LECTURE 30

Pain Modulation

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OBJECTIVES

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

- Describe the control of pain perception including:
  - Spinal modulation (Gate theory of pain control).
  - Supra spinal modulation (Special pain control analgesic system).
  - Pain modulation by opioid neurotransmitters.
- Sites & mechanism of pain relief.

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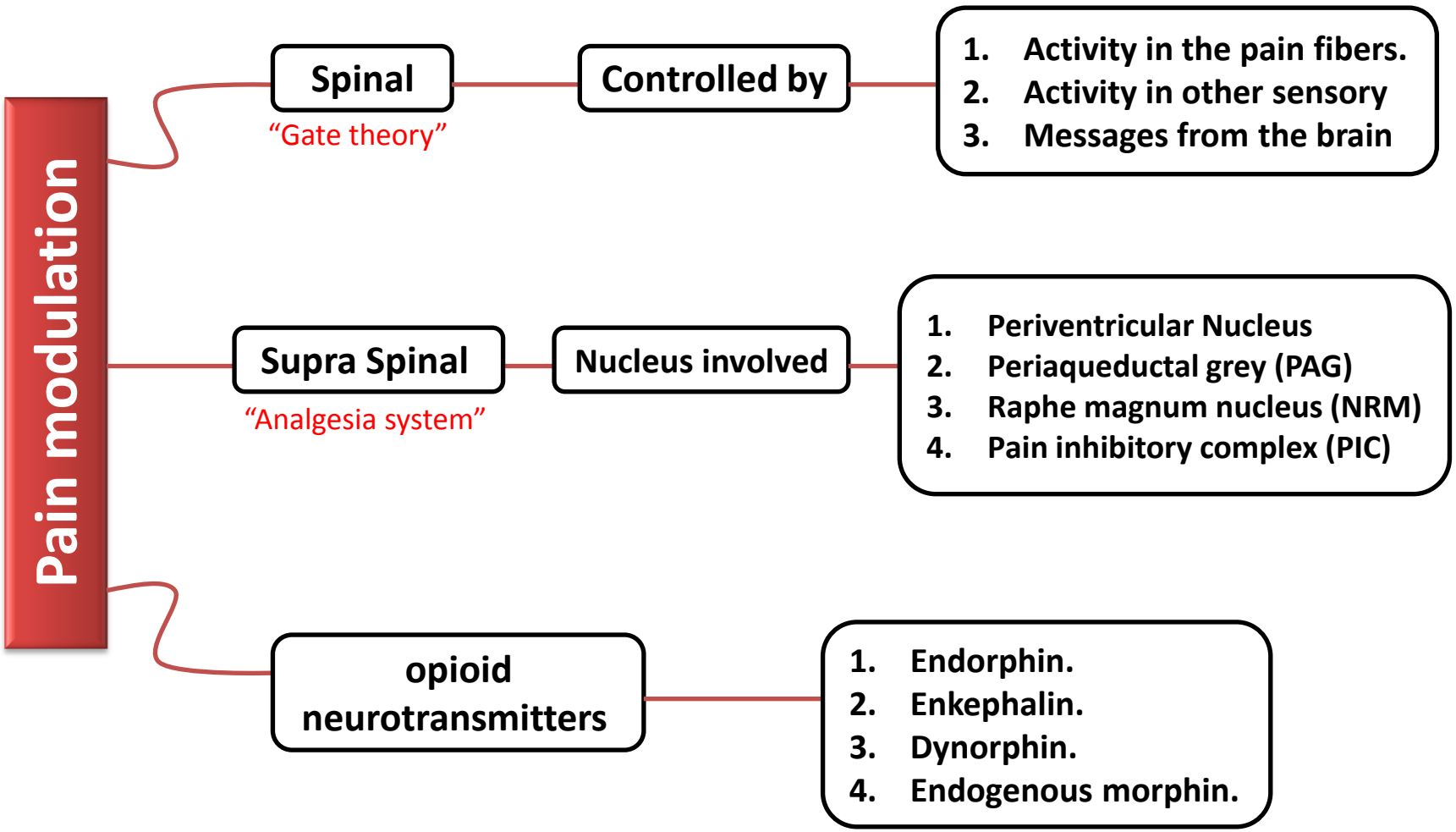
MIND MAP



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Pain Modulation

- Pain modulation means pain perception variability (which means changing your perception for painful stimulus; like you have a sever, noxious pain but you feel it just as a mild pain and vice versa).
- Pain modulation is influenced by:
  - Endogenous mechanism.
  - Exogenous mechanism e.g.:
    - Anesthesia.
    - Drugs like morphine.
    - Some medication has analgesic effect.
    - Surgical treatment for sever pain.

- Pain modulation can be discussed under following headings:
  - Spinal modulation of pain input:
    1. Gate theory of pain
  - Supra spinal modulation (Special pain control analgesic system):
    1. Role of periaqueductal grey matter (PAG).
    2. Role of Nucleus Raphe Magnus (NRM).
  - Pain modulation by opioid neurotransmitters eg:
    1. Endorphin, Enkaphalin, Dynorphin

The Gate Theory of Pain Control

There is a gate in the spinal cord which control pain entry. If it open you will perceive pain sensation and if it closed it will prevent or alleviated "decrease" pain sensation

Non-painful input closes the gate to painful input

Special neurons in the dorsal horn of spinal cord (SGR = substantia gelatinosa of rolando) form the gate through which pain impulses must pass to reach brain.
(SRG)= second order neuron of paleo-spinothalamic tract.

- Three variables control this gate: fiber affect the neuron in SRG:

1- A-delta fibers for fast pain*.
2- C-fibers for slow pain*.
3- A-beta fibers of the dorsal column system for light touch.

*1 and 2 are sensory pain fibers.

The Gate Theory of Pain Control

- This gate has the ability to block the signals from the A-delta and C fibers "at the level of spinal cord" preventing them from reaching the brain. To decrease pain sensation.

- Gate opened or closed by 3 factors:

  1. Activity in the pain fibers (A-delta and C-fibers).

     the release of neurotransmitter in these fibers: (Substance P in slow pain and Glutamate in fast pain) will stimulate the second order neuron of spinothalamic tract and opens the gate which will cause pain perception in the brain.

  2. Activity in other sensory nerves - like A-β fibers - closes the gate.

  3. Messages from the brain. Either by sending inhibitory impulses to close the gate or excitatory impulses to open it.

The Gate Theory of Pain Control

- How it works -

- Impulses coming along type C pain fibers cause the release of substance P from these fibers and tend to open the gate.
- While impulses coming along A-β fibers tend to keep the gate closed by process of presynaptic inhibition of C fibers (prevent the release of substance P from presynaptic neuron) and postsynaptic inhibition of secondary neurons in dorsal horn. (Hyperpolarization of postsynaptic membrane of second order neuron).
- If impulses in the C and A-Delta Fibers are stronger than the A-β Fibers the gate opens.
- If impulses in the A-β Fibers are stronger than the C and A-Delta Fibers the gate closes.
- A-delta fibers are always stronger. Fast pain will be felt rapidly.

The Gate Theory of Pain Control

- How it works -

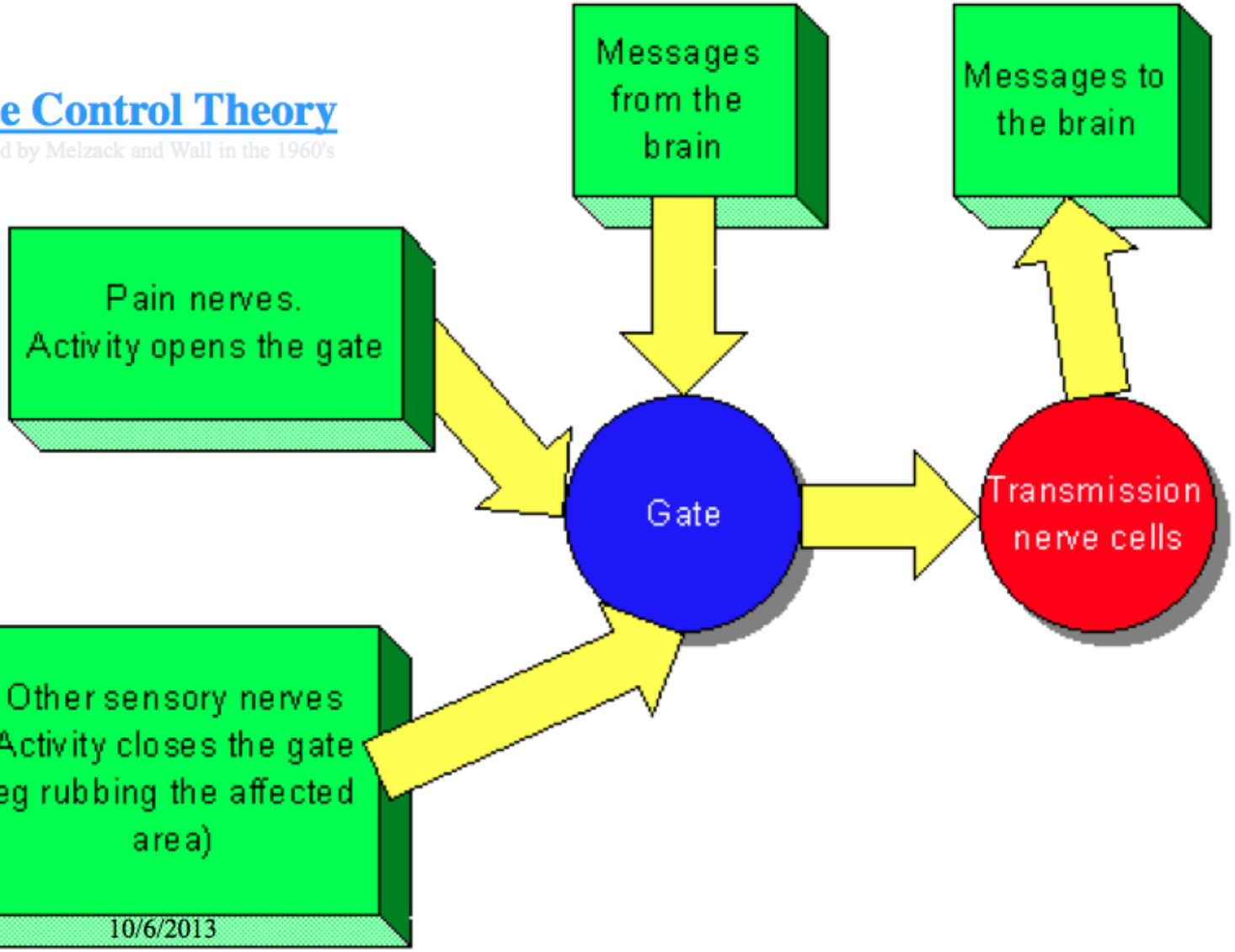
- The gate is under control of higher centers:

Specialized nerve impulses arise in the brain itself and travel down the spinal cord to influence the gate. This is called the central control trigger and it can send both inhibitory and excitatory messages to the gate sensitizing it to either C or A-β fibers.

- The inhibitory neurons make a pain blocking agent called Enkephalin "analgesic substance" . This is an opiate substance similar to heroin which can block Substance P "presynaptic inhibition" the neurotransmitter from the C fibers and this keeps the gate closed.

Gate Control Theory

Proposed by Melzack and Wall in the 1960's



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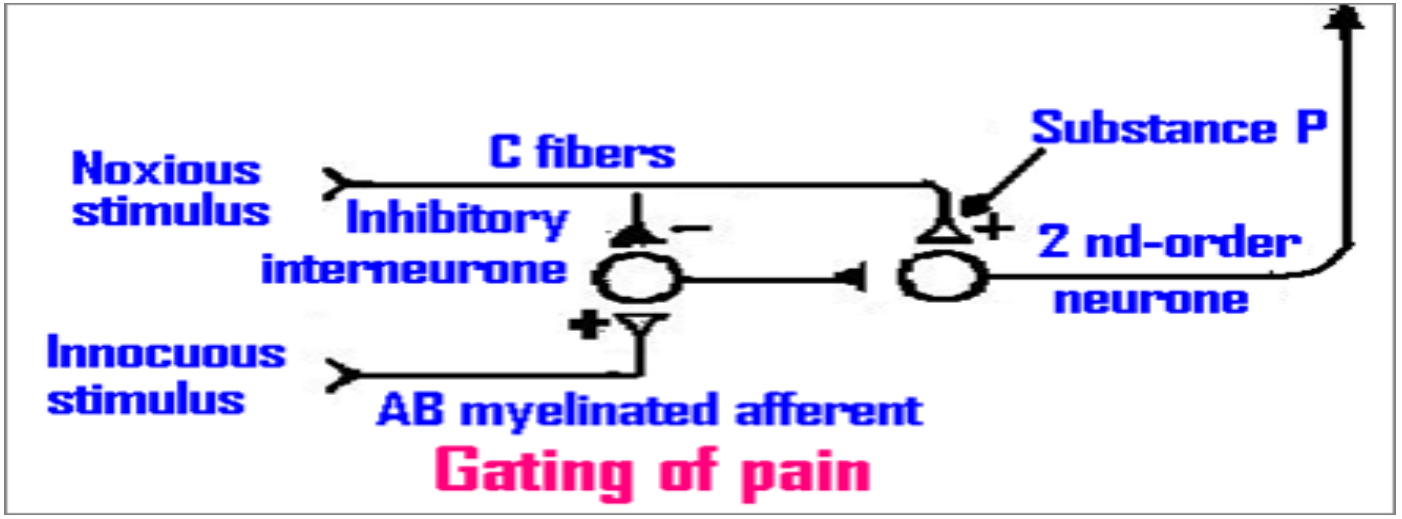
The Gate Theory of Pain Control

The gate theory explains the pain relief by skin rubbing, shaking the painful part, acupuncture (الابر الصينية) & Transcutaneous Electrical Nerve Stimulation (TENS).
All are supposed to stimulate mechanoreceptors that activate neurons of dorsal Column (A-beta fibers), the collaterals= "inhibitory interneurons" relieve pain.

Stimulation of mechanoreceptors will stimulate A-β fibers → stimulation of inhibitory interneurons → inhibit transmission along C-fibers. " indirect inhibition"



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Supra spinal modulation

(Special pain control analgesic system)

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

(1) Periventricular Nucleus in hypothalamus near third ventricle

(2) Periaqueductal grey (PAG) area in midbrain and periventricular areas of the mesencephalon and upper pons.

(3) Raphe magnum nucleus (NRM) (serotonin) in lower pons and upper medulla + the nucleus reticularis paragiganto cellularis (norepinephrine).

1+2+3 produce analgesic substances which decrease the pain transmission at the level of spinal cord and then alleviate pain sensation.

(4) Pain inhibitory complex (PIC) in dorsal horn of SC "PIC =inhibitory interneurons".

It consists of multiple short enkephalinergic neurons that terminate on central endings of pain conducting afferent fibers. "Type C fibers"

When stimulated the released enkephalin cause pre & postsynaptic inhibition of pain transmission i.e it prevents the release of substance P from pain nerve endings.

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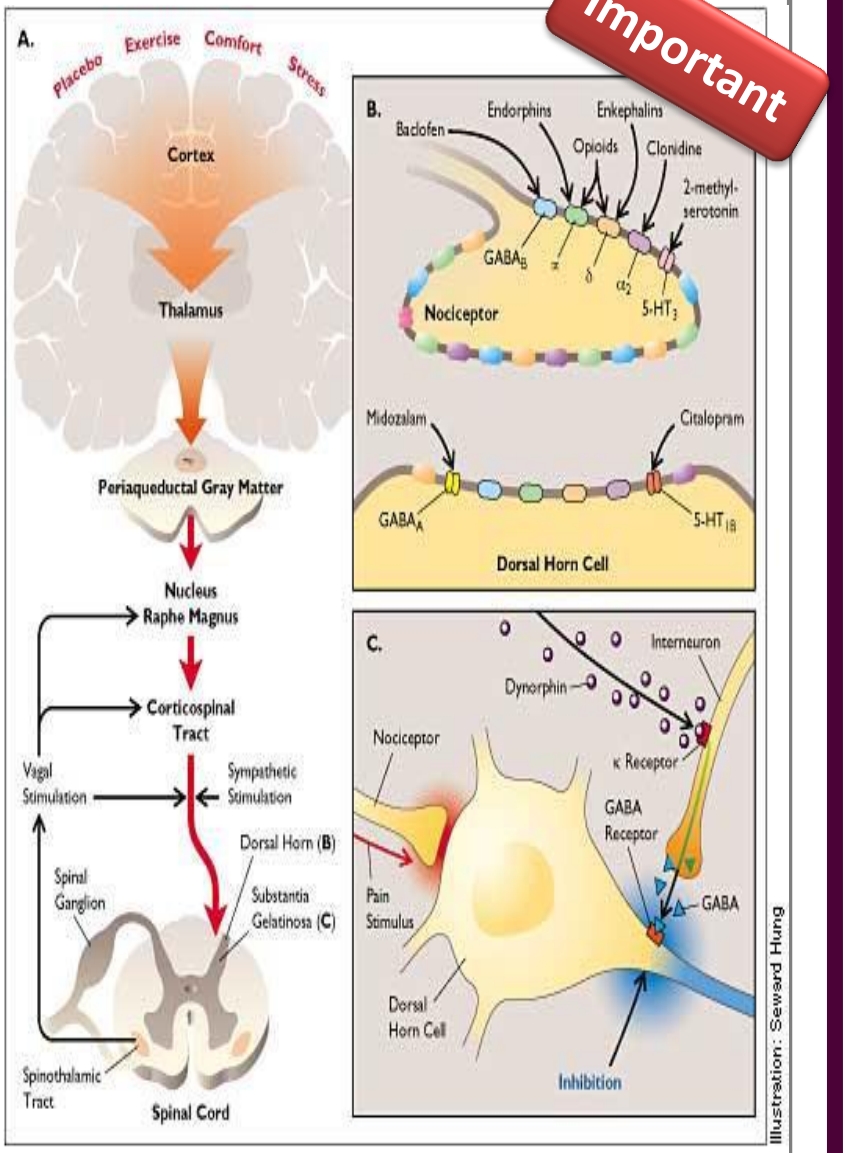
Analgesia occurs as follows:

- Periaqueductal grey (PAG) (2) area receives neuronal inputs from thalamus, hypothalamus (Periventricular Nucleus) (1), cerebral cortex.
- PAG projects neurons containing aspartate & glutamate that stimulate raphe magnus nucleus (RMN). (3)
- RMN projects serotoninergic neurons (secret serotonin), this in addition to noradrenergic neurons project from adjacent medulla to dorsal horn.

They block pain signals at spinel cord level by activating PIC. (4)

⟹ "release of Enkephalin block the release of substance P"



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How analgesia occur !

Periventricular (from cerebral cortex, thalamus & hypothalamus)

↓

Sends neuronal inputs to

↓

Periaqueductal grey *(which projects neurons containing Aspartate & Glutamate from their neurons endings)*

↓

To stimulates

↓

Raphe Magnus Nucleus in medulla (which projects serotonergic neurons secrete serotonin) in addition to NE from noradrenergic neurons from adjacent medulla to dorsal horn.

↓

*Block pain signals at **spinal cord level** by activating PIC (pain inhibitory complex) Leads to release of Encephalin which block the release of substance P.*

Opioid Receptor 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 fibers.**

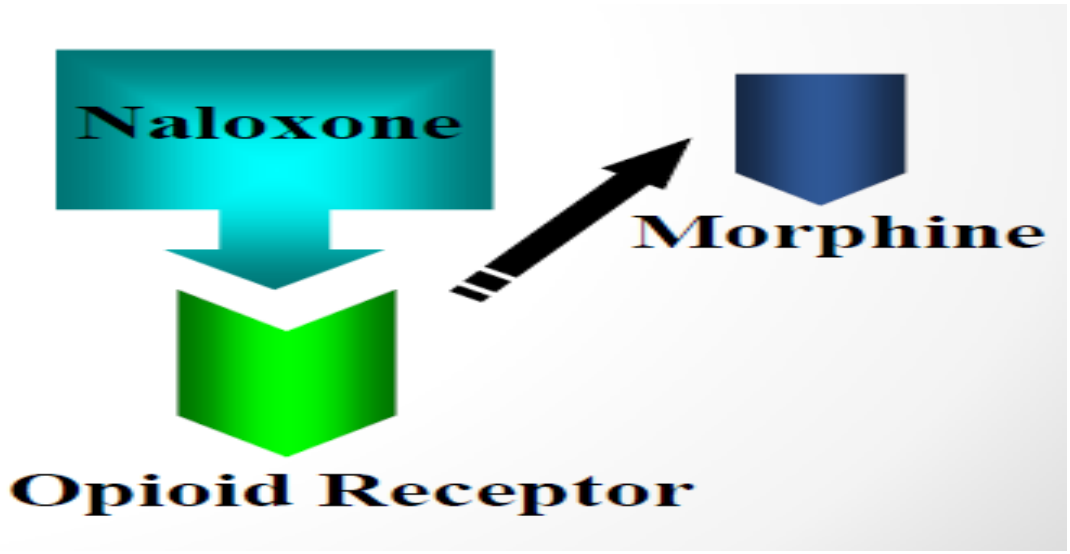
• Mechanism of opioid neurotransmitter action*:

- **Endorphin**: Neurons using endorphin or enkaphalin 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 (SGR)** responsible for inhibiting **the lamina I** nocioceptor-specific spinothalamic neurons.
- **Dynorphin**: In hypothalamus, PAG, reticular formation, and dorsal horn.
- **Endogenous morphin:** In terminals forming synapses with neuron having μ-opioid receptors in pain modulating pathways.

*الدكتورة قالت الأسماء هي المهمة و اللي حاب يستزيد يقرا الكلام المكتوب جنب كل اسم \ ولكن هذي المعلومات موجودة بالنص في سلايدات الاولاد

Opioid Antagonist
(Naloxone)

- Used to reverse opioid overdose e.g. drugs addiction – cancer patient
- Displaces receptor-bound opioids "competitive inhibition"
- Good for overcoming respiratory and CV depression



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Terms Frequently Used

Term	Meaning
Hyperalgesia	Excessive Pain "excessive sensibility to pain sensation"
Allodynia	Pain caused by any other sensation e.g. touch will cause pain.
Muscular Pain "cramps"	Less blood flow in the muscles (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. Under sever stress condition there is release of huge amount of opioid peptides so maybe this cause the painless.
Phantom pain	Pain felt in an amputated part long after amputation was done. "one explanation is that the amputated part is still represented in the cerebral cortex so irritation of nerve fiber ending by pressure will cause the pain sensation"
Thalamic Syndrome	Obstruction of the thalmogeniculate branch of the posterior cerebral artery Affects posterior thalamic nuclei. Prolonged severe pain. " hypersensitivity to pain"

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Terms Frequently Used

Term	Meaning
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 • Effected nerve is the trigeminal (5th cranial) nerve which is one of the most widely distributed nerve in the face. (its job is to carry sensation of the face)
Chronic pain	• Chronic pain can be considered as bad pain because it persist long after injury and is often refractory (anti) to pain killers • Longer than 3-6 months. • The cause maybe known (surgery) but many time unknown. • Chronic pain caused by nerve injury is called neuropathic pain.
Neuropathic pain	• Caused by the damage to peripheral nerve. • The distal cut end develops a scar tissue forming rounded ball (neuroma) which is sensitive to pressure. • Repeated activation causes continuous pain. • Examples: post herpetic neuralgia (chickenpox) and diabetic neuropathy (Injury of small blood vessel that supply nerves)

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Sites and mechanism of pain relief

- Block production of inflammatory mediators. e.g. Aspirin & Nonsteroidal anti-inflammatories.
- Sympathectomy can be useful. "cut the sympathetic supply"
- 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 (TENS).
- Stimulation of brainstem sites or administration of drugs which can modify Serotoninergic or adrenergic neurons. e.g. antidepressants.

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SUMMARY

- Pain modulation can be discussed under following headings:
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- Three variables control this gate:
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SUMMARY

- Impulses coming along Aβ fibers tend to keep the gate closed by process of presynaptic inhibition of C fibers and postsynaptic inhibition of secondary neurons in dorsal horn.

- The inhibitory neurons make a pain blocking agent called enkephalin which can block Substance P and thus close the gate.

- **Supra spinal modulation:**

  Its major constituents are:

  1- Periventricular N.

  2- Periaqueductal grey area.

  3- Raphe magnum nucleus.

  4-Pain inhibitory complex in dorsal horn of SC.

  It consists of multiple short enkephalinergic neurons

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QUESTIONS

Q1 – B
Q2 – D
Q3- enkephalin, pre & postsynaptic inhibition of pain transmission

1. Electrical stimulation in the periaqueductal gray elicits:

A. Circular movement
B. Analgesia
C. Tremors
D. Hyperactivity

2. The following nuclei are involved in the serotonergic descending modulation system of pain:

A. Locus coeruleus
B. Central gray
C. Ventral trigeminal area
D. Raphe nuclei

3. Complete: Stimulation of pain inhibitory complex will lead to the release of _____ Which cause _____

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THE END

If there are any Problems or Suggestions,
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THANK YOU