Physiology 435 team

PAIN MODULATION

Objectives:

- Describe the built-in pain suppression analgesic system including:
  - Spinal modulation (Gate theory of pain control).
  - Supraspinal modulation (special pain control analgesic system).
- **Pain modulation by opioid neurotransmitters.**
- **Appreciate that pain can be also facilitated.**
- **Know the site and mechanism of pain relief.**

Done by:

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Pain modulation:

Definitions:

- Pain perception **variability** "the degree to which a person reacts to pain".
- A decrease or increase in the sensation of pain 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 (disinhibition).**

Pain Inhibition: 1- Gate theory of pain control:

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

The gate (SGR) is controlled by 4 variable:

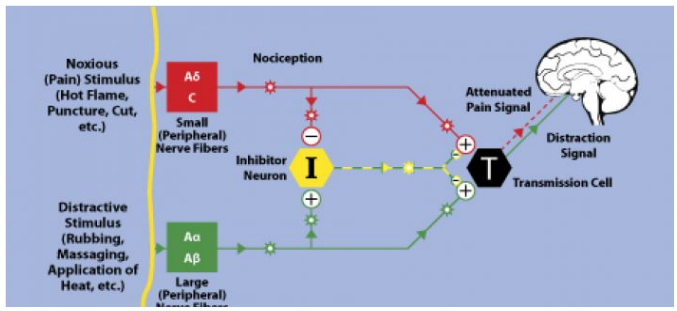
1. **C- fibers** (slow pain). "unmyelinated" → **open the gate.**
2. **A-Beta fibers** (**light** touch)"Myelinated - dorsal column system" → **close the gate**
1. **Inhibitory interneurons.** (between C-fibers and 2nd order neuron - When they're stimulated they inhibit the transmission of pain signals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

Gate opened or closed by 3 factors:

4. **Activity in the pain fibers → Opens** the gate → by **C**-nociceptors.
5. **Activity in other sensory nerves → Closes** the gate → by ***Beta***-fibers. "Like rubbing the affected area".
6. Messages **from the brain.**

Explanation: "not extra :)"

for better understanding,please follow with picture



- Projection neurons (T in the picture above) 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 **inhibit** the inhibitory neurons which will **open the gate**.
- While impulses coming along **Aβ fibers** tend to **keep the gate closed** by **activating the inhibitory neurons**.

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

- البيتا فايبرز تحمل الـ light touch sensation يعني ماتبينا كل شوي والثاني نحس بألم، فدائما تحرص على ان هالبوابة تقعد مقفلة.. كيف تحافظ على هالشيء؟ عن طريق تحفيز الـ inhibitory interneuron " خذ قهوة واشتغل 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 الـ substance p اللي تُفرز من السي فايبرز.. "فعمل السي فايبرز تثبيط المثبط يعني تفتح البوابة- الجملة ممكن تحوس بس فكروا فيها شوي.

So this theory implies that ***a non-painful stimulus can reduce transmission of the noxious stimulus***.

زبدة الكلام:

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

- The gate theory explains the pain relief by **skin rubbing**, **shaking the painful part**, Transcutaneous Electrical Nerve Stimulation (**TENS**[1]) & **acupuncture**.

- All are supposed to stimulate **mechanoreceptors** (A-beta fibers) that activate neurons of dorsal column, the collaterals relieve pain.

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 fibres, 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..

Pain Inhibition: 2- Supraspinal modulation (Special pain control analgesic system):

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

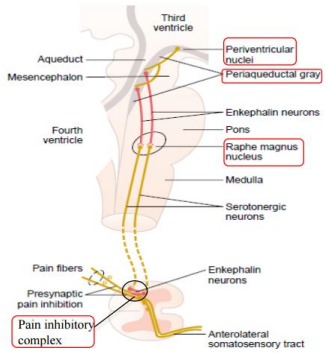
Its major constituents are:

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].
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 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.

[1] **Transcutaneous electrical nerve stimulation** (**TENS or TNS**) is the use of electric current produced by a device to stimulate the nerves for therapeutic purposes.
[2] A narrow channel in the mesencephalon that connects the third and fourth ventricles.

Analgesia occurs as follows:

- **Periventricular** nucleus projects to **PAG**[3].
- 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**[4].



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.

Summary:

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

Opioid peptides and pain modulation:

What are they?

- 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 **GABAergic** interneurons that normally suppress the **anti-nociceptor neurons**.
Enkephalin	It is used by interneurons in **lamina II** responsible for inhibiting the **nociceptive-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 pathway.

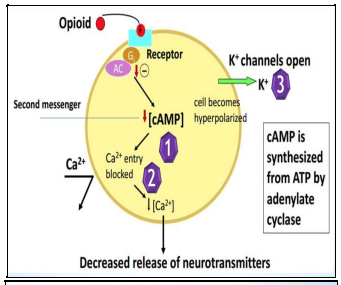
Mechanism of actions of opioid peptides on pain transmission:

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

Direct effect:	Indirect effect:
1. Inhibiting **discharge** of nociceptive neurons. 2. Inhibiting release of **substance P** from central terminal of nociceptive neurons. 3. Cause inhibition of dorsal horn **spinothalamic neuron**. Via K channel causing hyperpolarization.	1. Activating the descending inhibitory pathway by **exciting PAG neurons**. 2. 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.

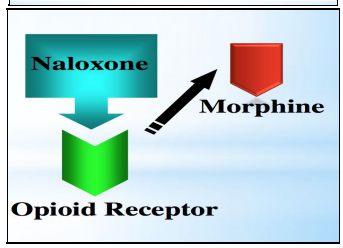
[3] Periaqueductal gray.
[4] Pain inhibitory complex.

Cellular actions of opioid peptides:



1. Reduce **cAMP** (second messenger) synthesis by **inhibiting** adenylyl cyclase.
2. Inhibiting opening of **Ca** channels, so **inhibiting transmitter release**.
3. Facilitate opening of **K** channels causing **hyperpolarization**.

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.

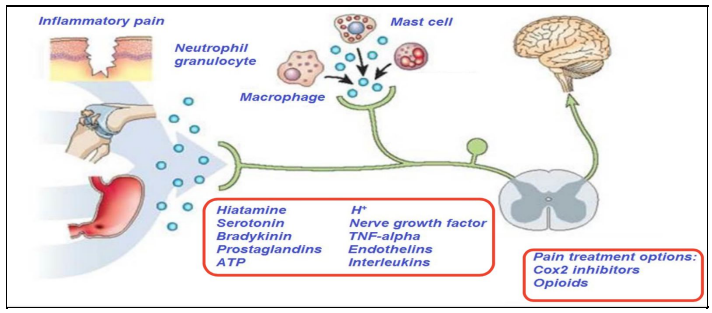
Pain Facilitation:1- Peripheral Sensitization.

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

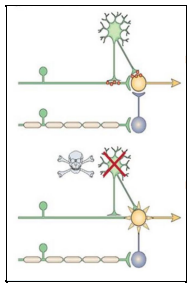
نراجع الفاونديشين شوي :)؟

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



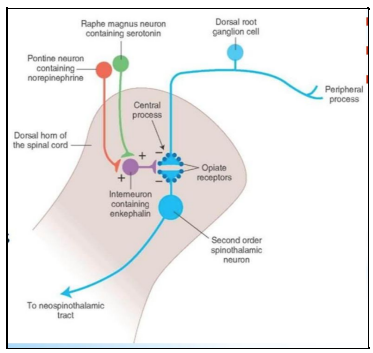
Pain Facilitation: 2-central Sensitization (disinhibition):



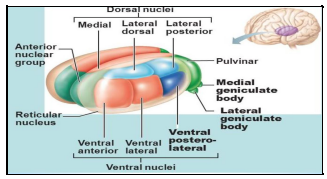
- Pain transmission is controlled by inhibitory interneurons.
- Loss of these inhibitory interneurons after excessive release of **glutamate** results in **increased excitability** of projection neurons "second order neurons of spinothalamic tracts" and thus **enhanced pain sensation**.

Neurotransmitter for pain modulation:

Non opioid:	- Serotonin. - Noradrenaline.	- The serotonergic and noradrenergic neurons are crucial in **supraspinal modulation**. - Destroying these neurons with neurotoxins blocks the their analgesic actions.
Opioid:	Enkephalin.	



Terms frequently used

Hyperalgesia:	Excessive pain e.g due to **sunburn.**
Allodynia:	Pain caused by any other sensation e.g **touch will cause pain.**
Muscular pain:	Less blood flow in the muscles e.g. **ischemia.**
Causalgia:	**Burning pain.**
Stress induced analgesia:	- Mild degree of pain is not felt if the other part of the body **has excessive pain.** - 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:	Pain felt in an **amputated** part long after amputation was done.
Thalamic syndrome:	**-Cause:** obstruction of the **thalamogeniculate** 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. **- Examples**. washing of face, combing hair, blast of air on face. **- It results from** compression of trigeminal nerve root **by blood vessels**.
Chronic pain:	- Chronic pain can be considered as **bad pain** because it persists long after injury and is often refractory to pain killers. **- Chronic pain caused by nerve injury** is called **neuropathic pain**. - E.g. prolonged pain due to cancer.
Neuropathic pain:	- Pain caused a primary lesions or dysfunction in the nervous system. **- Classification:** • **Central NP-Damage of CNS.** • **Peripheral NP-Damage of PNS.** - Resistant to current analgesic therapy. - Can persist for years. **- Clinical symptoms:** Hyperalgesia, allodynia, and spontaneous pain. **- Examples:** postherpetic neuralgia, diabetic neuropathy, and after chemotherapy.

site and mechanism of pain relief:

- Block production of inflammatory mediators.e.g. Aspirin and nonsteroidal anti-inflammatories. They block prostaglandins.
- Sympathectomy can be useful.
- Exogenously administration of opioid like drugs.
- Electrical stimulation of the **dorsal column** can alleviate pain originating below site of stimulation.
- Selective activation of large diameter afferent fibers by transcutaneous electrical nerve stimulation.
- Stimulation of brainstem sites or administration of drugs which can modify **serotonergic** or **adrenergic neurons** e.g. **antidepressants**.

★ **References:**

- 435 girls slides and notes.
- Wikipedia.