Pain Modulation

Objectives:

- ***Intensity of the pain can be altered by various extrinsic and intrinsic mechanisms***
- ***know gate-control hypothesis(spinal modulation)and role of body's own morphines, the opioid peptides***
- ***Supra spinal modulation (Special pain control analgesic system).***
- ***know about opioid receptors and are formed in the mid brain, brainstem and spinal cord.***
- **Appreciate that pain can also be facilitated**
- **Know the sites & mechanism of pain relief**

Bold & Italic objectives are included in the medical education guide

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Colour index:
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Editing file

وَأَن لَّيْسَ لِلْإِنسَانِ إِلَّا مَا سَعَىٰ

Terminology

Terminology	Definition
Pain modulation	a decrease or an increase in the sensation of pain caused by inhibition or facilitation of pain signals
Inhibition	Inhibition: ▪Spinal (segmental) inhibition: Gate control theory ▪Supraspinal (descending) inhibition
Facilitation	Facilitation: ▪Peripheral sensitization (release of chemicals after tissue injury) ▪Central sensitization (Dis-inhibition)
Hyperalgesia	Hyperalgesia Excessive Pain (e.g due to sun burn) Primary hyperalgesia: at receptor level " receptor dependent" -Secondary hyperalgesia: at tract level"the tract is hypersensitive""tract dependent"
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.
Muscular Pain	Less blood flow in the muscles (ischemia).
Causalgia	Burning pain.
Stress induced analgesia	Pain suppression response that occurs during or following exposure to a stressful or fearful stimulus.
Phantom pain sensations	Perceptions that an individual experiences relating to a limb or an organ that is not physically part of the body.
Thalamic Syndrome	It is a neurological condition that results from a brain stroke affecting the thalamus Patient suffers from prolonged severe pain Cause: Obstruction of the thalamogeniculate branch of the posterior cerebral artery. ▪ Affects posterior thalamic nuclei.
Trigeminal neuralgia	It is excruciating intermittent pain by stimulation of trigger area in the 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.

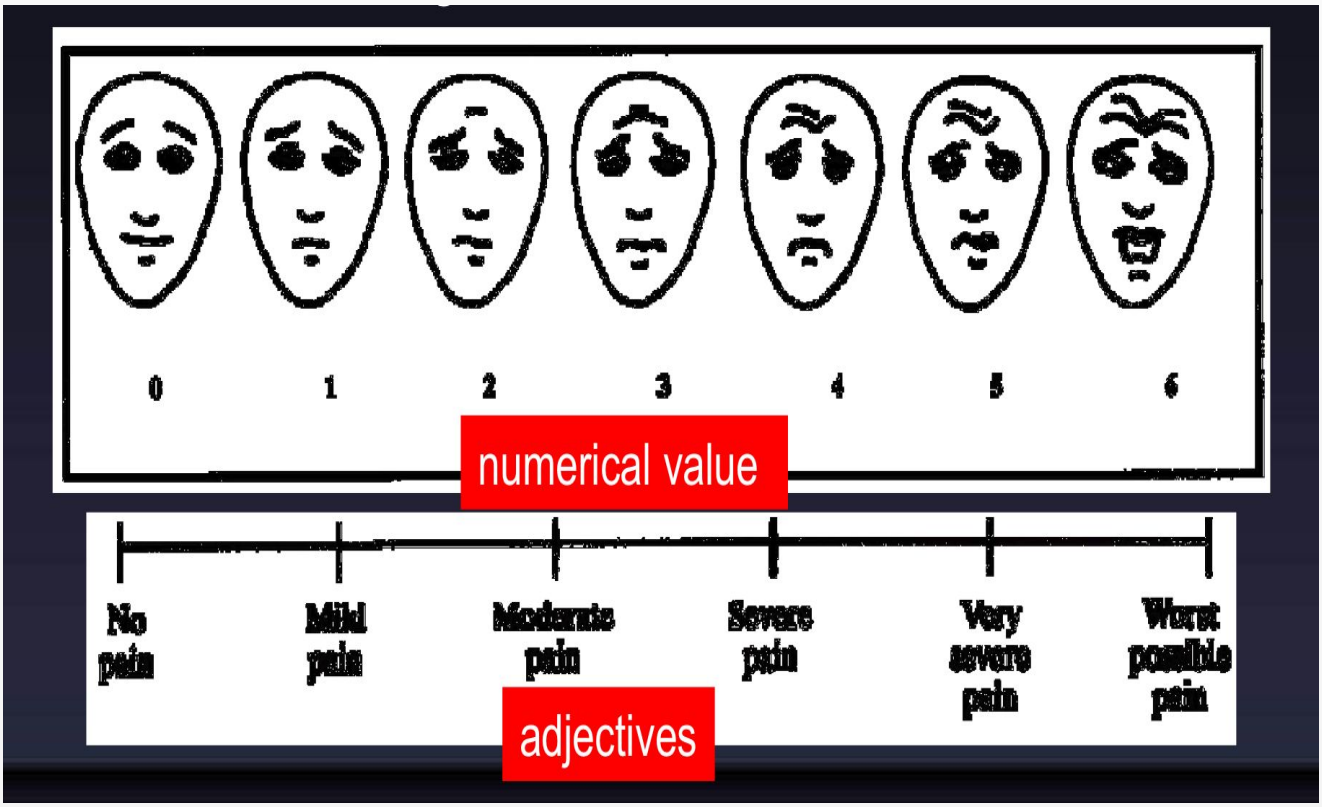
Introduction of Pain Modulation

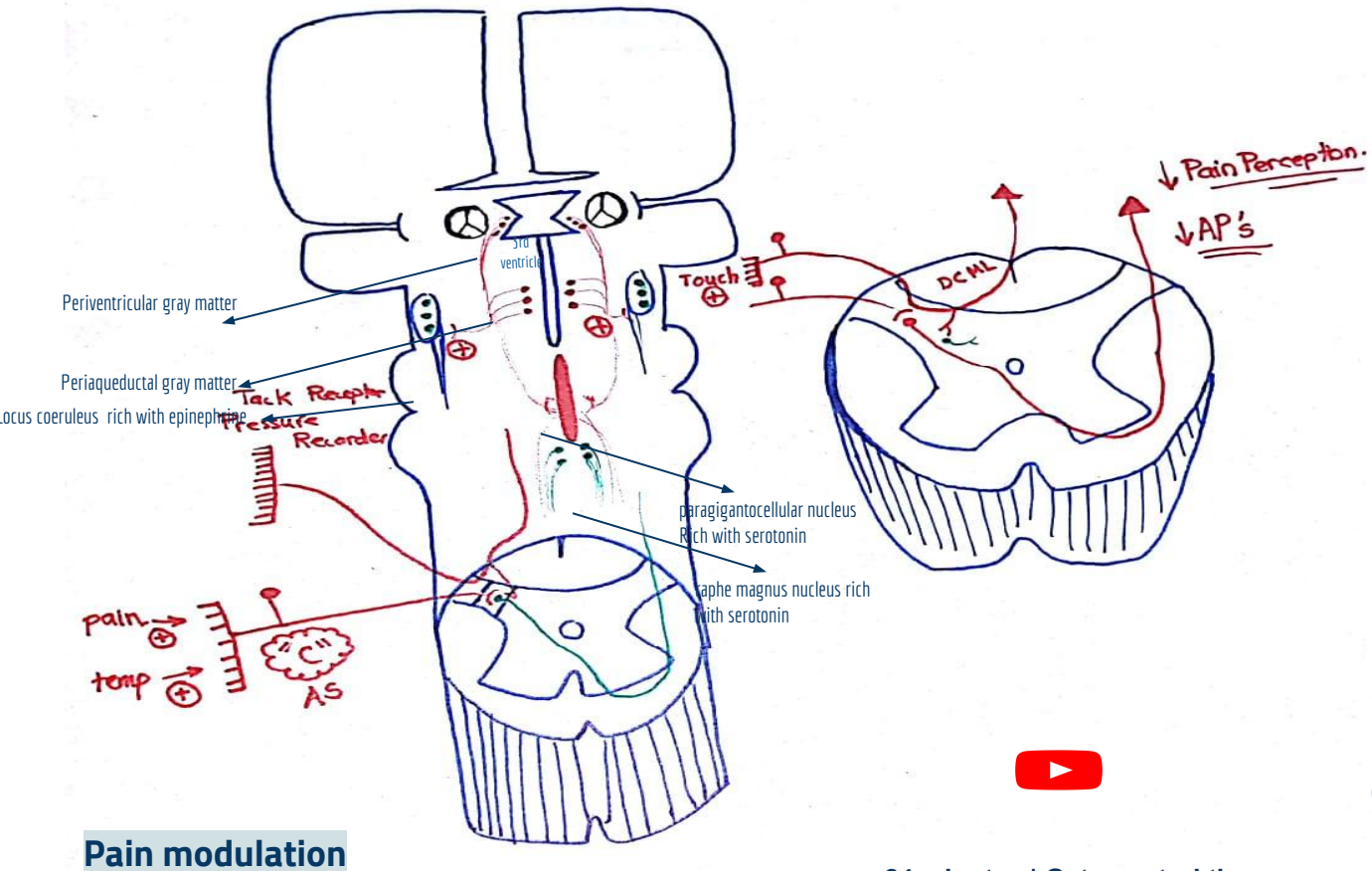
Definition of Pain Modulation:
-To change the pain perception or density by any means.

Pain is modulated by two primary types of **drugs** that work on the brain: analgesics and anesthetics.

Nociception consists of **four basic processes**:
1. **Transduction**—nociceptors free nerve endings "Stimulation of nociceptors"
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] or ascending tract.

-To modulate the pain, you should know firstly the grade or scale of the pain by whether numerical value or adjective chart. Because if you don't know the grade or scale of pain , how can you know that you have modulated the pain.





Pain modulation

24 minutes | Gate control theory

1- Gate control theory

First of all if we have pain we start to rubbing the area to decrease the pain but how this work ?

Remember in the dorsal horn we have 2 different afferent : first one is for the pain & second one is touch afferent , so these touch **fibers gives collateral** to the inhibitory interneurons and start release **GABA** (which will inhibit the cell body in the subtia gelatinosa)

Or **inhibit the action synaptic terminal of dorsal ganglia**

So now we inhibit the pathway and will decrease the action potential so if we decrease AP will **decrease the severity of the pain.**

2- descending Analgesic system -

All the three nucleus (**paragigantocellular nucleus** that

Rich with serotonin , **raphe magnus nucleus** rich with serotonin, **Locus coeruleus** rich with epinephrine) secreted special chemicals called endogenous opioids (**endorphins,Enkephalins,dynorphins** into the inhibitory neuron so then inhibit subtina gelatinosa which will lead to decrease the action potential.

How these nuclei know when to fire to stimulate the periaqueductal gray matter\periventricular gray matter ?

1 - through Ascending lateral system there are spinomesencephalic fibers coming out from it so they can stimulate periaqueductal gray matter

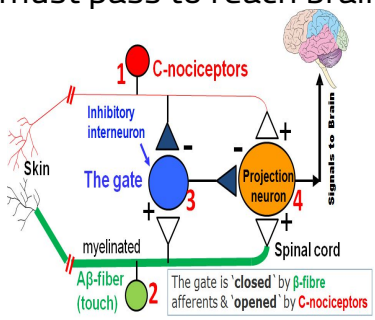
2- through limbic nuclei

3-sensory cortex

The Gate theory of pain control

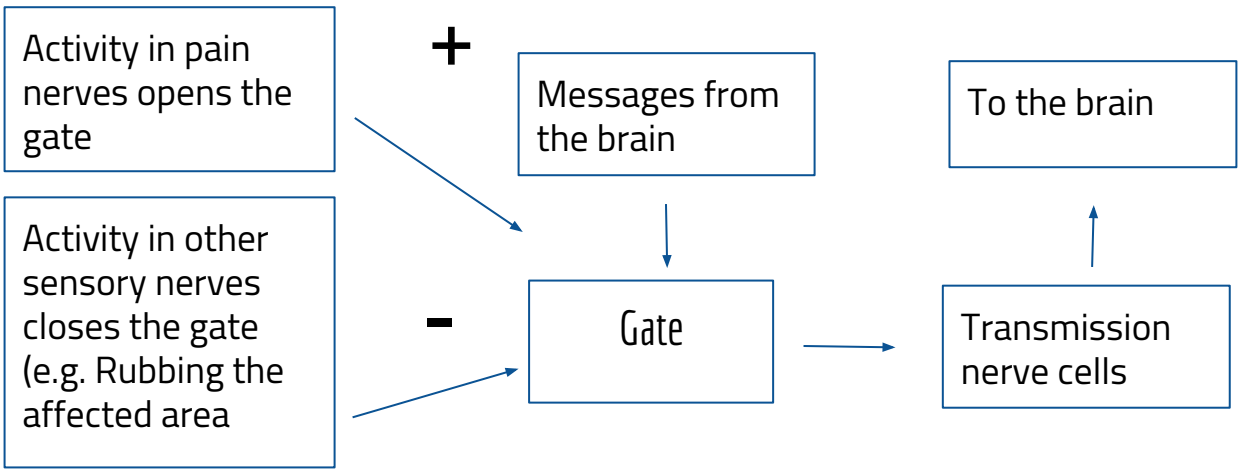
- Special neurons in the the dorsal horn of spinal cord (SGR) subtnia gelatinosa of Ronald form the gate through which pain impulses must pass to reach brain.

Four variables control this gate:



1. Type C- fibres (slow pain). unmyelinated -> open the gate.
2. Type A-β fibres (light touch). "Myelinated - dorsal column system -> close the gate .
3. Inhibitory interneurons.between C-fibers and 2nd order neuron - When they're stimulated they inhibit the transmission of pain signals - when they're inhibited they allow transmission "inhibition of inhibition.
4. Projection neuron.Second order neuron of the spinothalamic tracts.

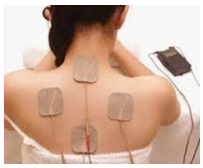
Gate opened or closed by 3 factors:

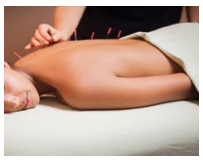


Conditions that open or close the gate:

	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

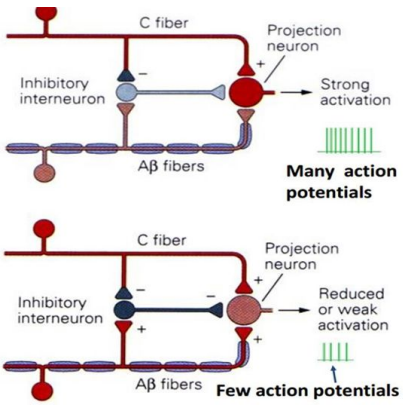
Gate of the pain theory





- The gate theory explains the pain relief by:
  Skin rubbing, Shaking the painful part, Transcutaneous Electrical Nerve Stimulation (TENS), Acupuncture
- All are supposed to stimulate mechanoreceptors that activate neurons of dorsal column, the collaterals relieve pain.

Explanation:



- 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 inhibitory interneuron.
- This theory implies that a non-painful stimulus can reduce transmission of a noxious stimulus.

الـ inhibitory interneuron زي الحارس اللي يحرس البوابة واللي يحرص على ان محد يمر من عندها و لا يفتحها .

- البيتا فايبرز تحمل الـ light touch sensation يعني ماتبينا كل شوي و الثاني نحس بألم، فدائما تحرص على ان هالبوابة تقعد مقفلة.. كيف تحافظ على هالشيء؟ عن طريق تحفيز الـ inhibitory interneuron " خذ قهوة و اشتغل ياصديقي وخلك سهران على حراسة البوابة! انتبه لحد يجي!".
- السي فايبرز تحمل الـslow pain فتبينا نحس بالألم.. طيب كيف؟ بتجي عند الحارس وبتعطيه حلاوة زي الأطفال علشان يلتهي عن الباب ويخليه مفتوح.. المصاصة هنا هي الـsubstance P اللي تُفرز من السي فايبرز .. "فعمل السي فايبرز تثبيط المثبط يعني تفتح البوابة- الجملة ممكن تحوس بس فكروا فيها شوي.

زبدة الكلام:

- **Beta-fibers** → light touch → activate inhibitory interneuron → close the gate.
- **C-Fibers** → slow pain → inhibit inhibitory interneuron → open the gate.

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 **enkephalin**.
- **Enkephalin** is an opiate substance similar to heroin which can block substance P, the neurotransmitter from the C fibers, and this keeps the gate closed.

موب قلنا ان البوابة تنفتح او تنكسر بـ3 عوامل.. تكلمنا عن أول عاملين اللي هم السي فايبرز و البيتا فايبرز .. الحين بدينا نتكلم عن العامل الثالث اللي هو تحكم الـbrain. كيف يتحكم؟ يرسل إشارات عن طريق نوروز معينة تخلي البوابة حساسة للفايبرز اللي يبيها..

Supra spinal modulation (Special pain control analgesic system)

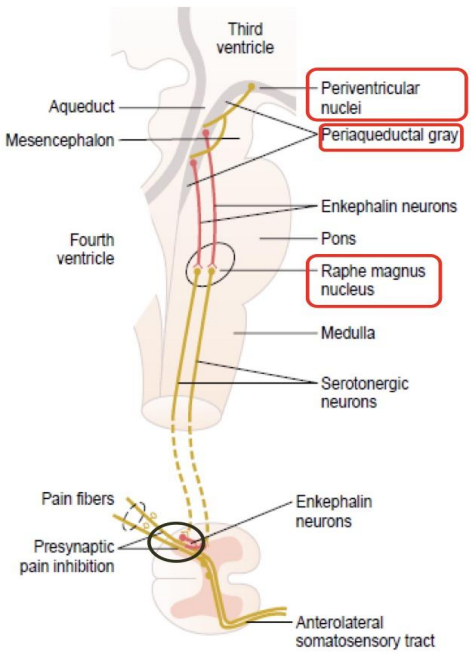
- This is a specific system that blocks pain transmission in CNS.

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 magnus 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 enkephalinergic neurons that terminate on central endings of pain conducting afferent fibers. ● When stimulated the **release enkephalin** cause pre & postsynaptic inhibition of pain transmission. ● It prevents the release of substance P from pain nerve endings.

Analgesia occurs as follows:

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



Summary:
Periventricular nucleus → PAG "aspartate + glutamate" → RMN "serotonin" + NE "from locus coeruleus" → activation of PIC → pain blocking.

❖ Opioid Peptides and Pain Modulation

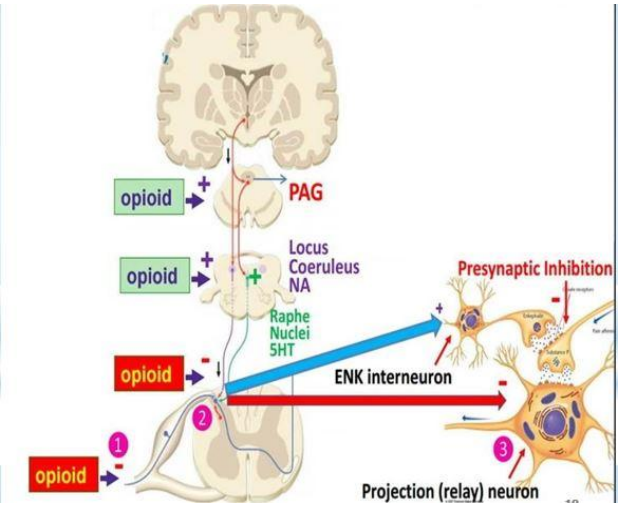
Opioid peptides are **morphine-like** substances present in body.

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

تلخبطتوا ؟ ببساطة احنا نثبط عمل الجابا اللي كانت تسوي تثبيط في Anti -nociptor



Encephalin: 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.

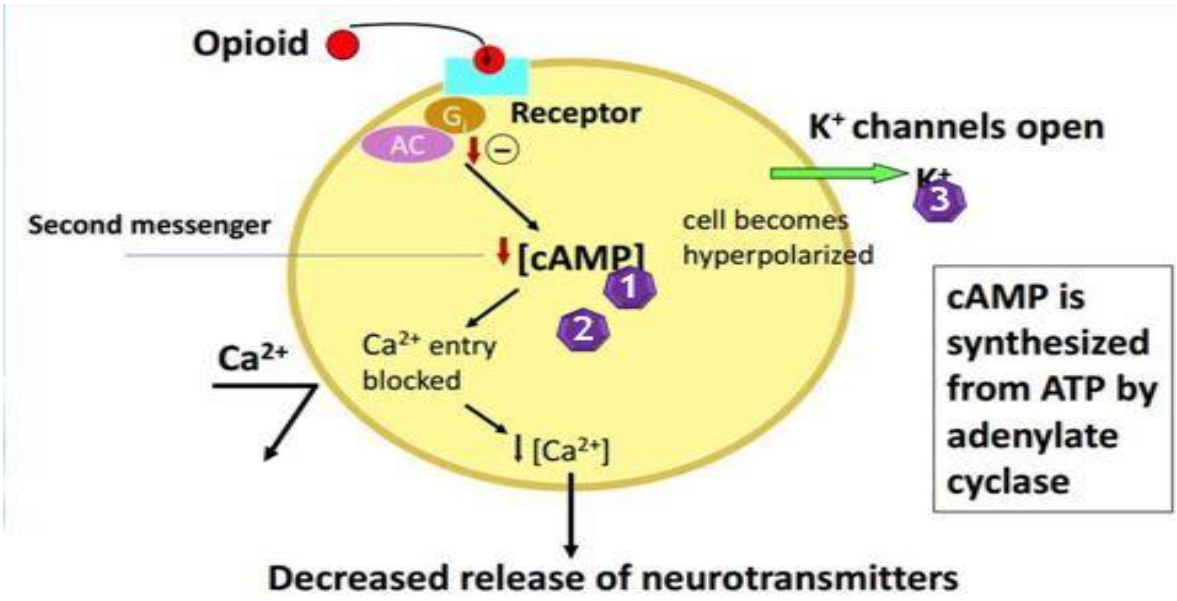
Endogenous morphine: In **terminals** forming synapses with neuron having μ-opioid receptors in pain modulating pathways.

Mechanism of actions of Opioid peptides on pain transmission

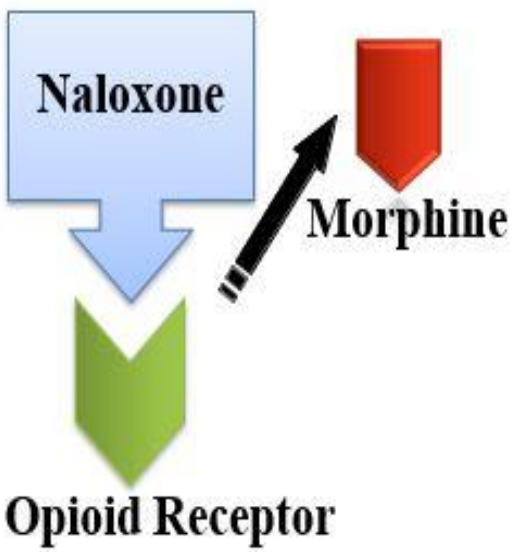
They exerts their analgesic effects by acting at various sites in peripheral & CNS

Direct effect	Indirect effect
Inhibiting discharge of nociceptor neurons	Activating the descending inhibitory pathway be exciting PAG neurons
Inhibiting release of substance P from central terminal of nociceptor neurons	Activating neurons in the brain stem which release NE and serotonin which suppress pain transmission directly or indirectly via activation of enkephalinergic containing inhibitory interneurons
Cause inhibition of dorsal horn spinothalamic neuron. Via K channel causing hyperpolarization.	

Cellular actions of Opioid peptides



- Reduction of cAMP (second messenger) synthesis by inhibiting Adenyl cyclase
- Inhibition of transmitter release by inhibiting opening of Ca^{++} channels
- Hyperpolarization by facilitating opening of voltage gated K^{+} channels



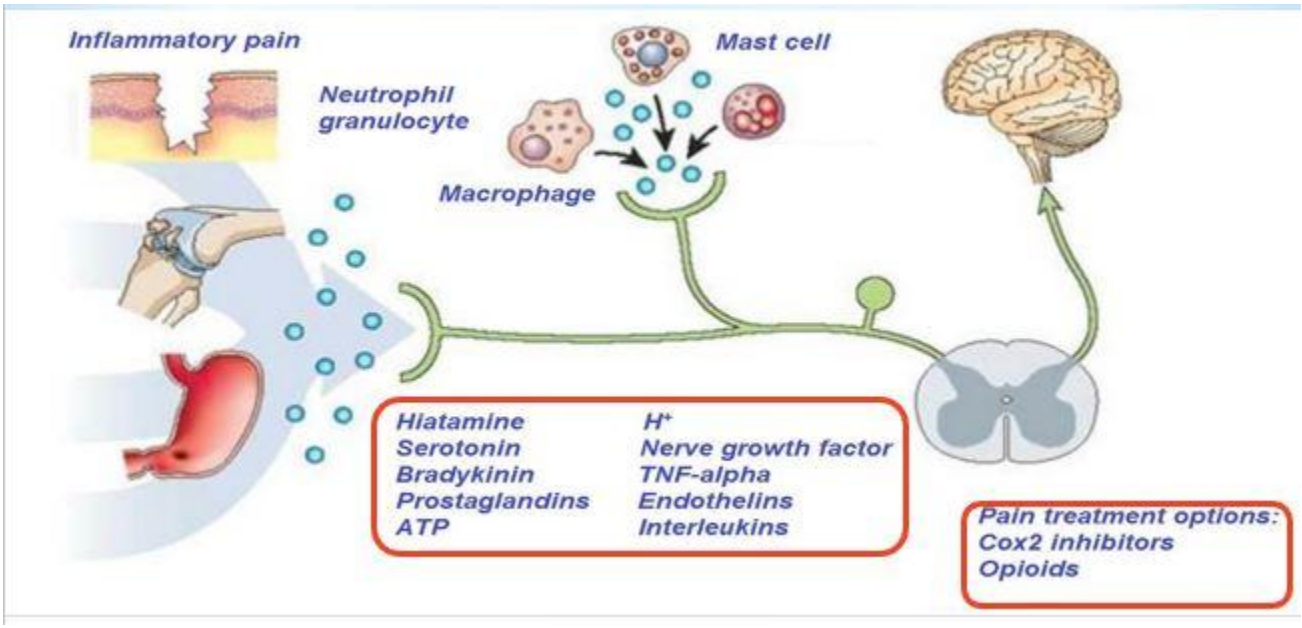
Opioid Antagonist: Naloxone

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

هو بكل بساطة يتنافس مع الاوبيودز زي المورفين على نفس الريسبتور، فيقل تأثير المورفين و الاوبيودز بشكل عام.

❖ Pain Facilitation

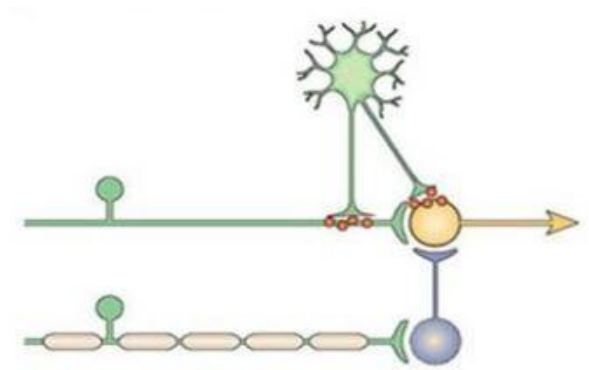
Pain Facilitation: Peripheral Sensitization



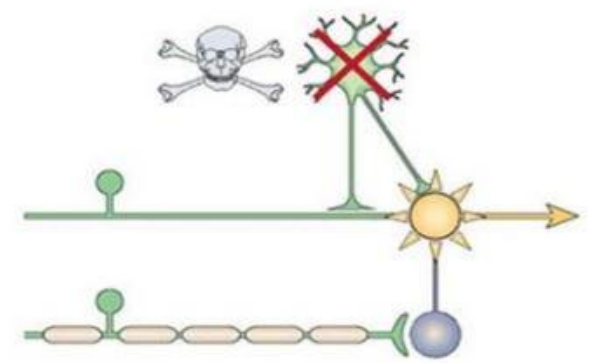
➢ Inflammatory mediators can directly activate nociceptors or cause their sensitization (decrease threshold)

نراجع الفاوندیشین شوي :)؟
Acute inflammation is characterized by 5 cardinal signs: **rubor** (redness), **calor**(increased heat), **tumor** (swelling), **dolor** (pain), and **functio laesa** (loss of function) .
كيف صار هالـpain؟ عن طريق الـinflammatory mediators بروستا قلاندن على سبيل المثال

Pain Facilitation: Dis-inhibition

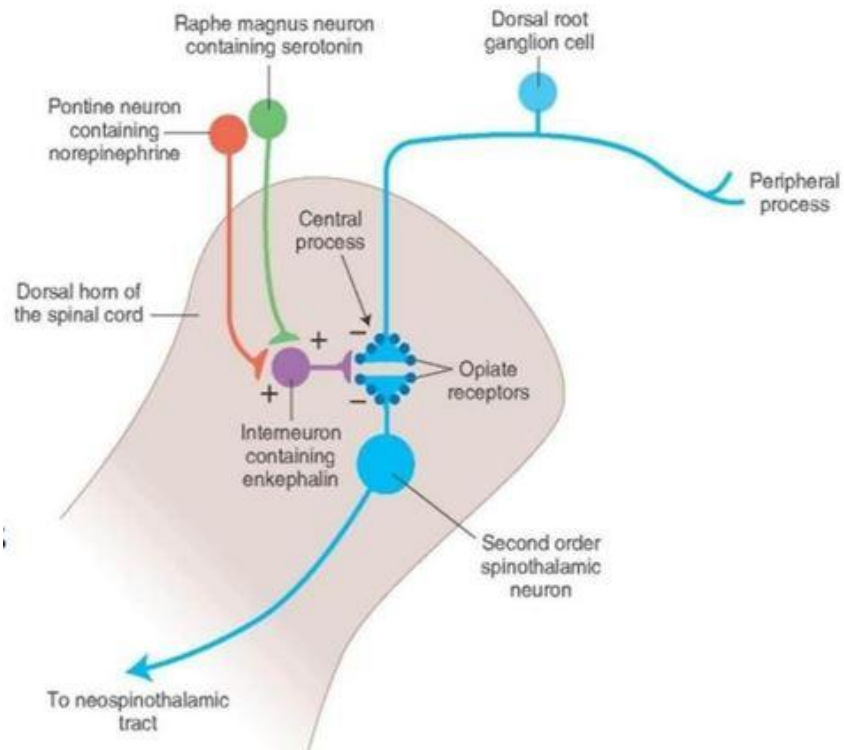


- Pain transmission is controlled by inhibitory interneurons



- Loss of these inhibitory interneurons after excessive release of glutamate results in increased excitability of projection neurons (second order neurons of spinothalamic tracts) 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

❖ mechanism of pain relief

- Block production of inflammatory mediators .e.g. Aspirin & nonsteroidal anti-inflammatories.They block prostaglandins.
- 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

Questions

1. **A 10-year-old boy cuts his finger with a pocketknife and immediately applies pressure to the damaged area with his other hand to partially alleviate the pain. Inhibition of pain signals by tactile stimulation of the skin is mediated by which type of afferent neurons from mechanoreceptors?**

A) α-type A. B) β-type A. C) δ-type A. D) Type C

2. **Stimulation of which brain area can modulate the sensation of pain?**

A) Superior olivary complex. B) Locus ceruleus
C) Periaqueductal gray area. D) Amygdala

3.**Which of the following is a group of neurons in the pain suppression pathway that uses enkephalin as a neurotransmitter?**

A) Postcentral gyrus B) Nucleus raphe magnus
C) Periaqueductal gray area D) Type AB sensory fibers

4. **Which of the following conditions can open the gate which means the pain pathway will not be inhibited?**

A)Focusing on the pain. B) Rest C) Medications D) Positive emotions