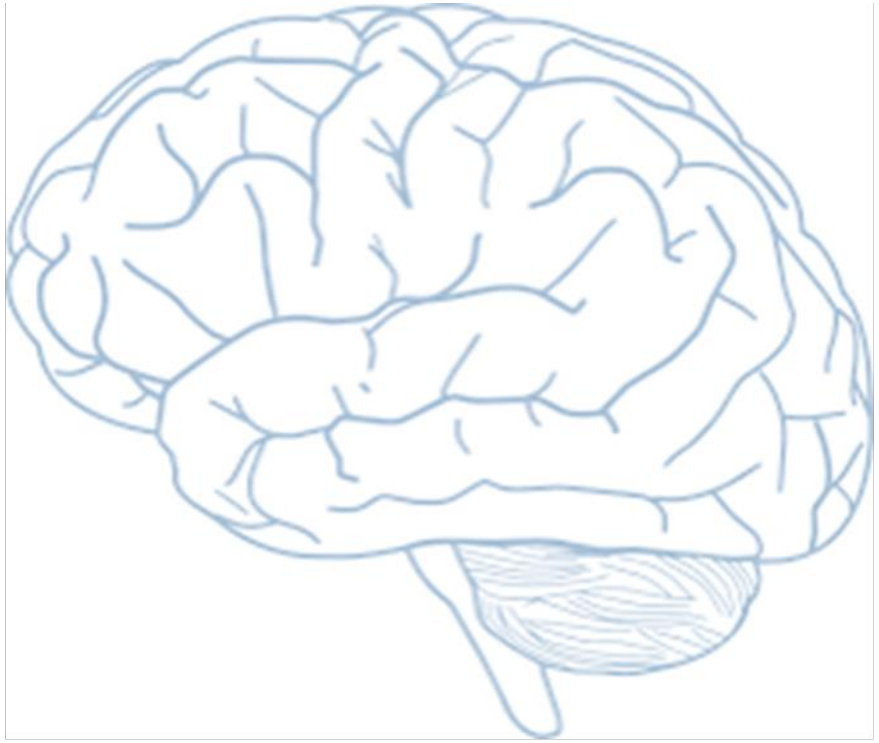
MEDICINE
KING SAUD UNIVERSITY

تمت المراجعة
شوق الأحمري & عبدالعزيز العنقري

Physiology Team 436



CNS PHYSIOLOGY

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

Lecture No.27

"When You Feel Like Quitting, Think About Why You Started"

Pain modulation

Objectives:

1. Intensity of the pain can be altered by various extrinsic and intrinsic mechanisms, extrinsic mechanism such as rubbing or shaking of an injured area. Or applying ice pack, or stimulation with an electric vibrator at the site of pain all gives some relief from pain, pain can be modulated by giving analgesic drugs e.g.morphine.
2. Describe orally and evaluate critically the mechanism of pain by extrinsic and intrinsic factors as a team. (Cognitive / team work)
3. Reduce the intensity of pain with two methods by applying ice pack and stimulating the site of pain by electric vibrator on a mannequins (Psychomotor)
4. Prescribe independently at least one analgesic medicine with its correct route and dose (Cognitive / Psychomotor).

What is pain modulation ?

- It means pain perception variability (the degree to which a person reacts to pain).
- i.e. A decrease or an increase in the sensation of pain caused by inhibition or facilitation of pain signals.

- Inhibition:
  - Spinal (segmental) inhibition: Gate control theory.
  - Supraspinal (descending) inhibition.

- Facilitation:
  - Peripheral sensitization (release of chemicals after tissue injury).
  - Central sensitization (Dis-inhibition).

Nociceptive & Neuropathic Pain

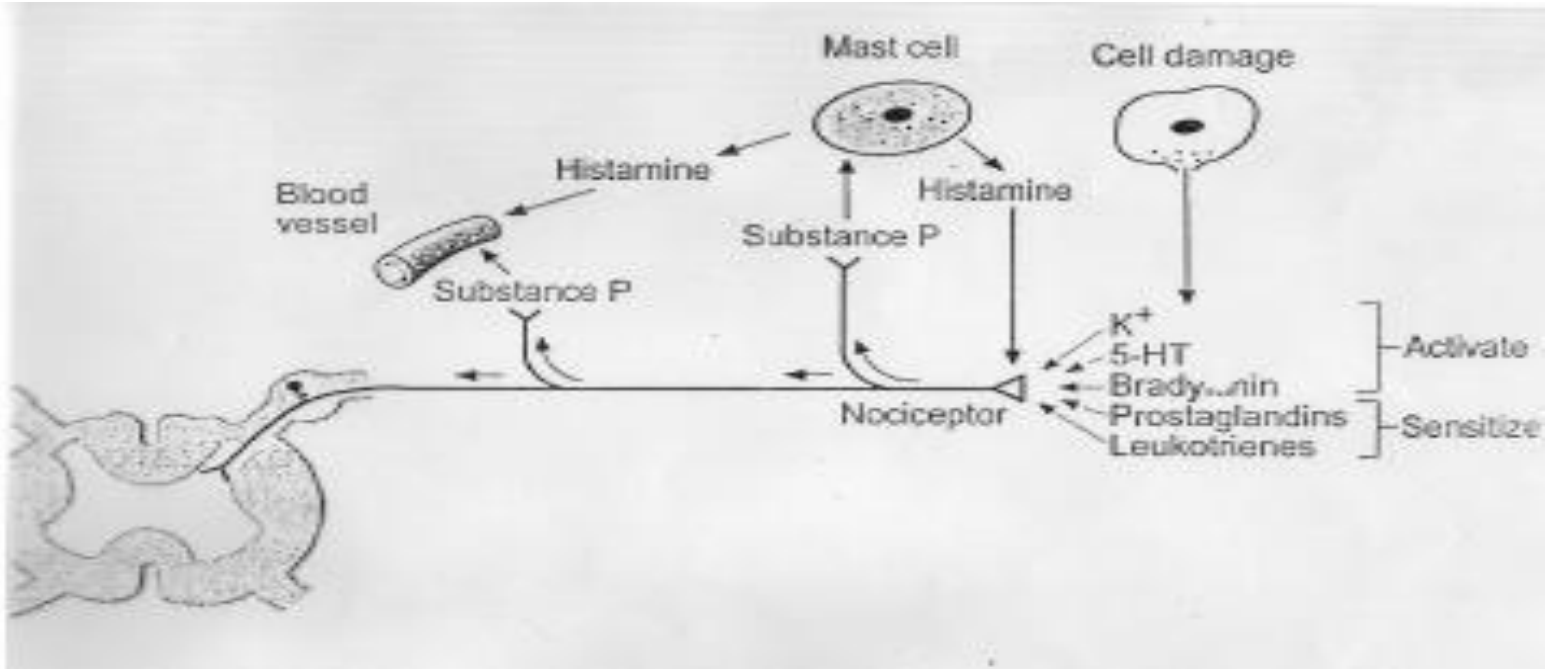
- Nociceptive: pain is detected by specialized transducers connected to A-delta and C-fibers (stimuli from somatic and visceral structures).
- Neuropathic: pain damage to nerves (trigeminal
- neuralgia, postherpetic pain, diabetic neuropathy).

- 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.

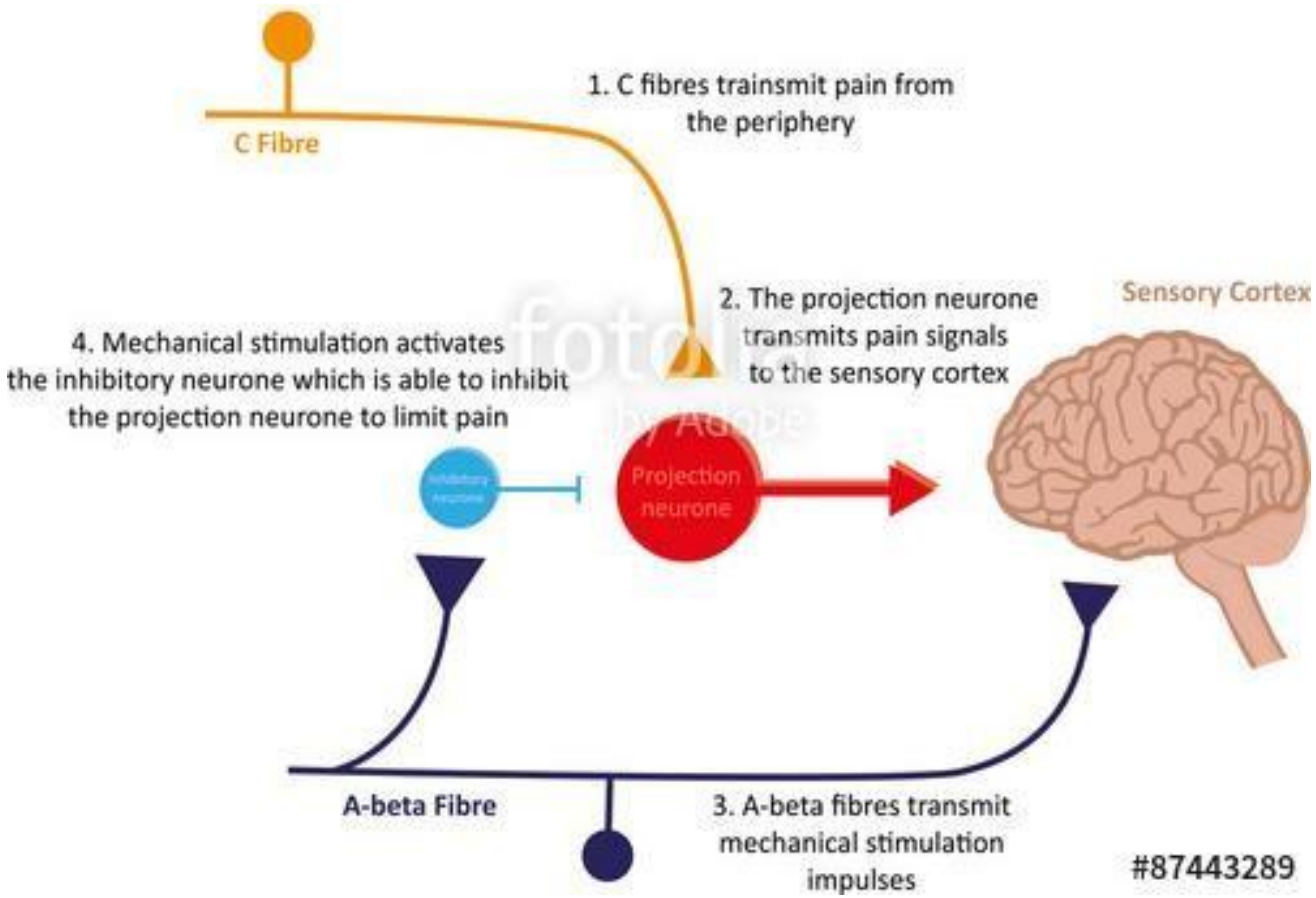


The gate theory of pain control

- Special neurons in the the dorsal horn of spinal cord (SGR) form the gate through which pain impulses must pass to reach brain.

- 4 types of neurons are involved:

1. C- fibres (slow pain) or {C-nociceptor}.
2. A-Beta fibres (light touch).
3. Inhibitory interneurons.
4. Projection neuron.



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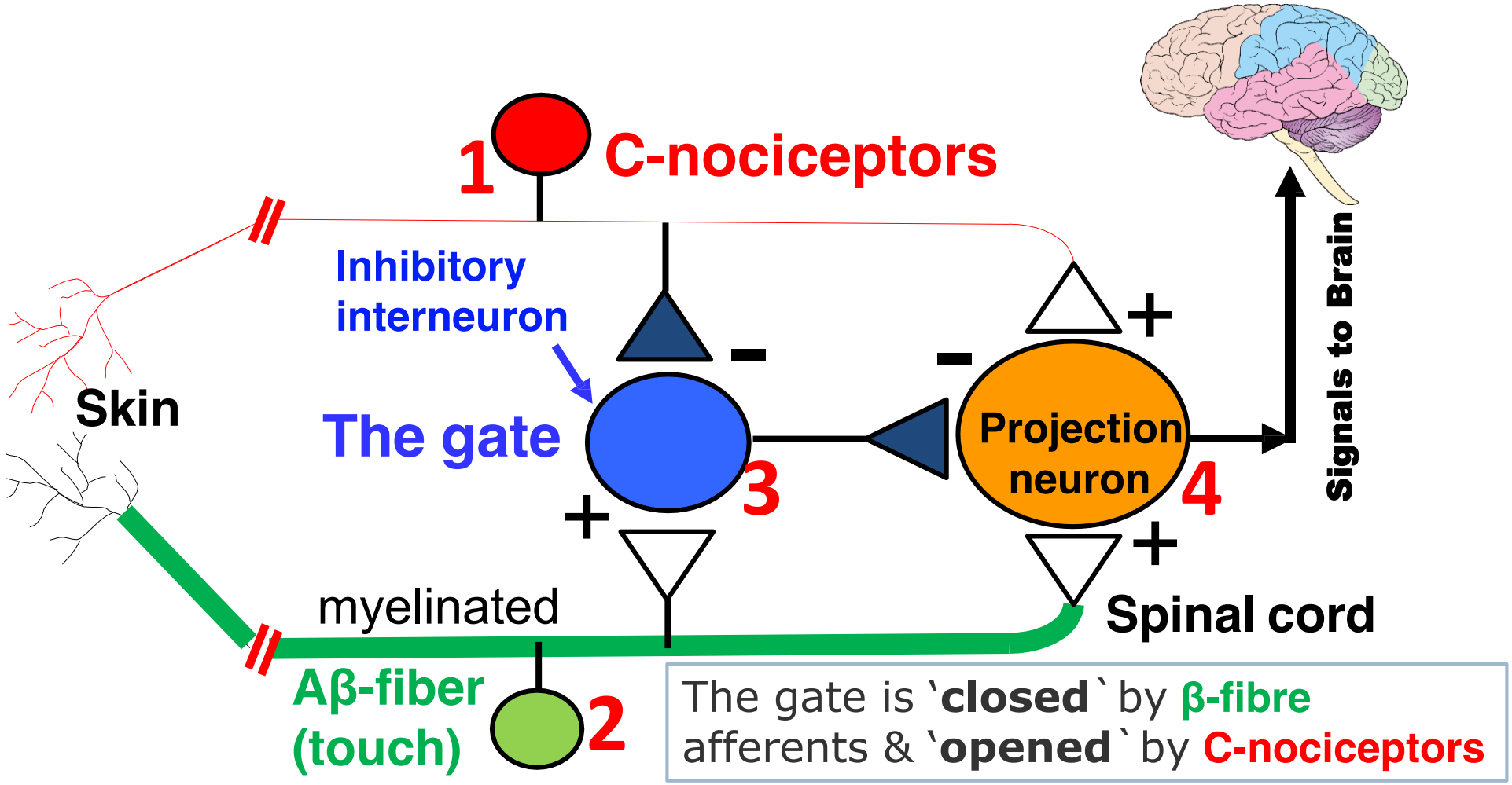
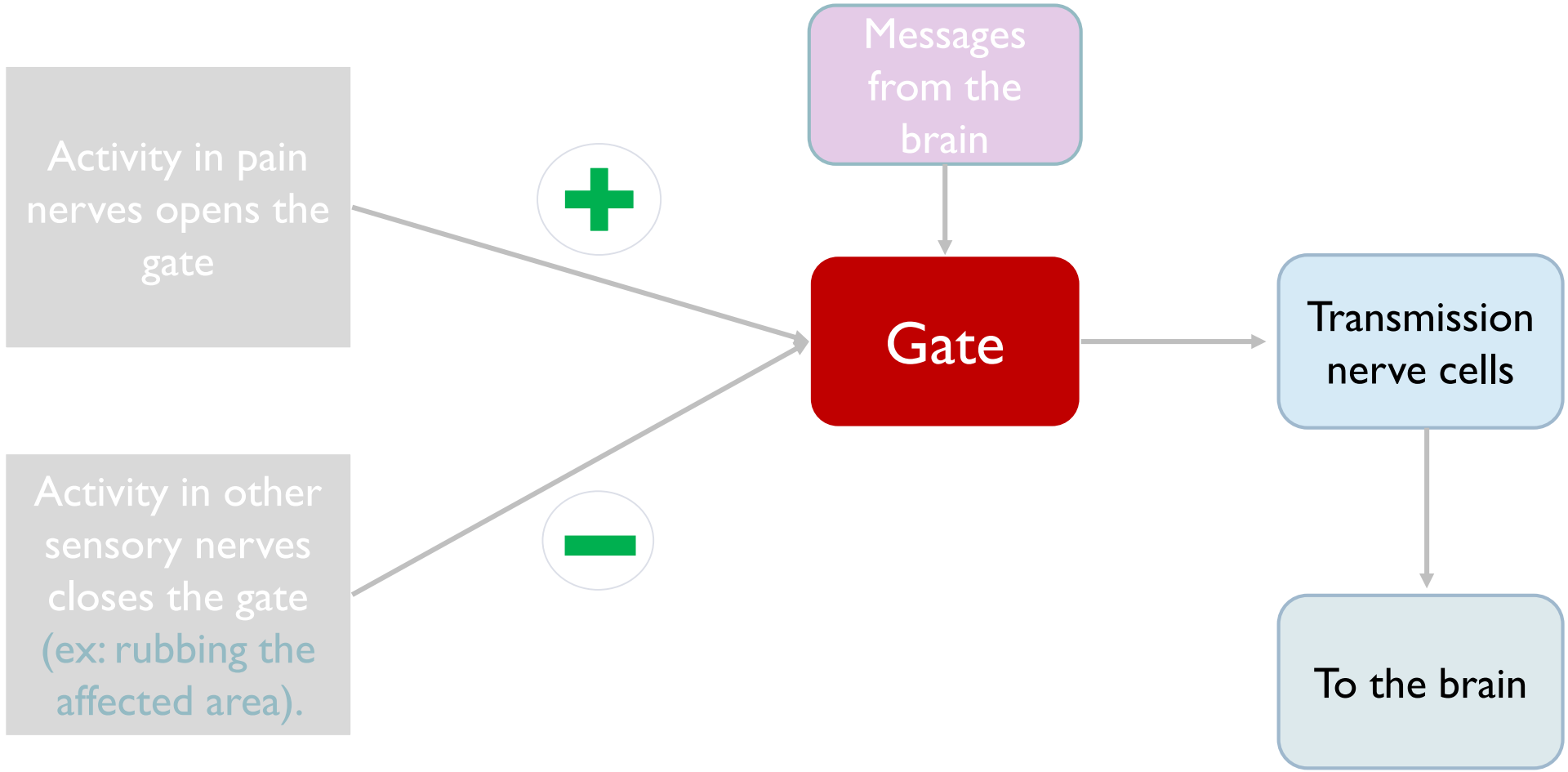
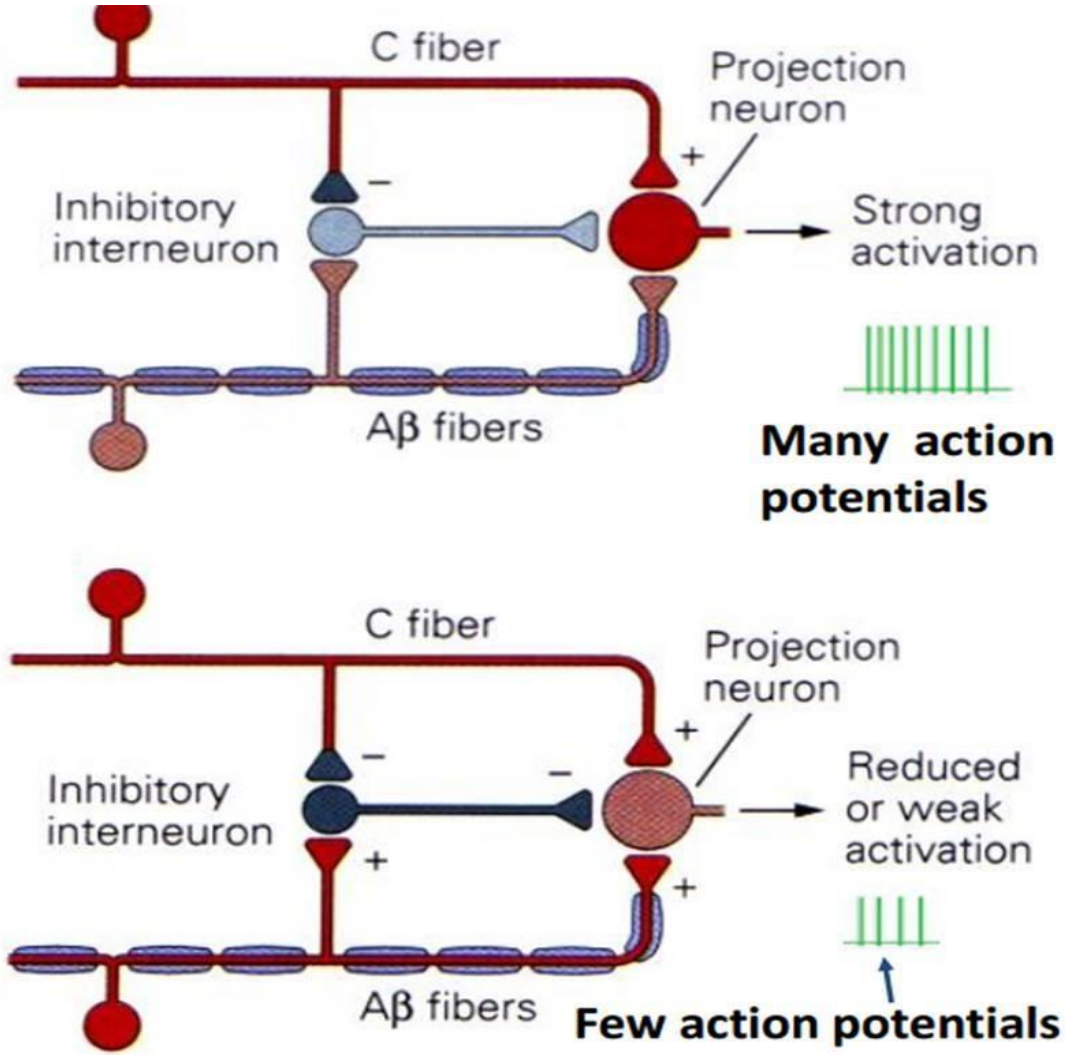

1
C-nociceptors
Inhibitory interneuron
Skin
The gate
3
Projection neuron
4
Signals to Brain
myelinated
Spinal cord
Aβ-fiber (touch)
2
The gate is 'closed' by β-fibre afferents & 'opened' by C-nociceptors

Gate opened or closed by 3 factors



Cont.

- Projection neuron receives input from both C-fibers and Aβ fibers.
- Impulses coming along type C pain fibers cause the release of substance P from these fibers and inhibits the inhibitory interneuron (open the gate).
- While impulses coming along Aβ fibers tend to keep the gate closed by activating the inhibitor interneuron(close gate).
- This theory implies that a non-painful stimulus can reduce transmission of a noxious stimulus.



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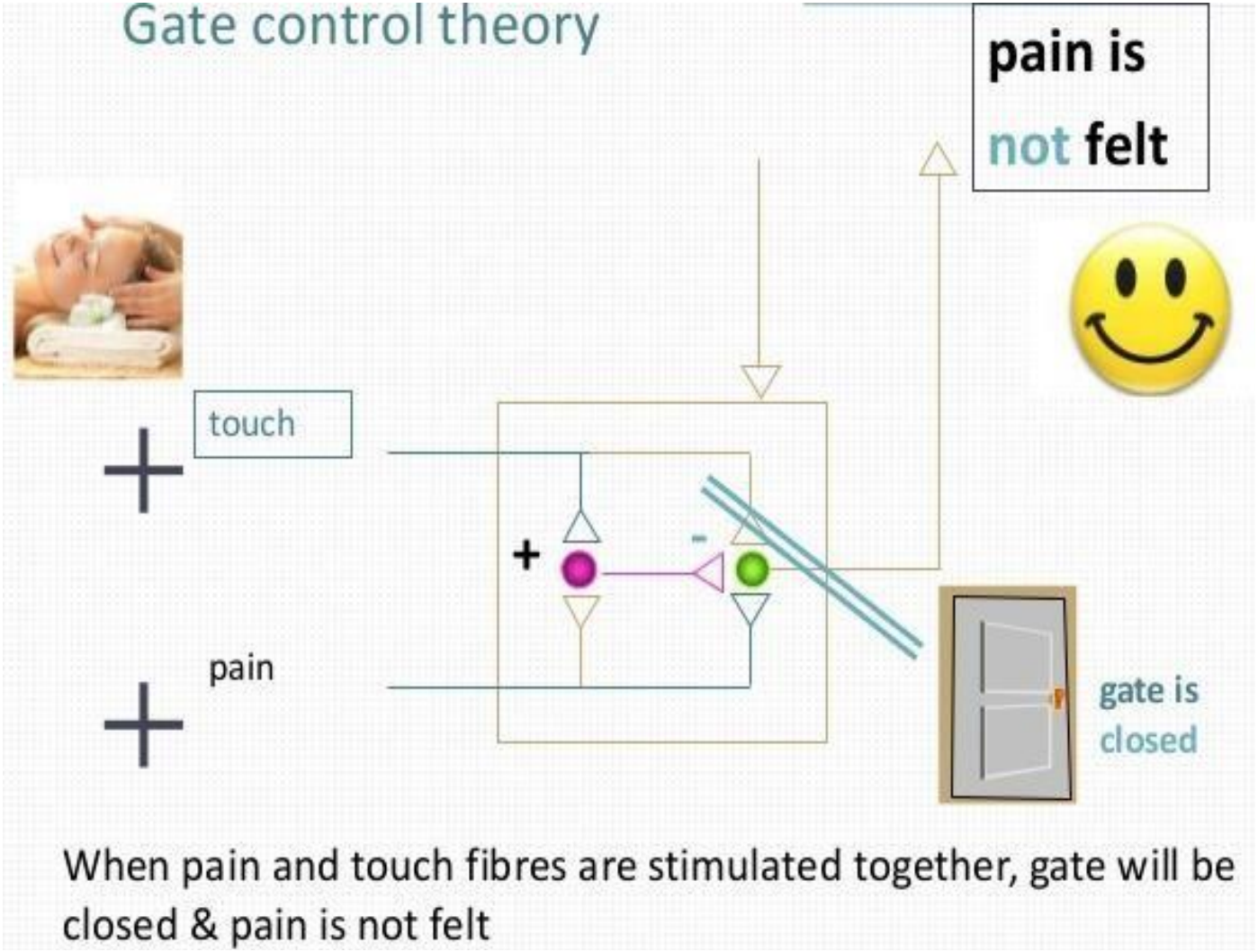
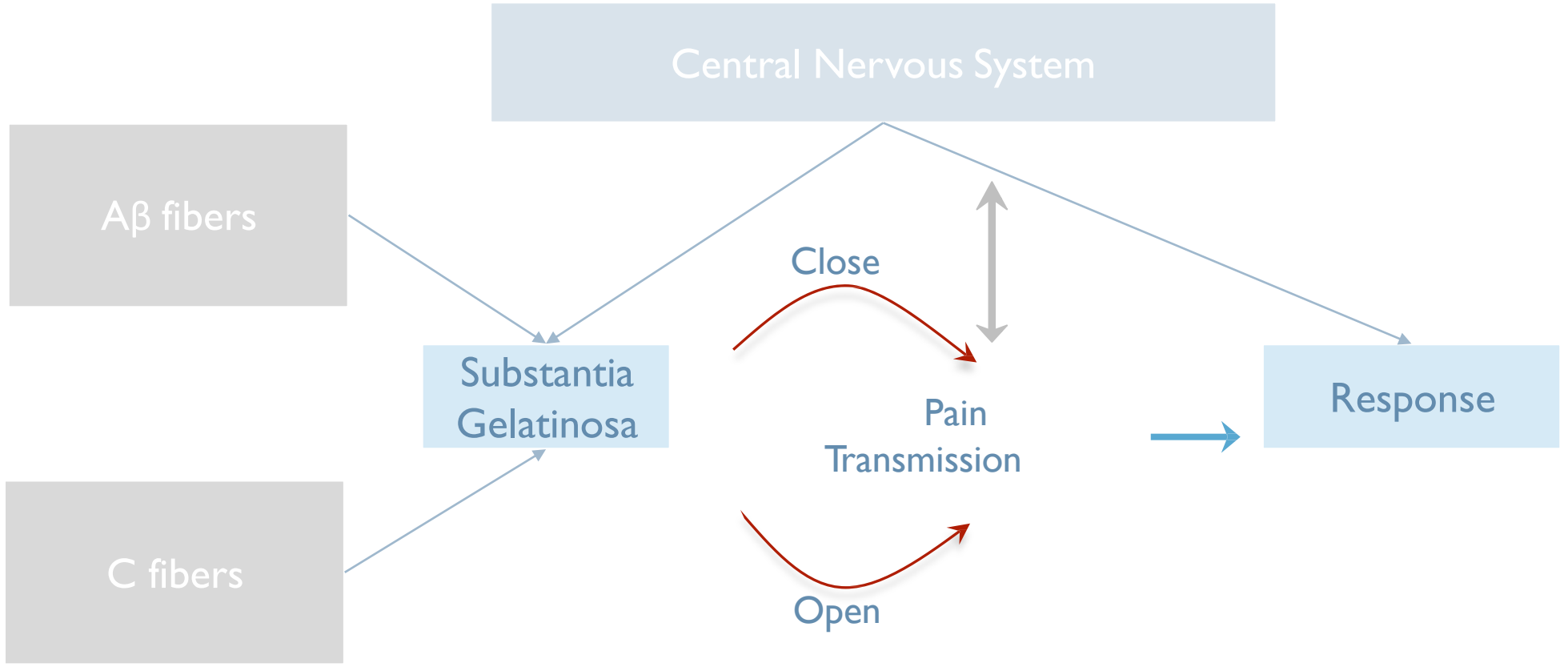
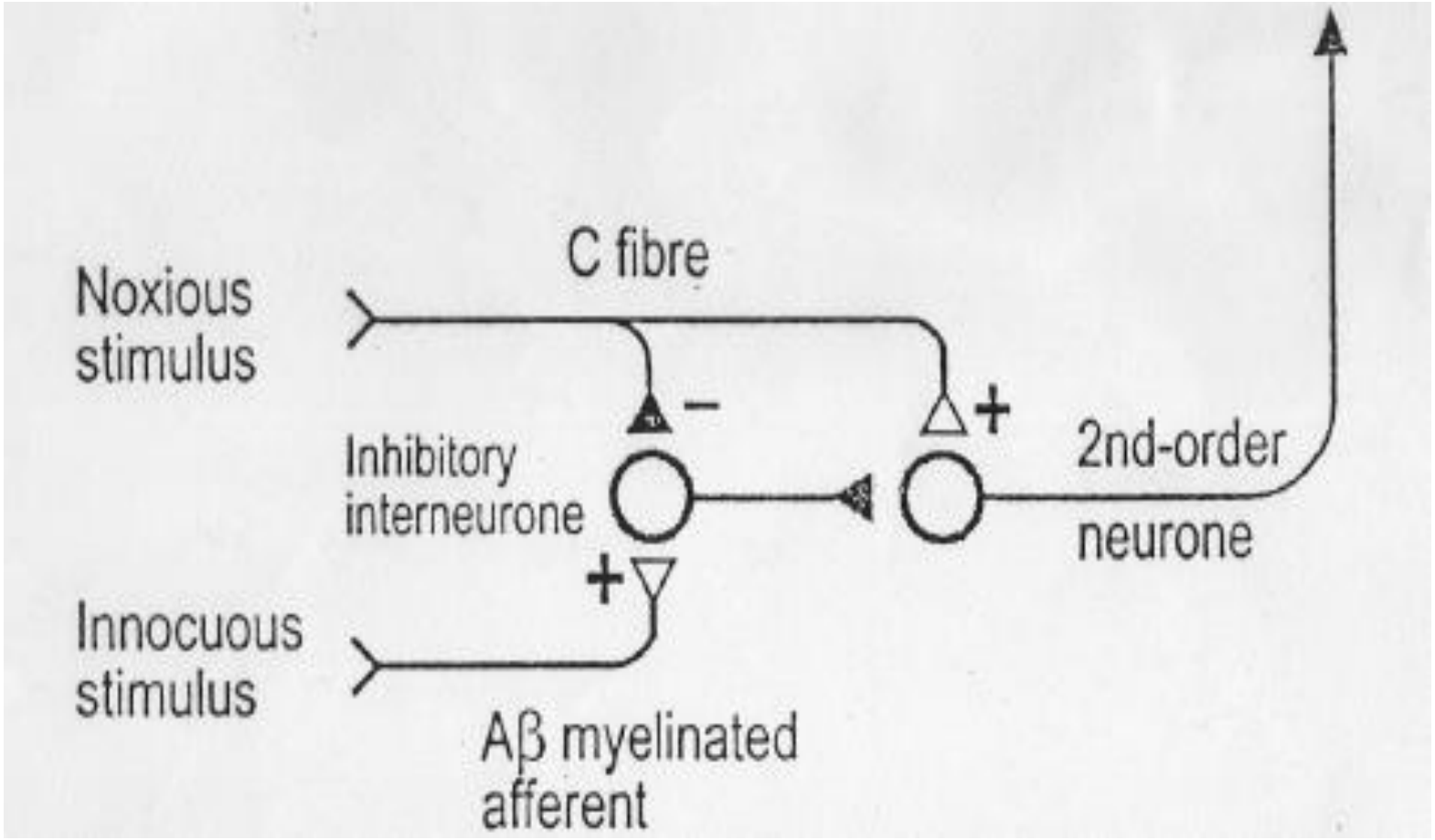

Gate control theory
pain is
not felt
touch
pain
+
-
gate is
closed
When pain and touch fibres are stimulated together, gate will be closed & pain is not felt

Cont.


Central Nervous System
Aβ fibers
C fibers
Substantia Gelatinosa
Close
Pain Transmission
Open
Response

Cont.



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

Conditions that open or close the gate

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, ex: 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

Cont.

- The gate-control theory is the basis for:
- The gate theory explains the pain relief by skin rubbing, shaking the painful part, trans cutaneous electrical nerve stimulation TENS & acupuncture.
- All are supposed to stimulate mechanoreceptors that activate neurons of dorsal column, the collaterals relieve pain.

What is the central control trigger

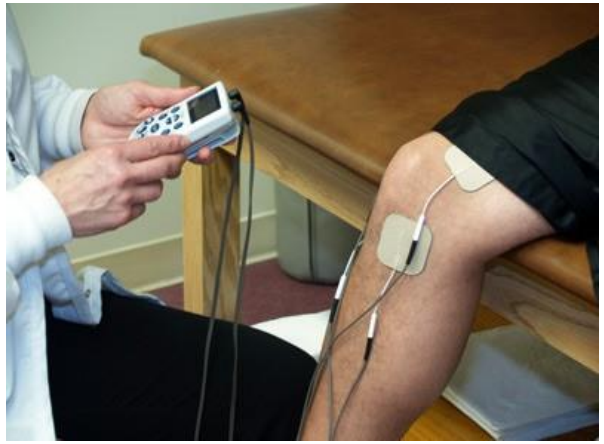
- Specialised nerve impulses arise in the brain itself and travel down the spinal cord to influence the gate.
- It can send both inhibitory and excitatory messages to the gate sensitising it to either C or A-β fibres.
- The inhibitory neurons make a pain blocking agent called encephalin.
- Encephalin is an opiate substance similar to heroin which can block substance P, the neurotransmitter from the C fibers, and this keeps the gate closed.

Transcranial direct current stimulation (TDCS)

1. 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.
2. This current flow can increases or decreases the neuronal excitability in the specific area being stimulated, based on which type of stimulation.
3. 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.

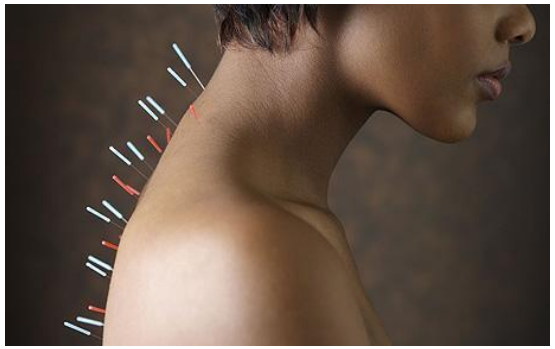
Transcutaneous electrical nerve stimulation (tens)

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



Inhibition of pain transmission by tactile sensory signals

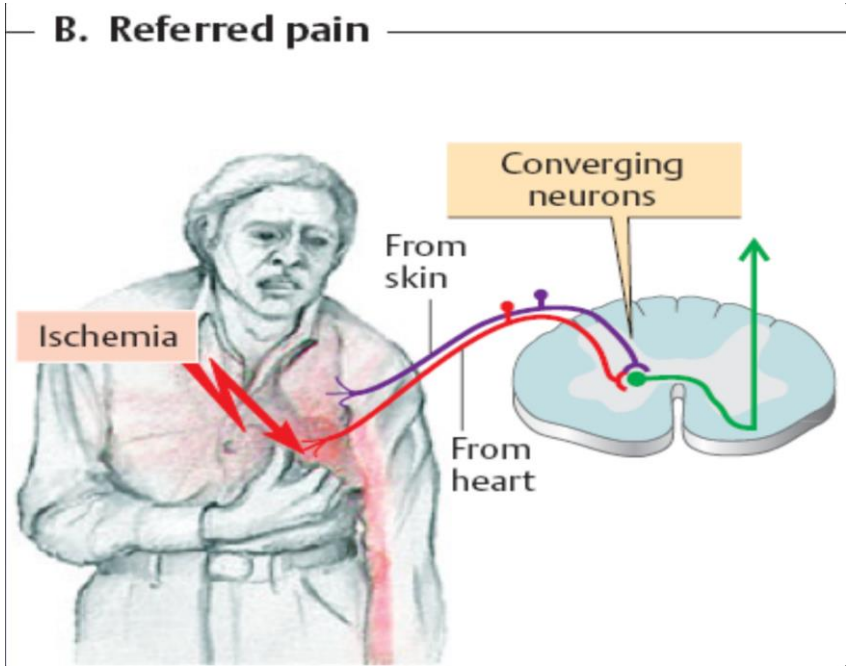
- Stimulation of large type Aβ sensory fibers from peripheral tactile receptors depress transmission of pain signals from the same body area by lateral inhibition in the spinal cord.
- The simultaneous physical and psychogenic excitation of the central analgesia system is the basis of pain relief by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



Referred pain Cont.

- 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.

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



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- Dermatomal rule:
- 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.

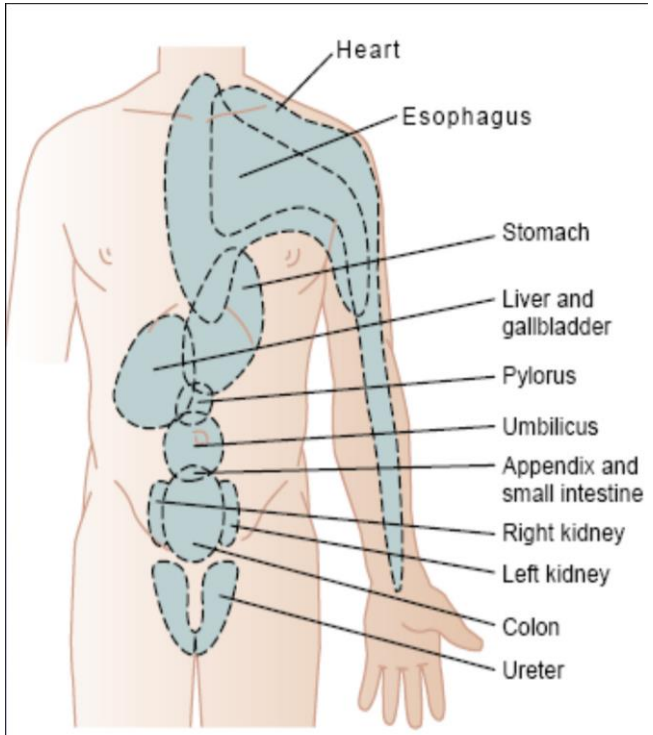


Figure 48–6

Surface areas of referred pain from different visceral organs.

Cont.

- Localization of visceral pain "visceral" and the "parietal" pain transmission pathways.
- When pain is both localized and referred it is called radiating pain.

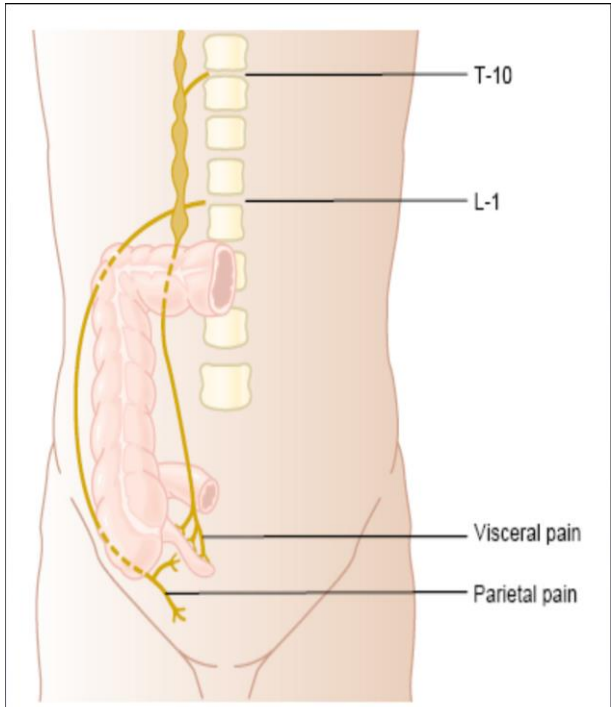


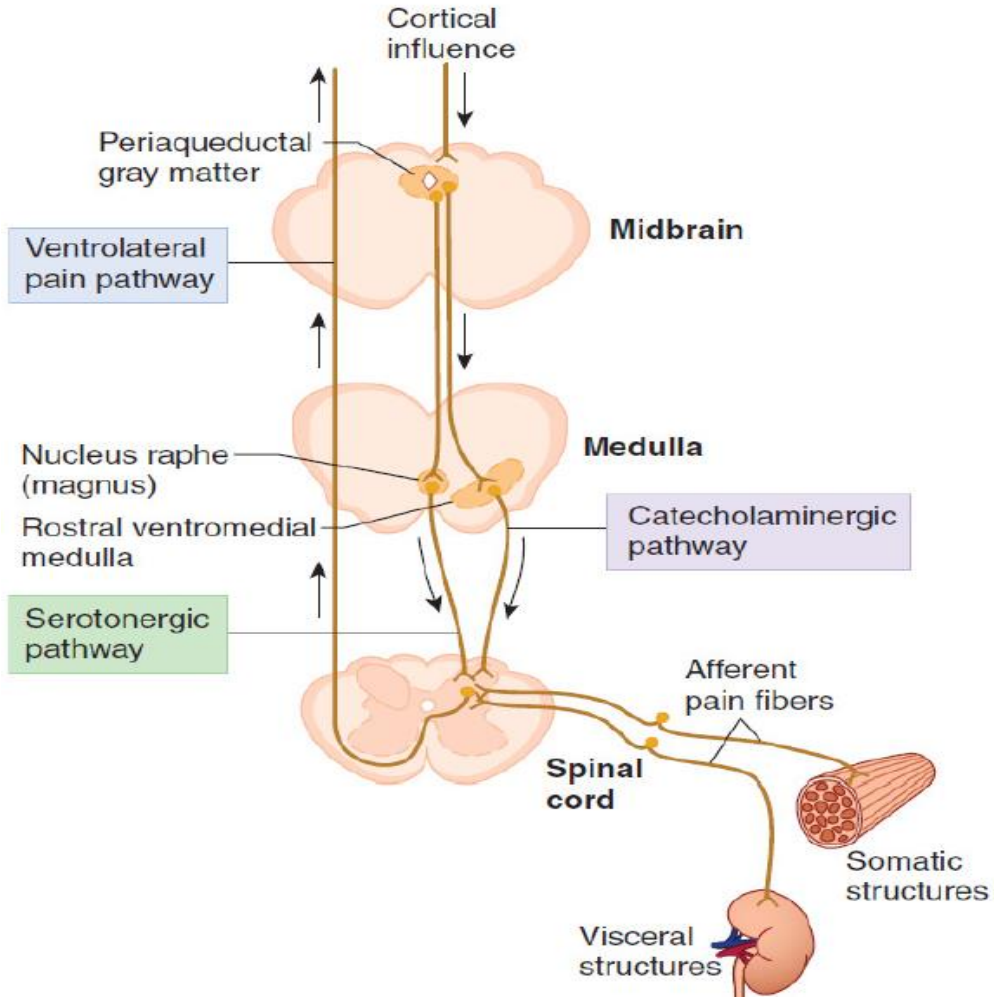
Figure 48–7

Visceral and parietal transmission of pain signals from the appendix.

Pain suppression ("analgesia") system in the brain and spinal cord

Ascending Pain Pathway

Descending Pain Pathway



Supra spinal modulation (special pain control analgesic system)

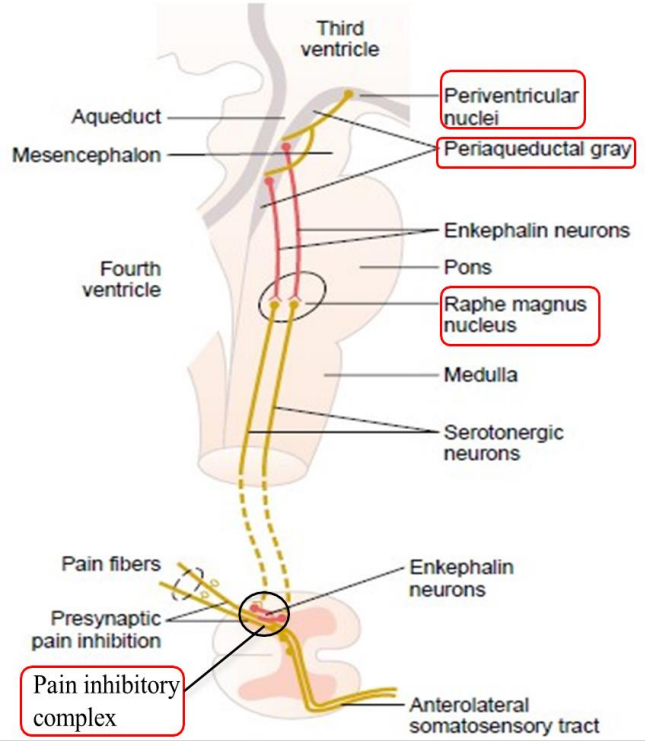
- This is a specific system that blocks pain transmission in CNS. Its major constituents are:

1. The periventricular and periaqueductal gray areas: of the mesencephalon and upper pons surround portions of the third and fourth ventricles and the aqueduct of Sylvius.

2. Raphe magnum nucleus: a thin midline nucleus located in the lower pons and upper medulla.

3. Pain inhibitory complex: In dorsal horn of SC. It consists of multiple short encephalinergic neurons that terminate on central endings of pain conducting afferent fibers.

- When stimulated, the released encephalin cause pre & postsynaptic inhibition of pain transmission.
- It prevents the release of substance P from pain nerve endings.



Analgesia system of the brain and spinal cord, showing (1) inhibition of incoming pain signals at the cord level and (2) presence of enkephalin-secreting neurons that suppress pain signals in both the cord and the brain stem.

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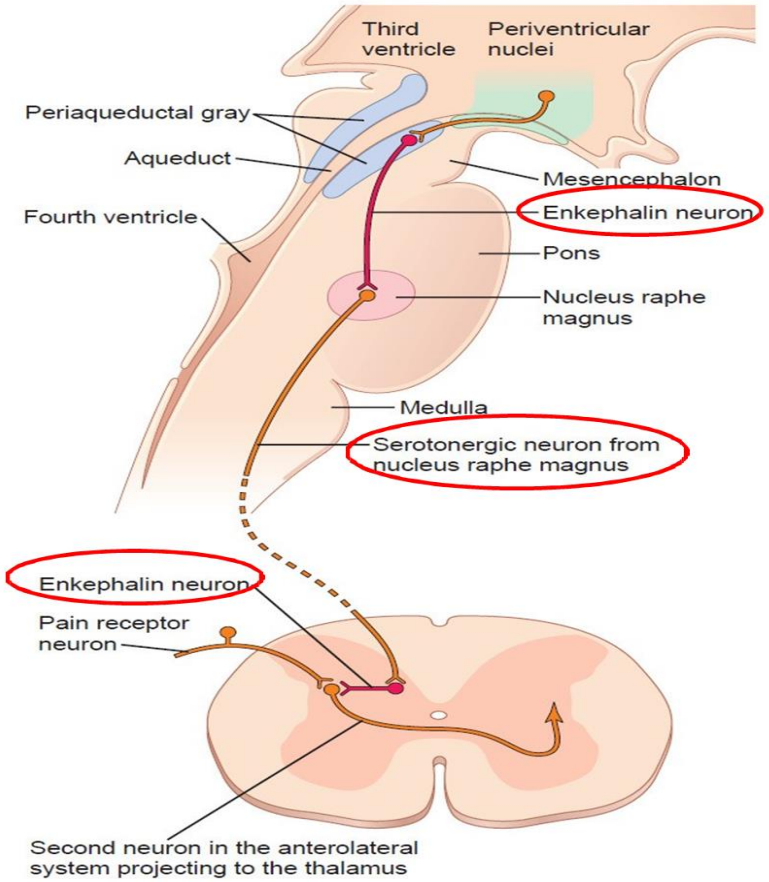
Supra spinal modulation (special pain control analgesic system)

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 encephalin.
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.

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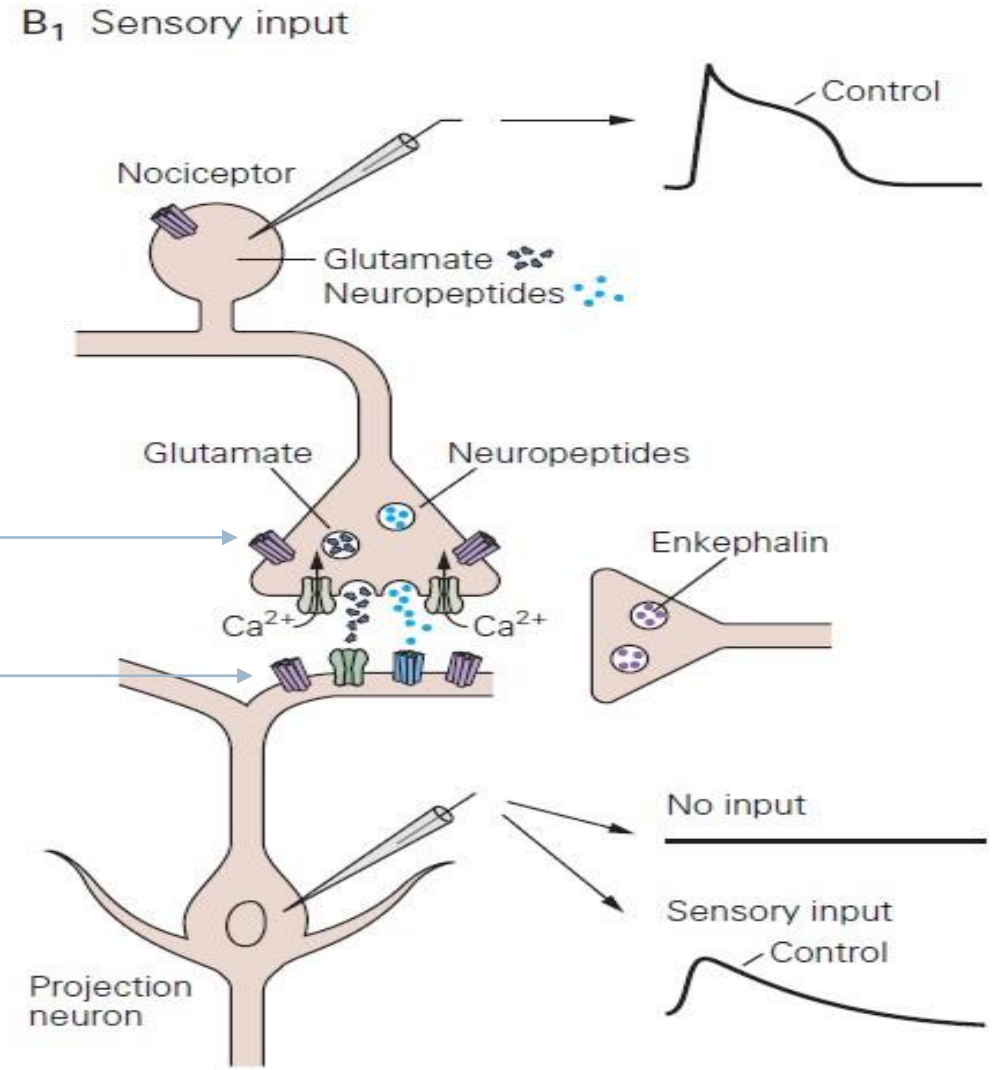
Activation of the presynaptic OR leads to a decrease in Ca^{++} influx, resulting in a decrease in release of glutamate and substance P.

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

- Decrease 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.



Opioid peptides and pain modulation

- Opioid peptides are morphine-like substances present in body.
- They are natural analgesic substances that act by binding to opiate receptors in analgesic system and dorsal horn of sc on central ending of pain conducting pain fibers.

- Site of release of opioid peptides:
  - Endorphin: Are found in PAG where they inhibit GABAnergic interneurons that normally suppress the anti-nociceptor neurons.
  - Enkephalin: It is used by interneurons in lamina II responsible for inhibiting the nocioceptor-specific spinothalamic neurons.
  - Dynorphin: In hypothalamus, PAG, reticular formation, and dorsal horn.
  - Endogenous morphine: In terminals forming synapses with neuron having μ-opioid receptors in pain modulating pathways.

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Mechanism of actions of opioid peptides on pain transmission

- They exerts their analgesic effects by acting at various sites in peripheral & CNS:

A. Direct effect:

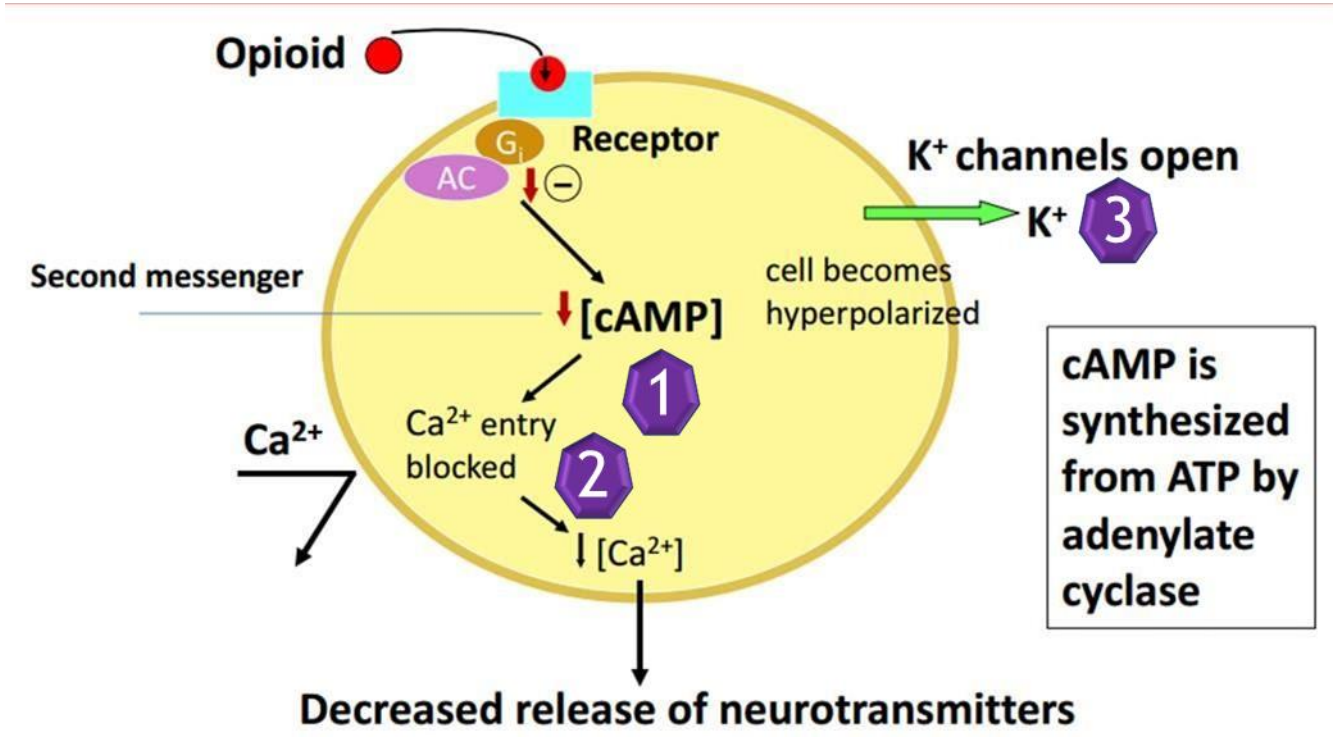
- Inhibiting discharge of nociceptor neurons.
- Inhibiting release of substance P from central terminal of nociceptor neurons.
- Cause inhibition of dorsal horn spinothalamic neuron.

B. Indirect effect:

- Activating the descending inhibitory pathway be exciting.
- PAG neurons.
- Activating neurons in the brain stem which suppress pain transmission directly or indirectly via activation of encephalinergic containing inhibitory interneurons.

Cellular actions of opioid peptides

- Reduction of cAMP synthesis by inhibiting Adenyl cyclase.
- Inhibition of transmitter release by inhibiting opening of Ca++ channels.
- Hyperpolarization by facilitating opening of voltage gated K+ channels.

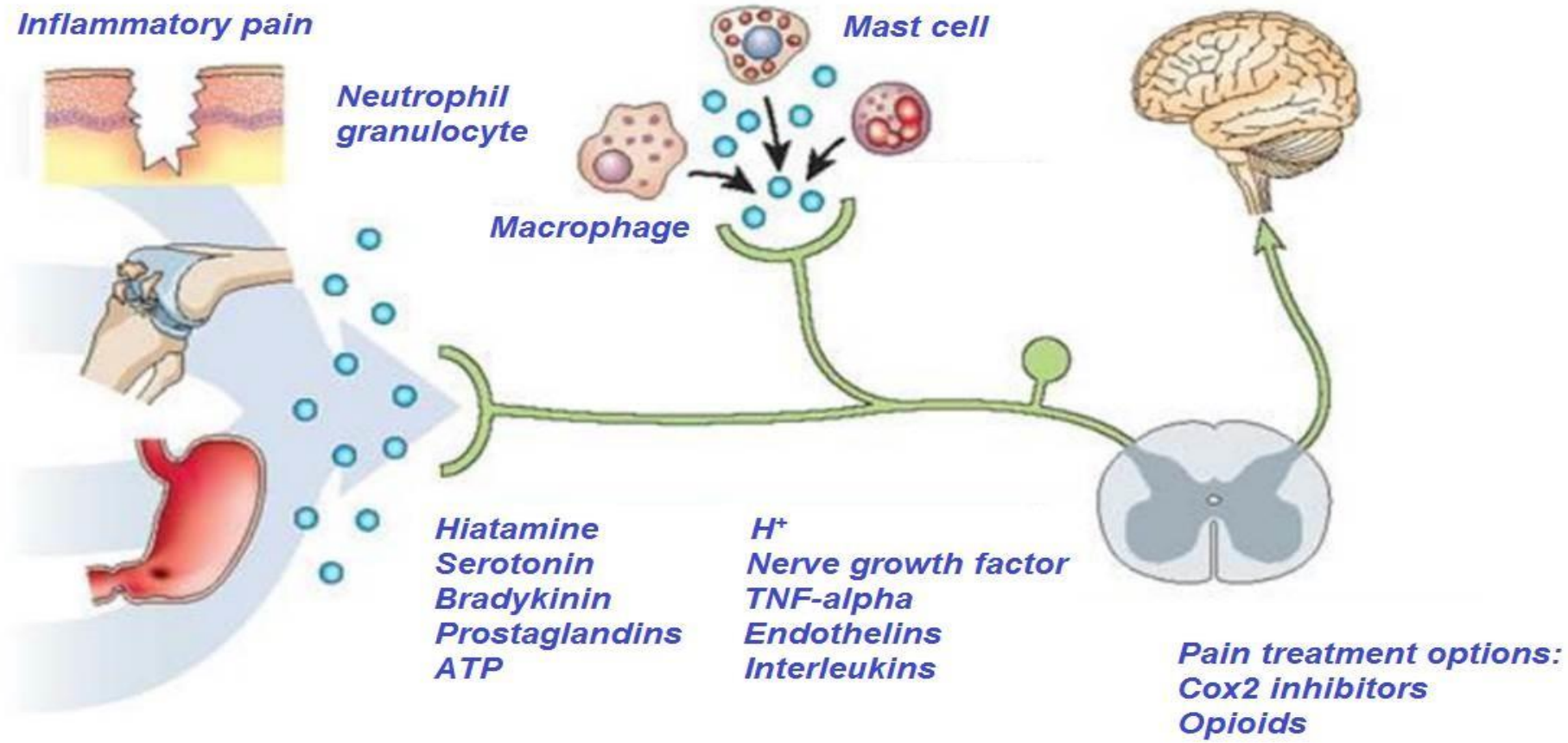


Opioid Antagonist: Naloxone

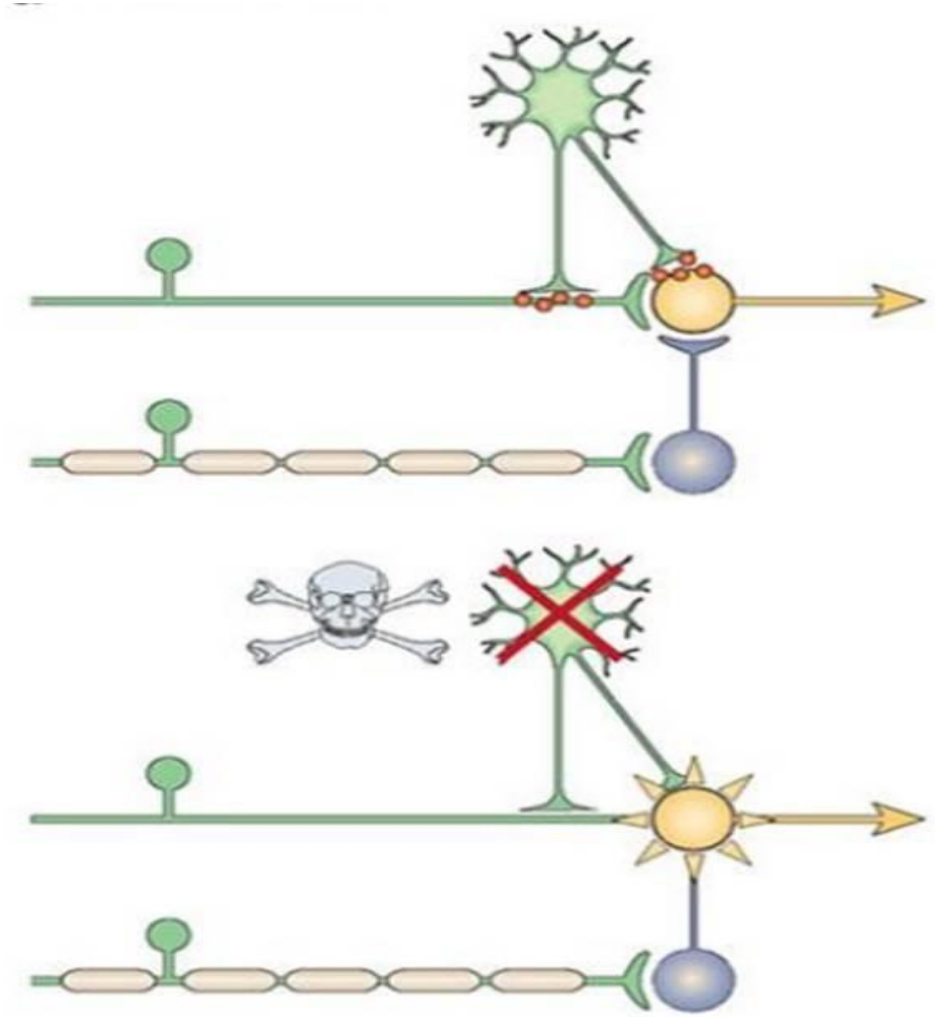
- Used to reverse opioid overdose.
- Displaces receptor-bound opioids.
- Good for overcoming respiratory and CV depression.

Pain facilitation: peripheral sensitization

- Inflammatory mediators can directly activate nociceptors or cause their sensitization (decrease threshold).



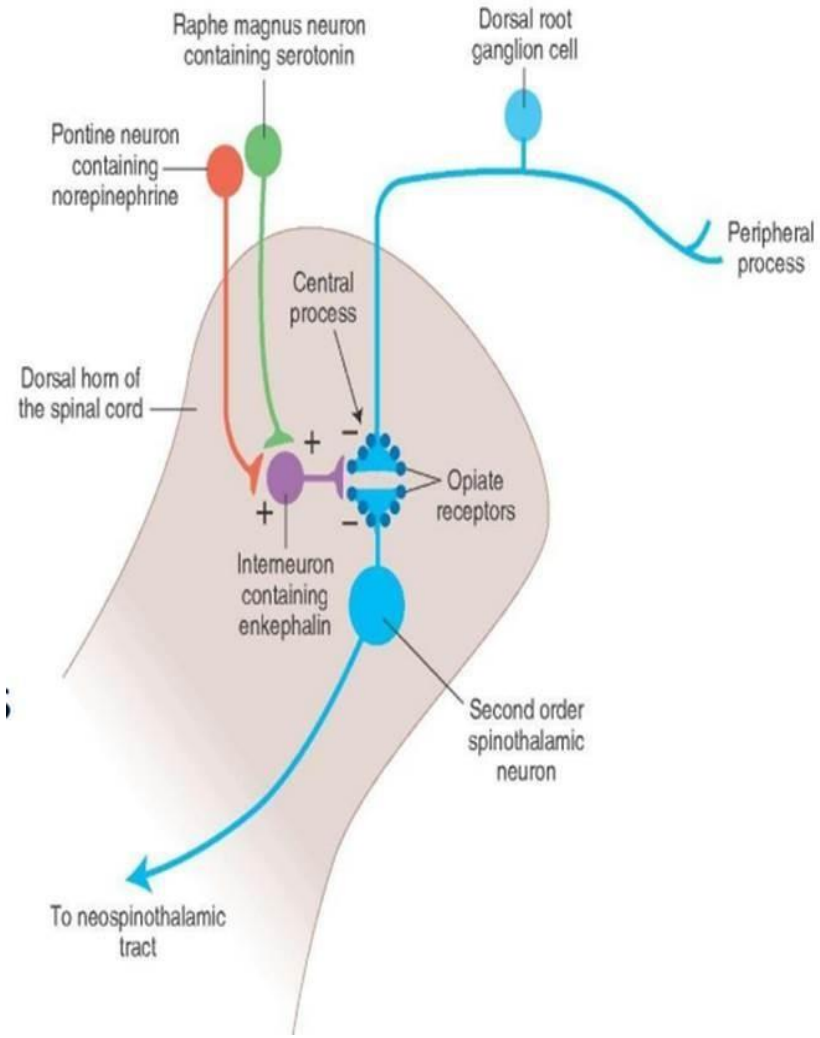
Pain Facilitation: Dis-inhibition



Pain transmission is controlled by inhibitory interneurons

Loss of these inhibitory interneurons after excessive release of glutamate results in increased excitability of projection neurons and thus enhanced pain sensation

Neurotransmitters for pain modulation

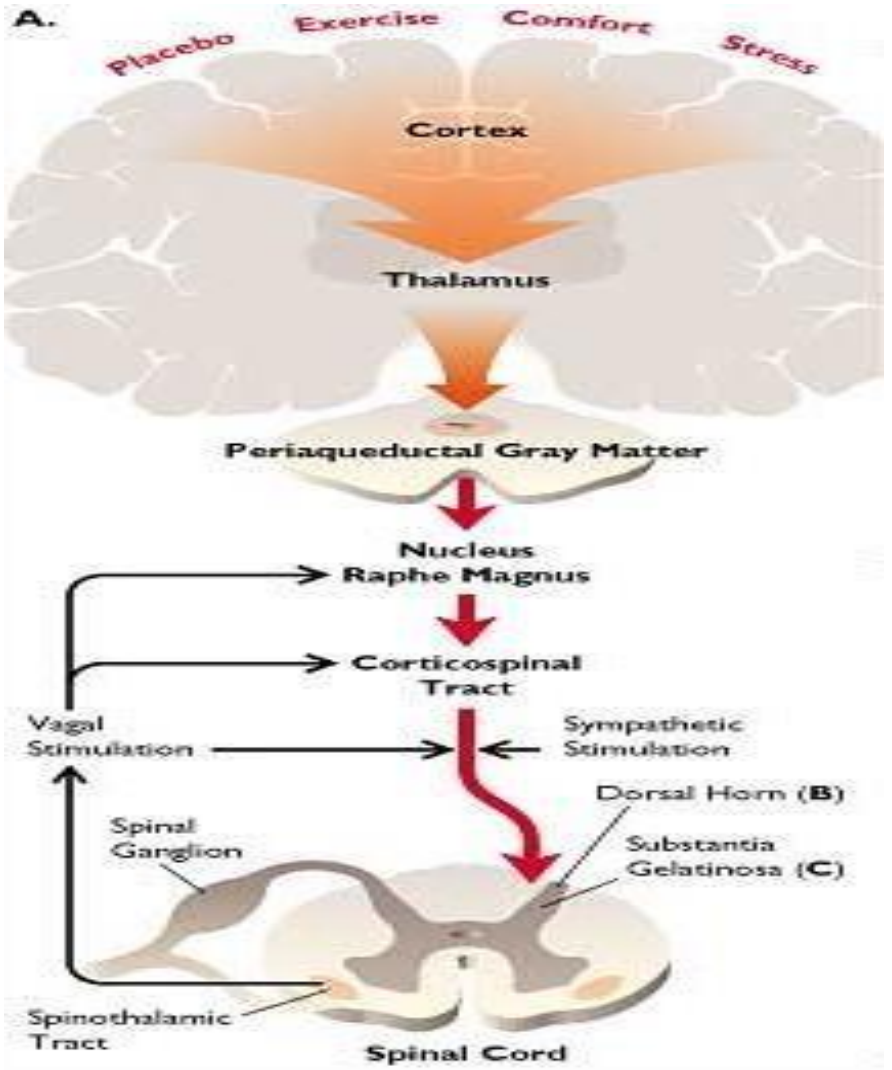


- Serotonin
- Noradrenaline
- Encephalin

- The serotonergic and noradrenergic neurons are crucial in the supraspinal modulation.
- Destroying these neurons with neurotoxins blocks the their analgesic actions.

Analgesia occurs as follows

- Periventricular nucleus projects to PAG.
- PAG projects neurons containing aspartate & glutamate that stimulate raphe magnus nucleus (RMN).
- RMN projects serotoninergic neurons, this in addition to noradrenergic neurons project from locus coeruleus in medulla to dorsal horn. They block pain signals by activating PIC.



Congenital analgesia

- 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.

Stress induced analgesia

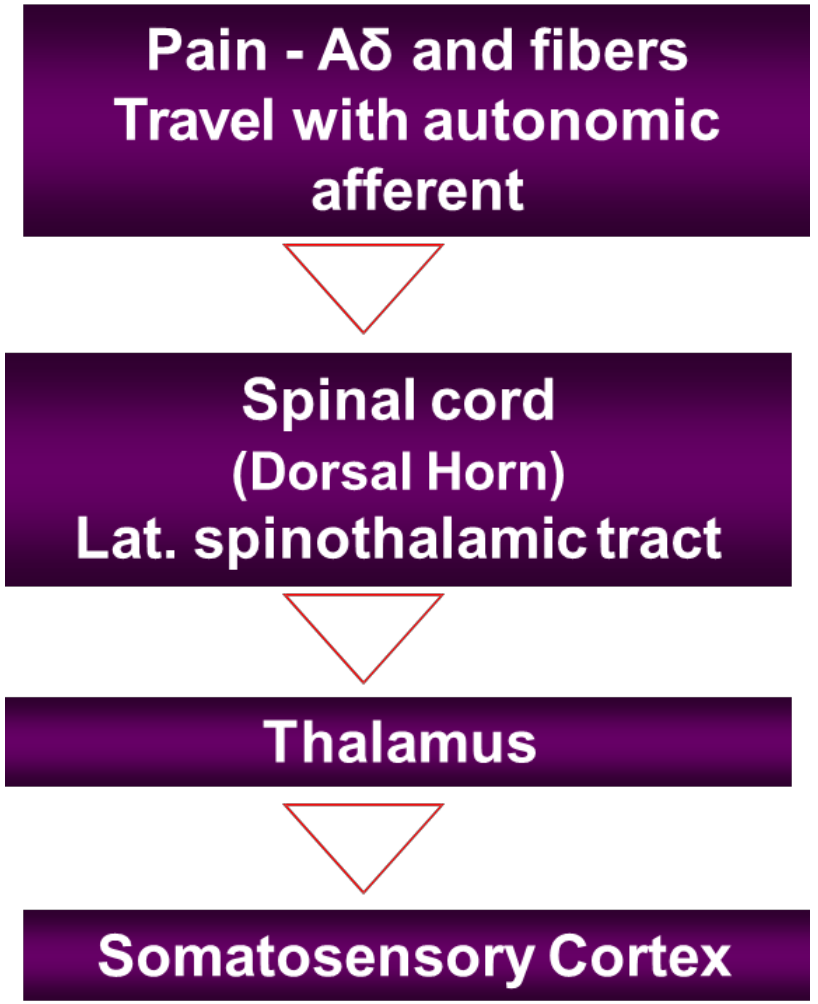
- Pain suppression response that occurs during or following exposure to a stressful or fearful stimulus.
- It's a well known phenomenon seen when the soldier is wounded in battle field but feels no pain until the battle is over.
- The cause is not known may be it is similar to gate control hypothesis.

Phantom pain sensations

- Perceptions that an individual experiences relating to a limb or an organ that is not physically part of the body.

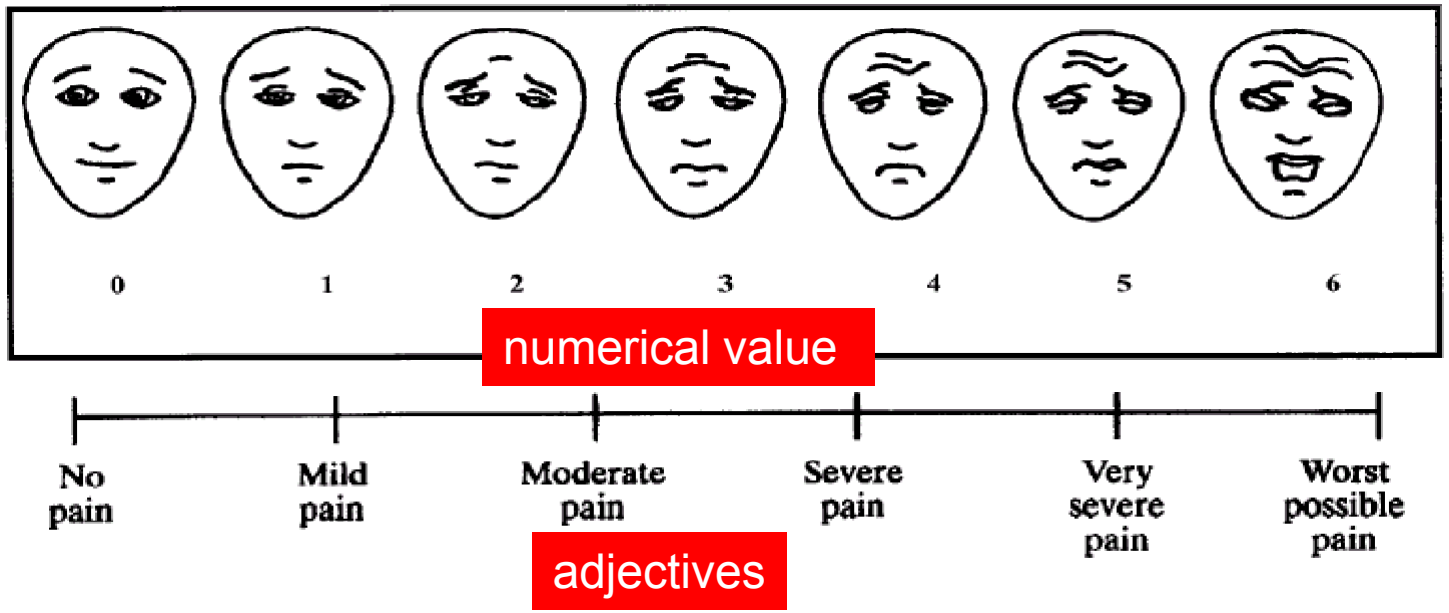
Characteristics of visceral pain

- 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.



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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.

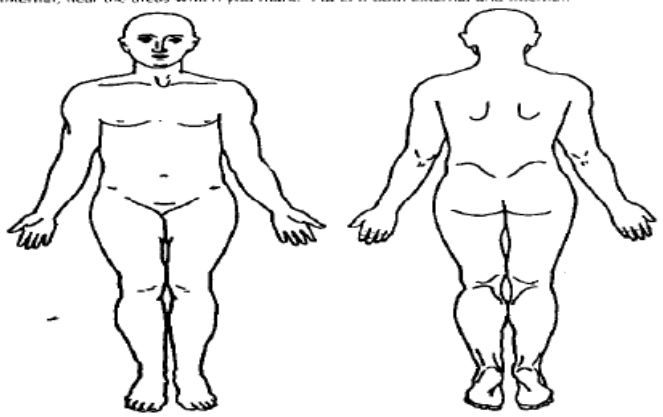
Part 2. What Does Your Pain Feel Like?

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 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 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? _____

ONLY IN MALES' SLIDES

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.

Fibromyalgia: pain without injury

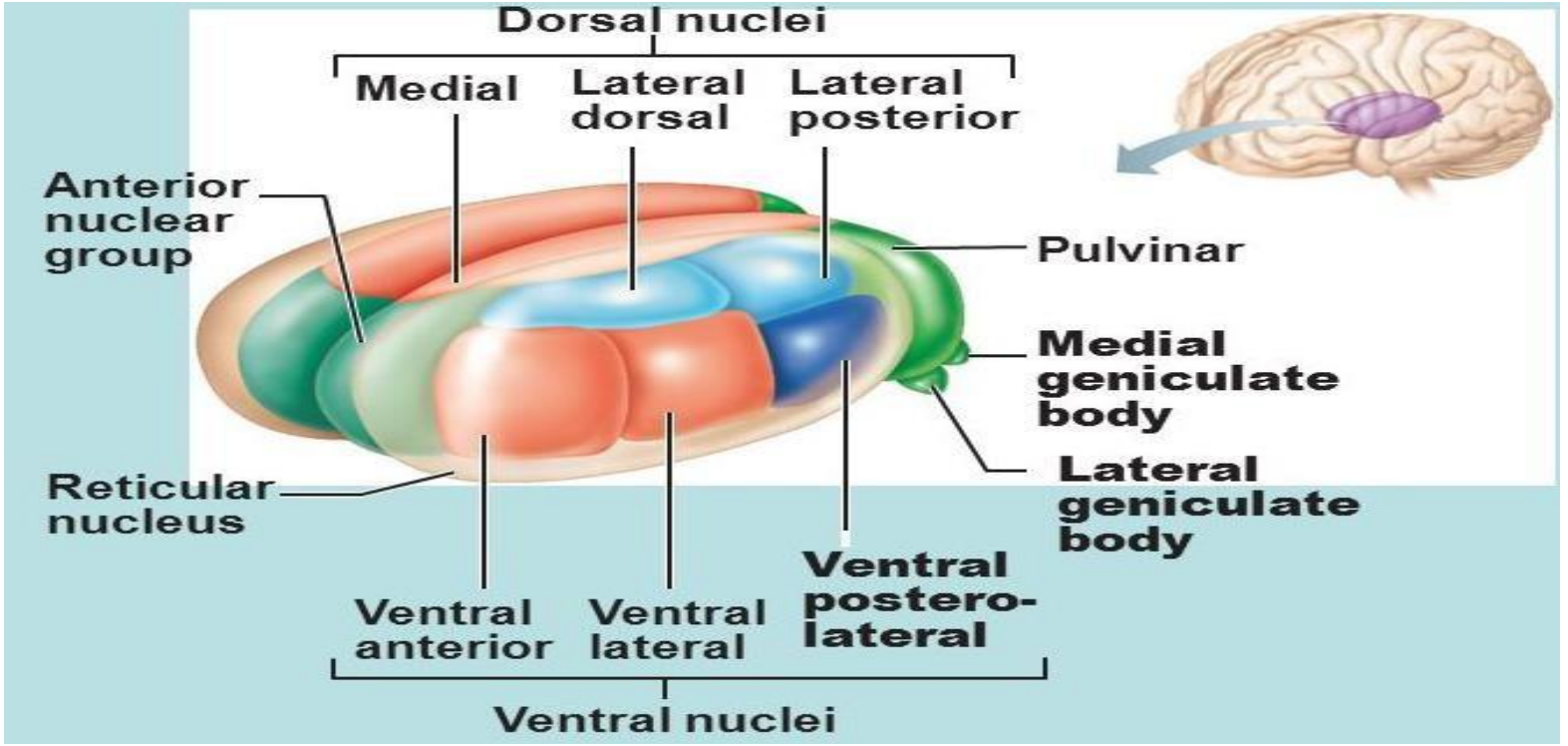
- The occurrence of body-wide pain in the absence of tissue damage, as in fibromyalgia, interferes with all aspects of a person's life and undermines their credibility.
- The problem is that normal activities can be exhausting, sleep is disturbed, the ability to concentrate is impaired, gastrointestinal 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.

Thalamic syndrome

- It is a neurological condition that results from a brain stroke affecting the thalamus.
- Cause: Obstruction of the thalmogeniculate branch of the posterior cerebral artery.
- Affects posterior thalamic nuclei.
- Causes prolonged severe pain.



Trigeminal neuralgia

- It is excruciating intermittent pain by stimulation of trigger area in the face.
- e.g. Washing of face, combing hair, blast of air on face.
- It results from compression of trigeminal nerve root by blood vessels.

Neuropathic pain

- Pain caused by a primary lesion or dysfunction in the nervous system.
- Classification:
  - Central NP-Damage of CNS
  - Peripheral NP- Damage to PNS
- Resistant to the current analgesic therapy.
- Can persist for years.
- Clinical symptoms: Hyperalgesia, allodyni and spontaneous pain
- Examples: post herpetic neuralgia, diabetic neuropathy
- and after chemotherapy.

Mechanism of pain relief

- Block production of inflammatory mediators .e.g. Aspirin & nonsteroidal anti-inflammatories.
- Exogenously administration of opioid like drugs.
- Sympathectomy can be useful.
- Electrical stimulation of the dorsal column.
- Selective activation of large diameter afferent fibers by transcutaneous electrical nerve stimulation.
- Stimulation of brainstem sites or administration of drugs which can modify serotoninergic or adrenergic neurons e.g. antidepressants.

This 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

- This 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

- Pink color refer to (ONLY IN FEMALES' SLIDES)
- Brown color refer to (ONLY IN Males' SLIDES)

Hyperalgesia	Excessive Pain (e.g due to sun burn)
Allodynia	Pain caused by any other sensation e.g. touch will cause pain.
Muscular Pain	Less blood flow in the muscles (ischemia).
Causalgia	Burning pain.
	burning pain Both develop after wound or disease has ended. Triggered by a simple stimulus e.g. breeze or vibration.
Stress analgesia	Mild degree of pain is not felt if the other part of the body has excessive pain.
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.

Applied

ONLY IN MALES' SLIDES

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.

Summary

1. Pain can be modulated by the balance of activity between nociceptive and non-nociceptive afferent inputs (the gate control theory)
2. Pain can be controlled by central mechanisms through pain control descending inhibitory pathways
3. Endogenous opioids contribute to the pain control system
4. Serotonin and noradrenaline are the other non-opioid neurotransmitters that are involved in pain control mechanisms
5. Pain modulation is bidirectional: can be inhibited or facilitated during chronic pain states

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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.)