السلام عليكم

ورحمة الله وبركاته

Pain Modulation

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Objectives

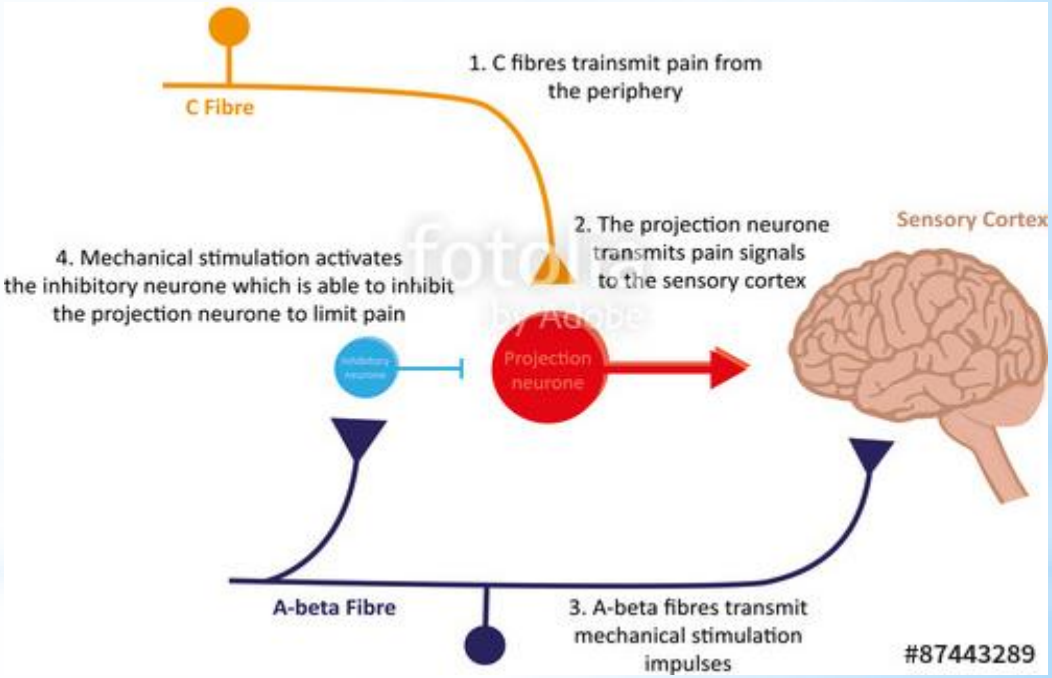
- Describe the built-in pain suppression analgesic system including:
  - Spinal modulation (Gate theory of pain control).
  - Supra spinal modulation (Special pain control analgesic system).
- Pain modulation by opioid neurotransmitters.
- Appreciate that pain can also be facilitated
- Know the sites & mechanism of pain relief

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)

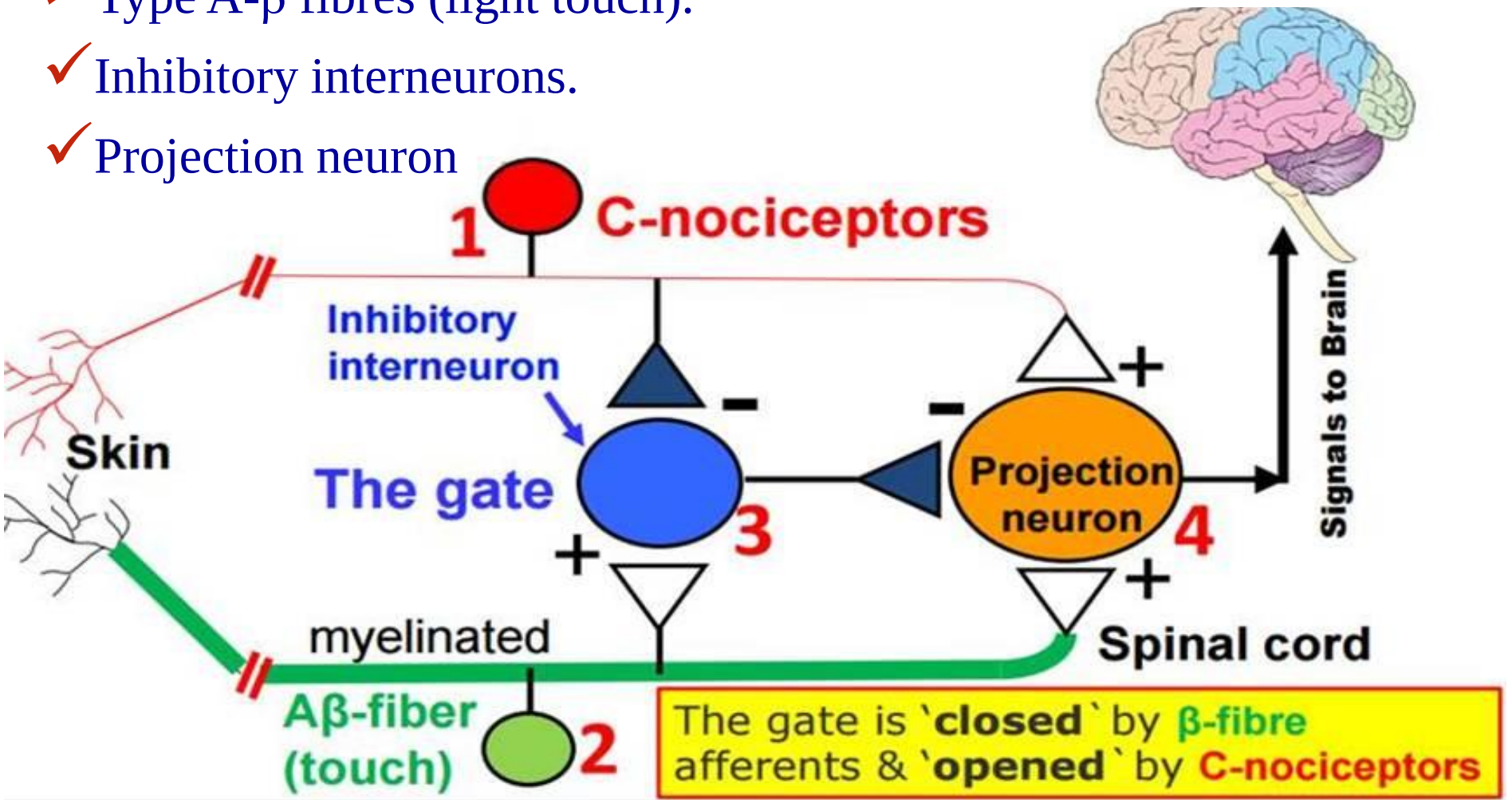
The gate theory of pain control

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

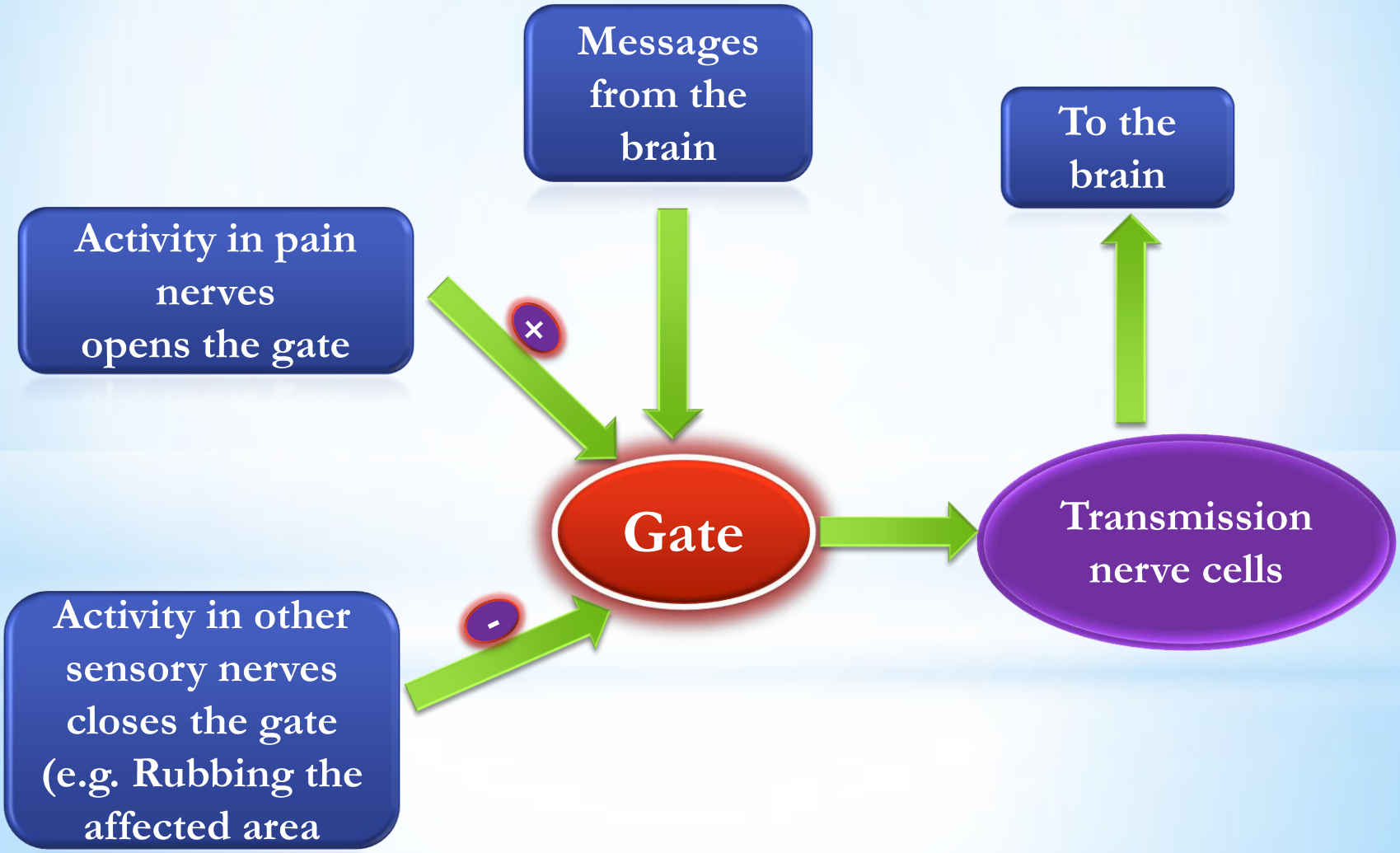


Four variables control this gate:

- ✓ Type C- fibres (slow pain).
- ✓ Type A-β fibres (light touch).
- ✓ Inhibitory interneurons.
- ✓ Projection neuron

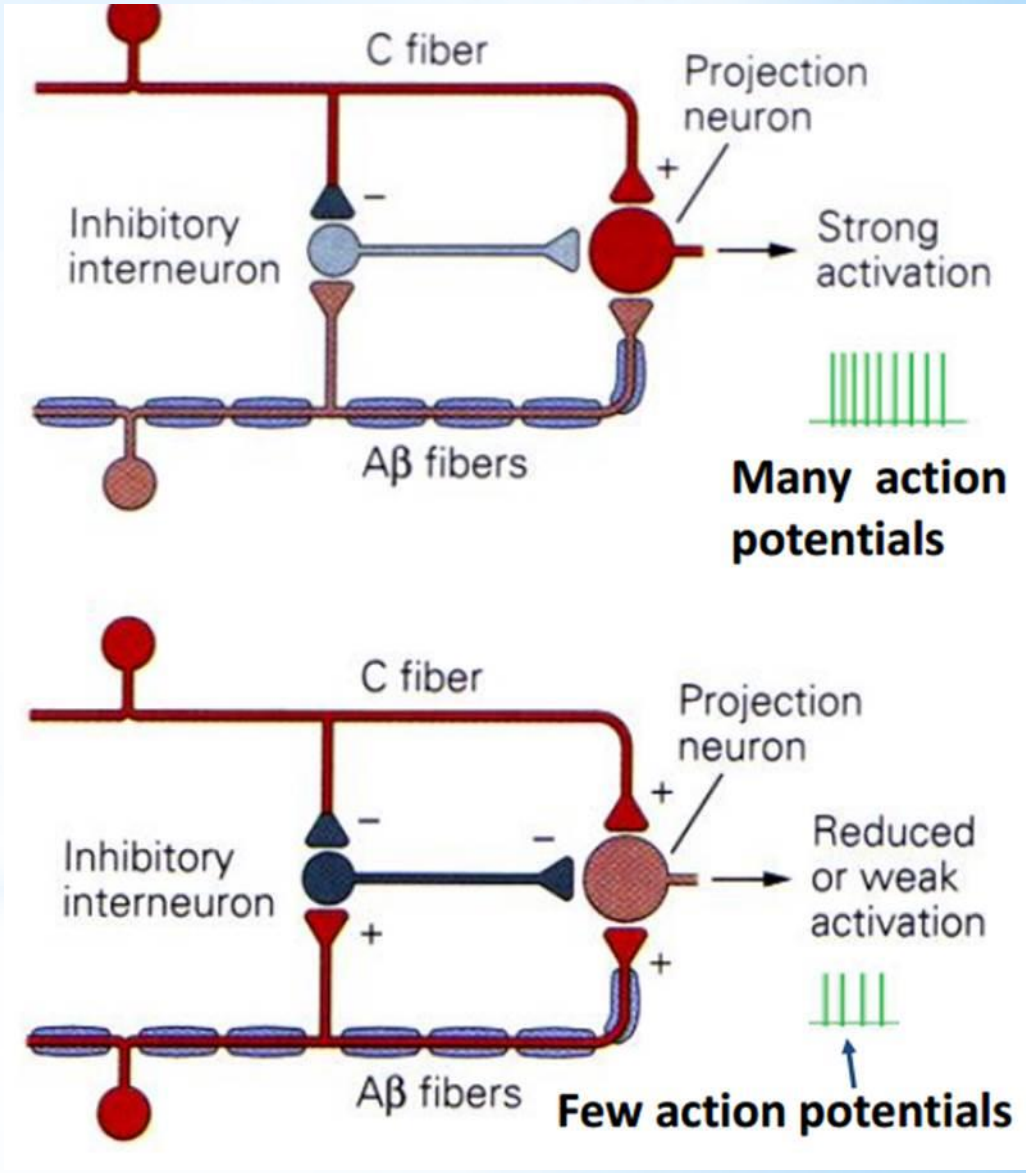


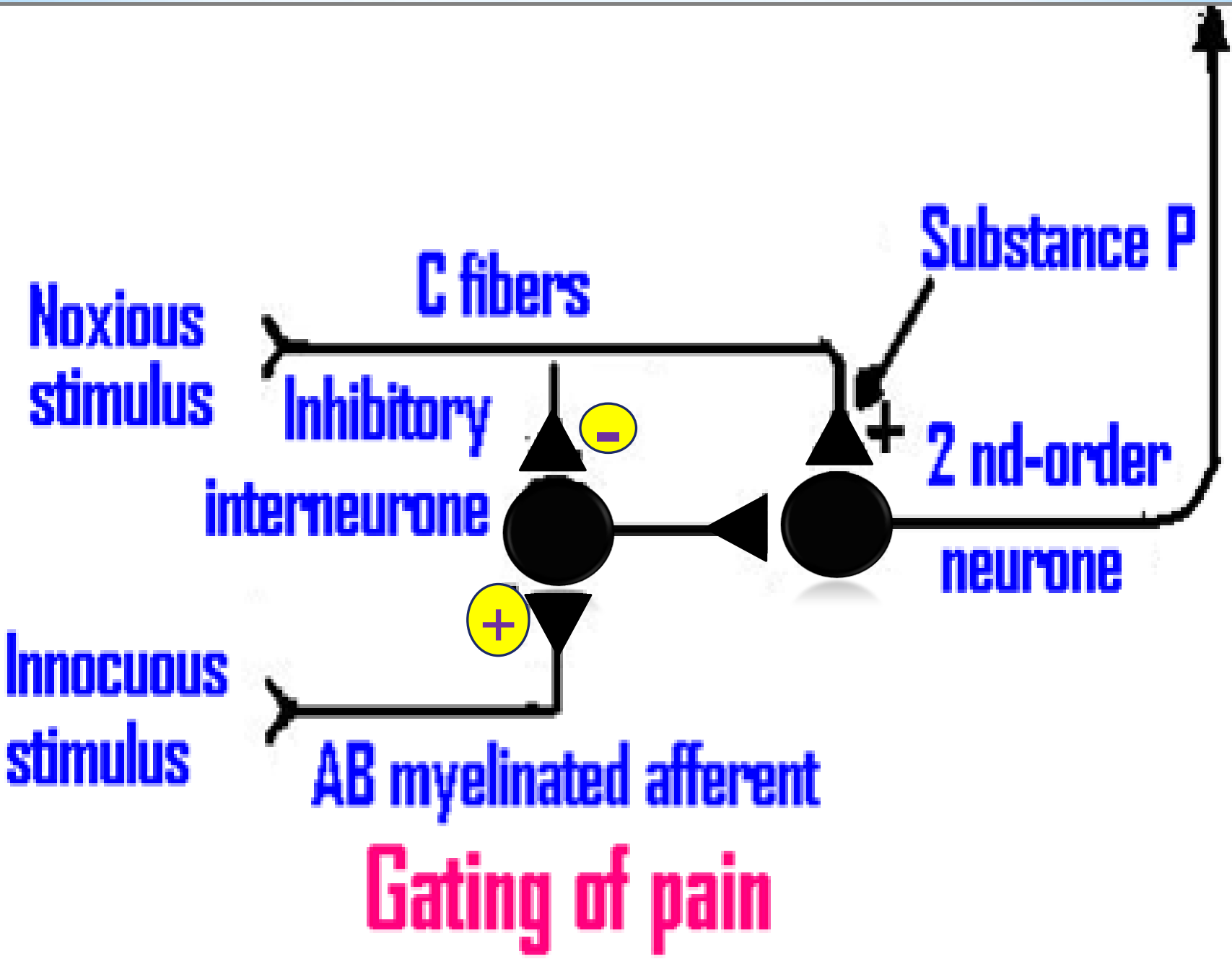
Gate opened or closed by 3 factors:



The gate theory of pain control (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 inhibitory interneuron.
- This theory implies that a non-painful stimulus can reduce transmission of a noxious stimulus.




Substance P
C fibers
Noxious stimulus
Inhibitory interneurone
2 nd-order neurone
Innocuous stimulus
AB myelinated afferent
Gating of pain

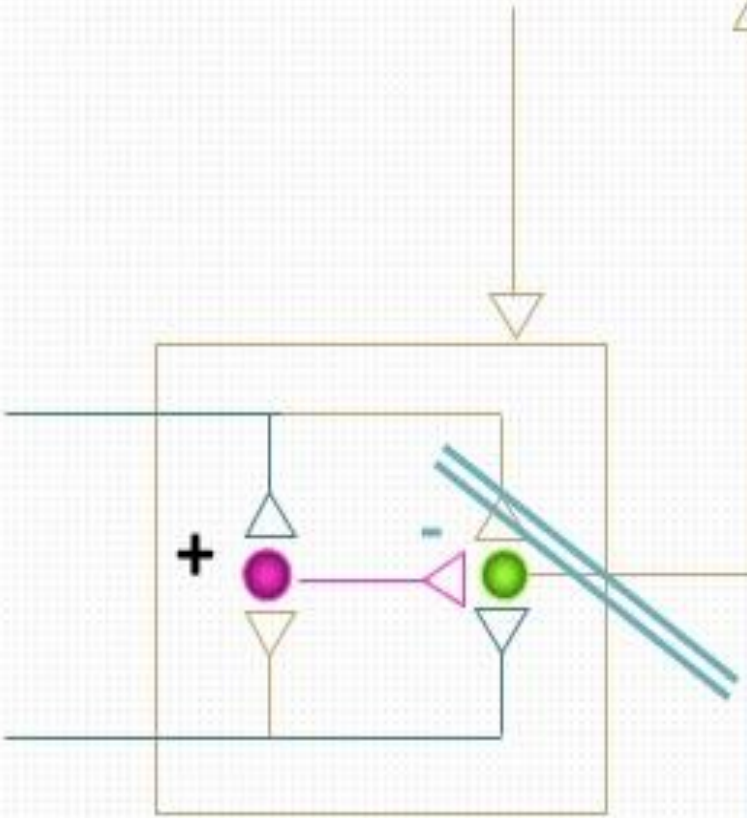
Gate control theory

touch

+

pain

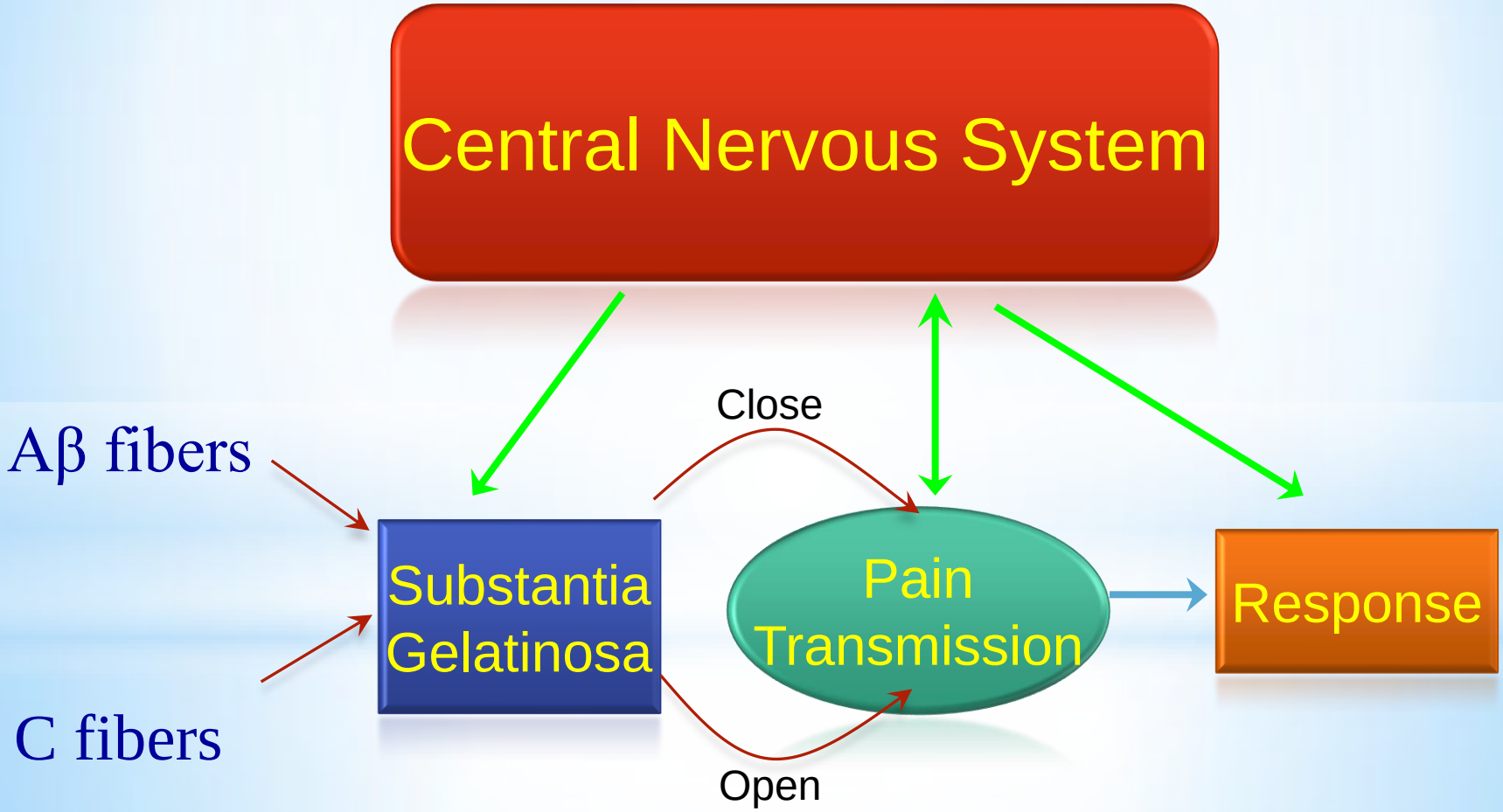
+



pain is not felt

gate is closed

When pain and touch fibres are stimulated together, gate will be closed & pain is not felt


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

- 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

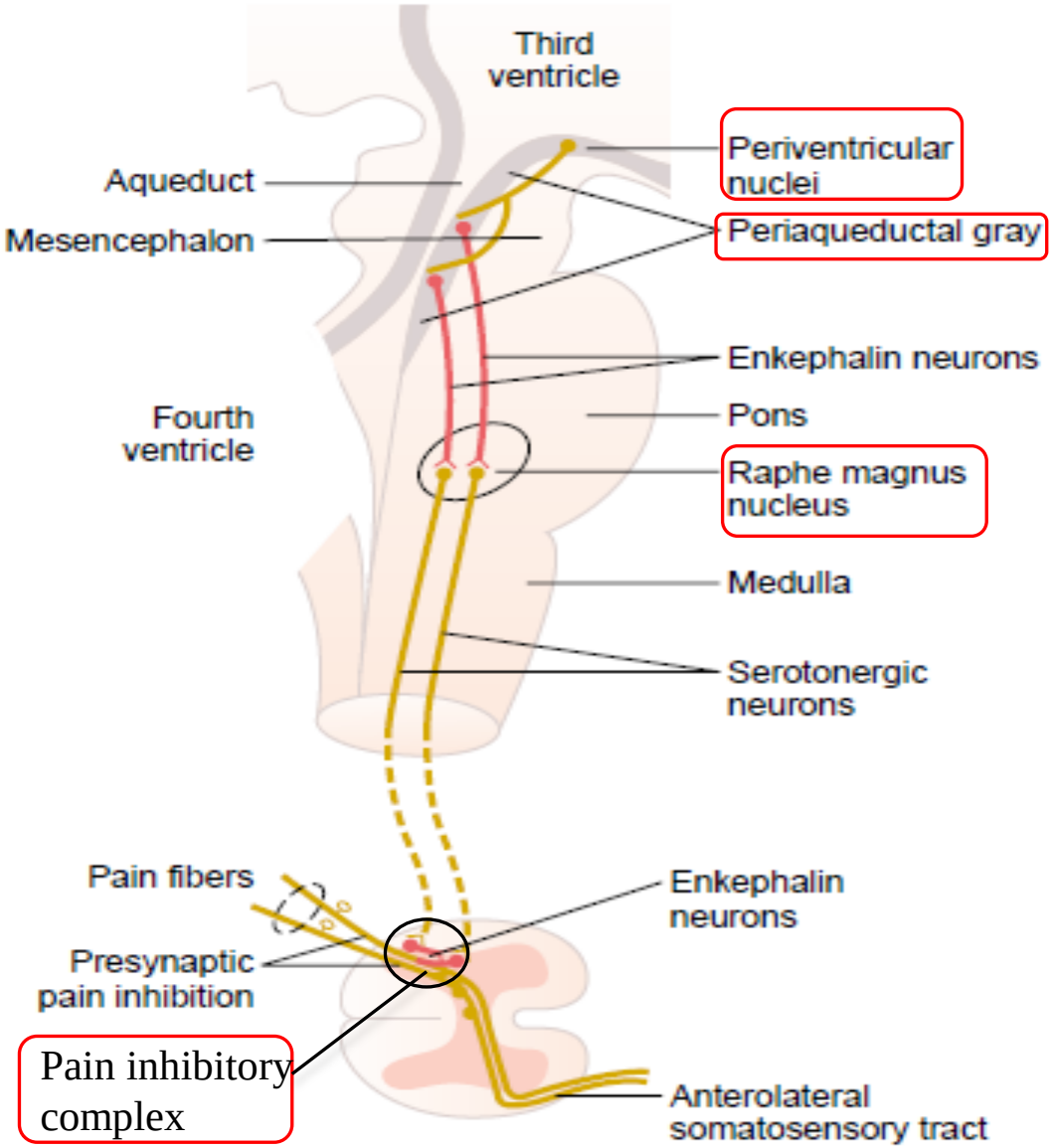
- Specialised nerve impulses arise in the brain itself and travel down the spinal cord to influence the gate.
- It can send both inhibitory and excitatory messages to the gate sensitising it to either C or A-β fibres.
- The inhibitory neurons make a pain blocking agent called encephalin.
- Encephalin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

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.

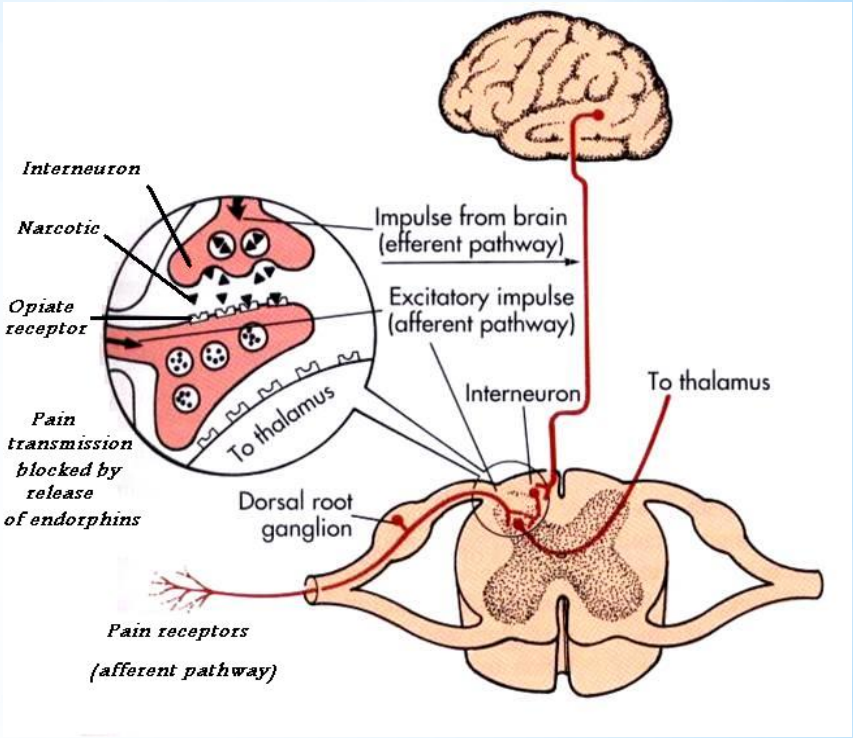


Analgesia system of the brain and spinal cord, showing (1) inhibition of incoming pain signals at the cord level and (2) presence of *enkephalin-secreting neurons* that suppress pain signals in both the cord and the brain stem.

3- ***Pain inhibitory complex***

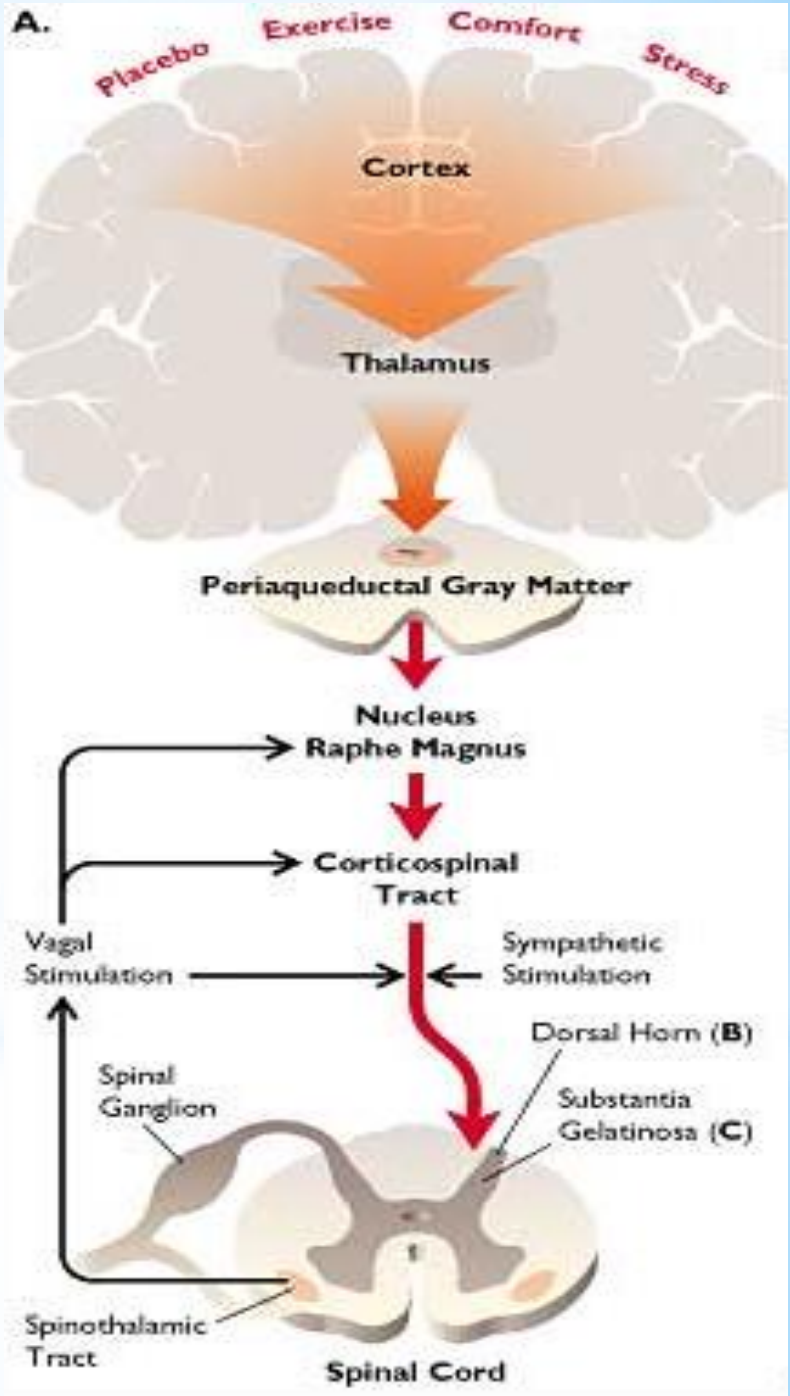
In dorsal horn of SC. It consists of multiple short encephalinergic neurons that terminate on central endings of pain conducting afferent fibers.

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



Analgesia 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.

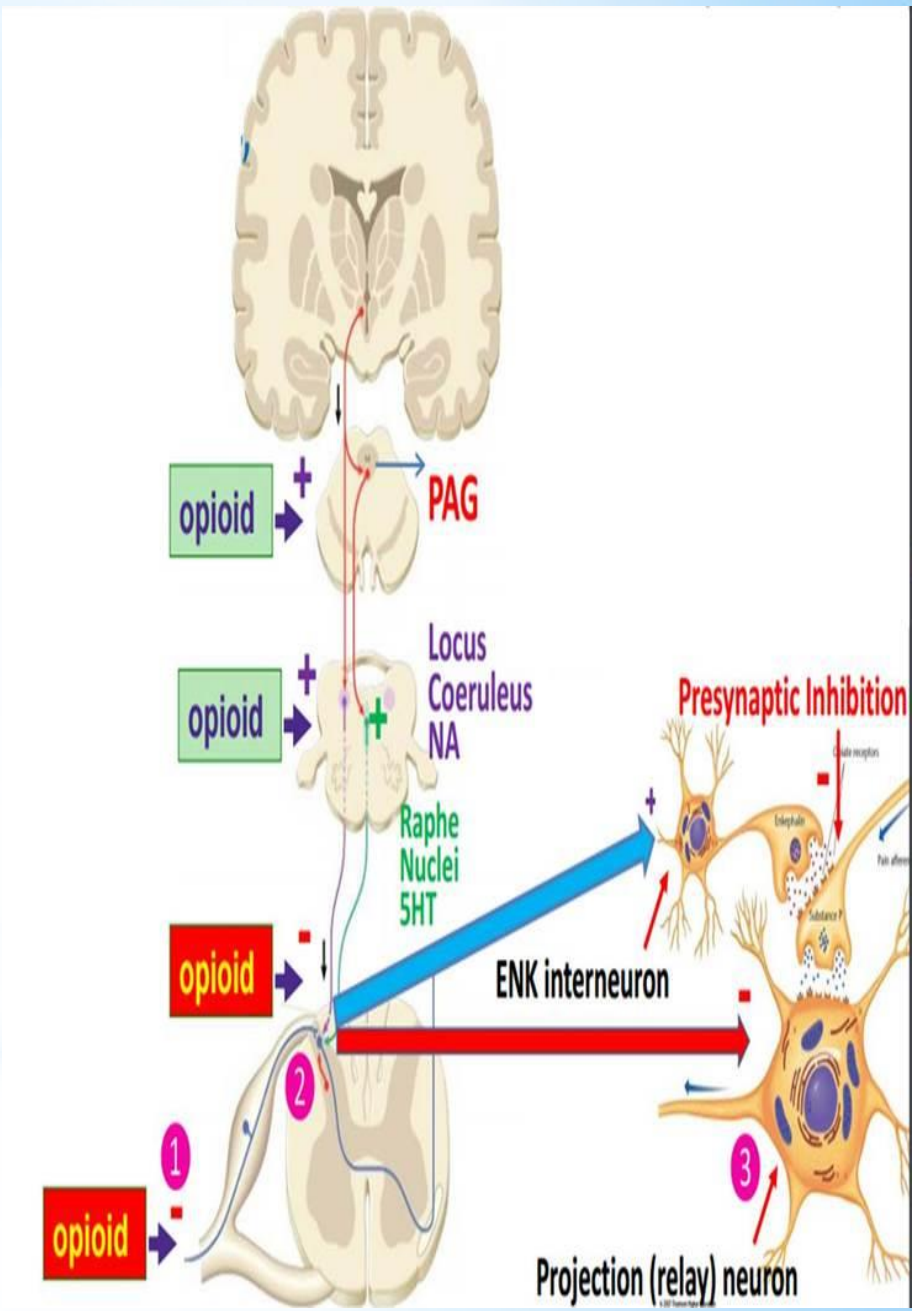


Opioid Peptides and Pain Modulation

- 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: A**re found in PAG where they inhibit GABAnergic interneurons that normally suppress the anti-nociceptor neurons
- **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

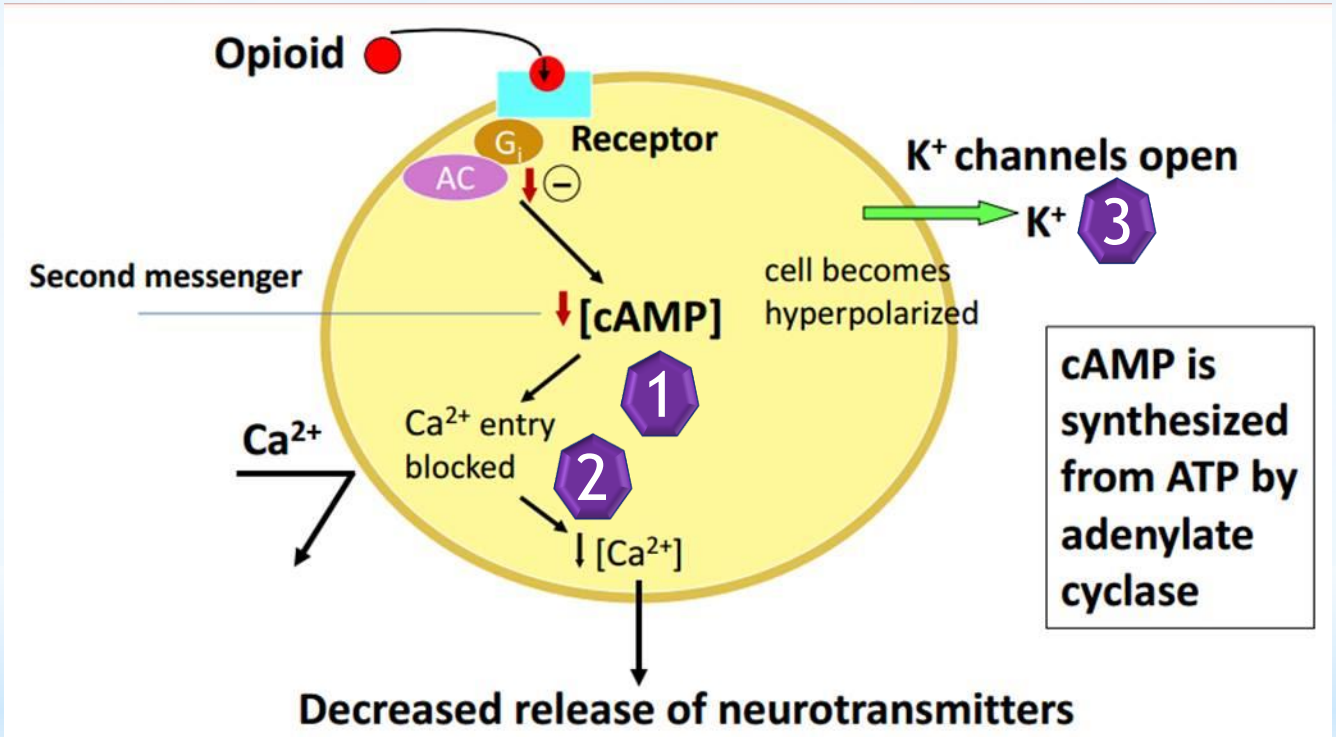
A-Direct effect

- 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

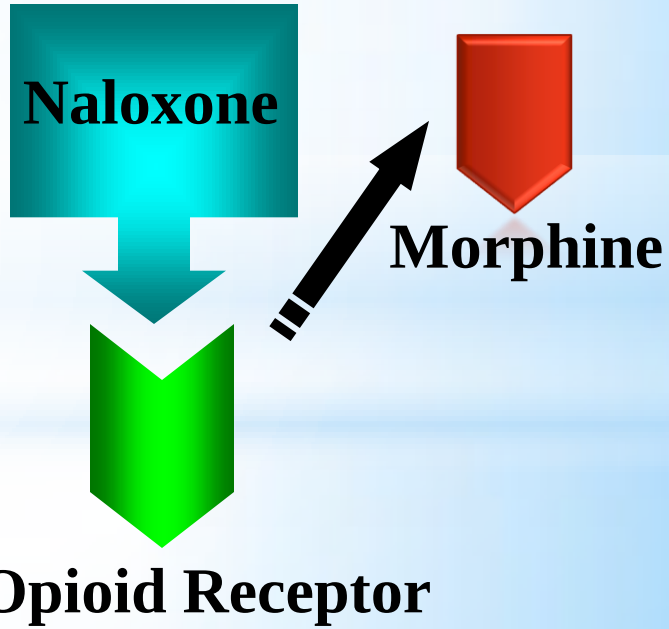
Cellular actions of Opioid peptides



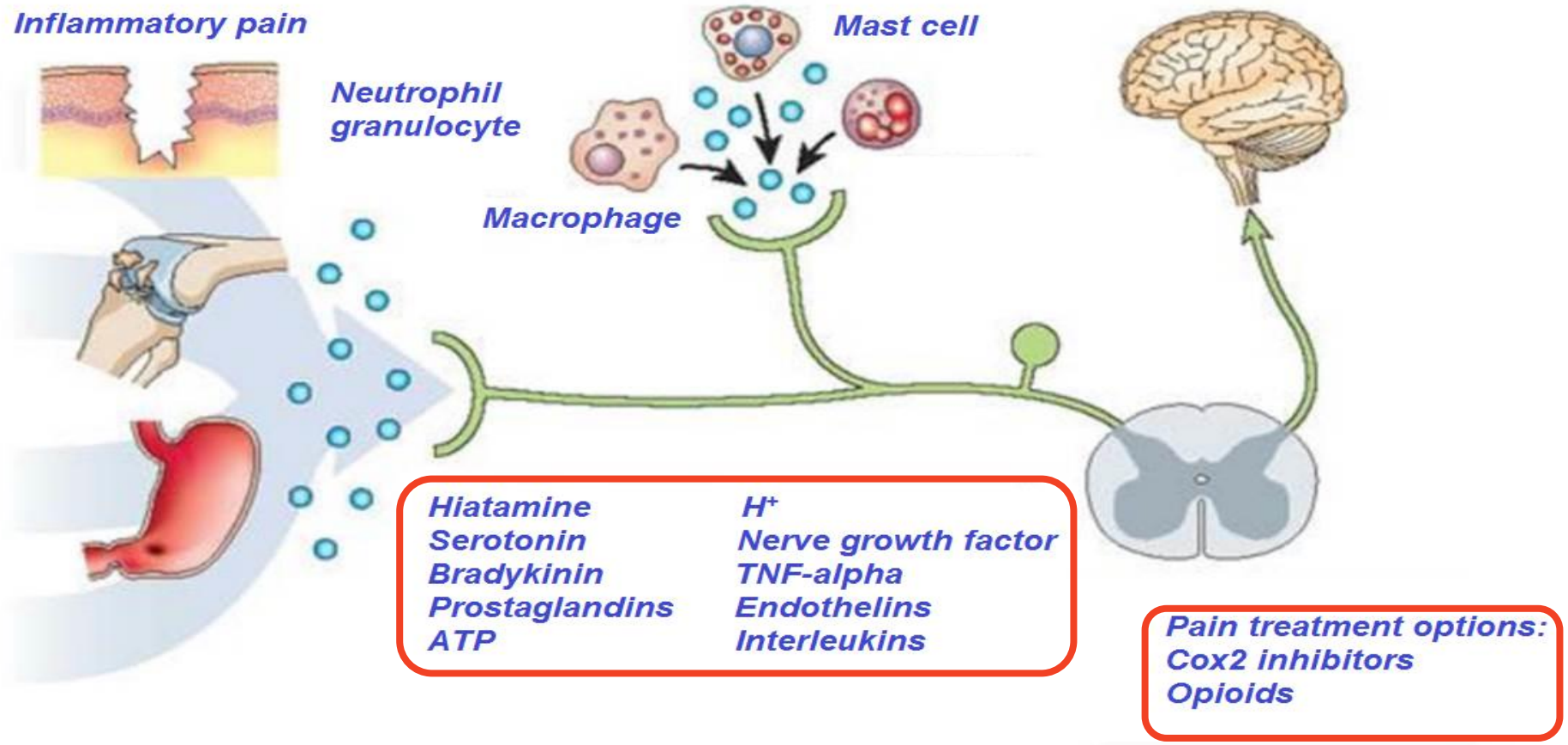
- Reduction of cAMP synthesis by inhibiting Adenyl cyclase
- Inhibition of transmitter release by inhibiting opening of Ca^{++} channels
- Hyperpolarization by facilitating opening of voltage gated K^+ channels

Opioid Antagonist: Naloxone

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

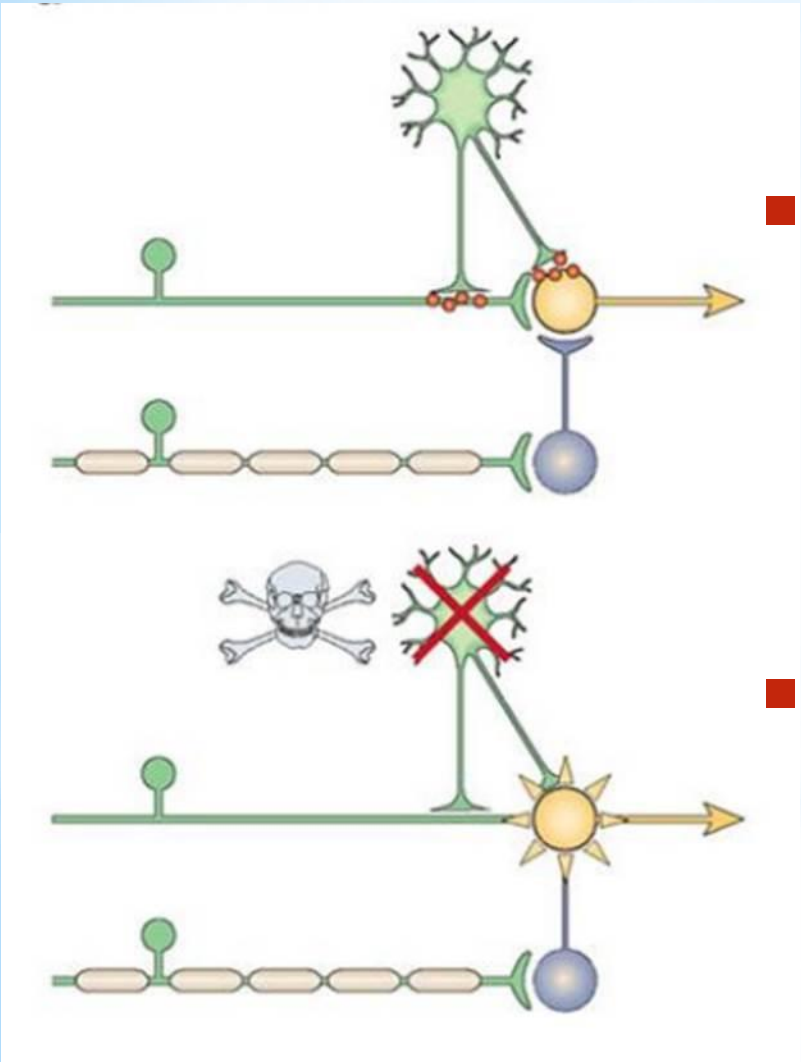


Pain Facilitation: Peripheral Sensitization



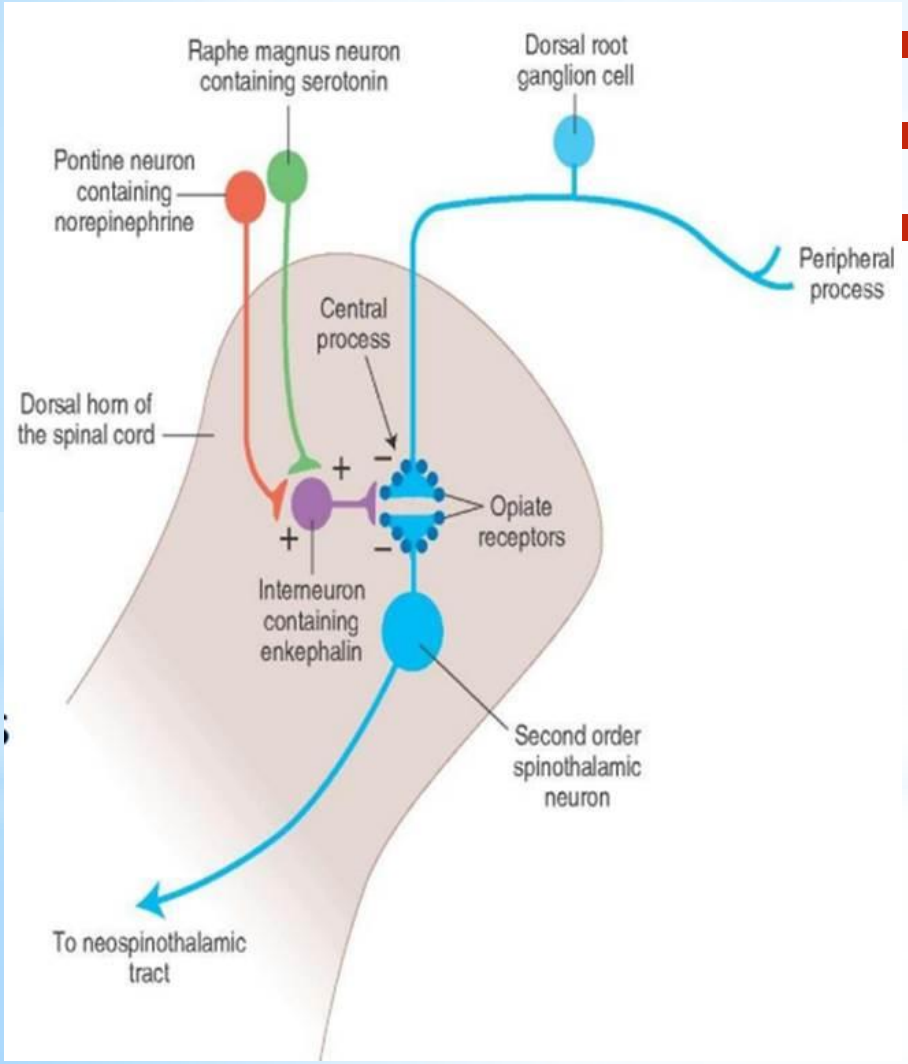
- Inflammatory mediators can directly activate nociceptors or cause their sensitization (decrease threshold)

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

Terms frequently used

- **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.

Stress induced analgesia

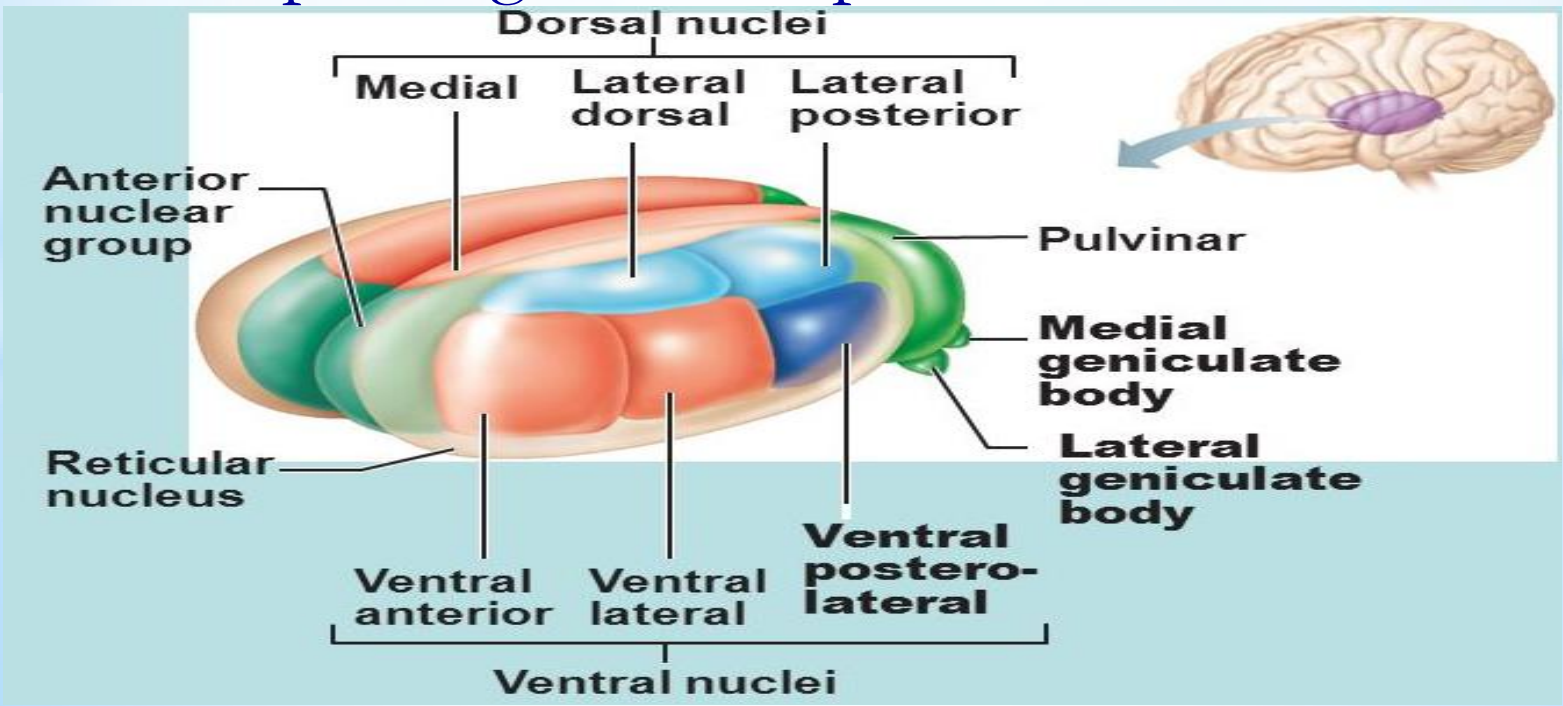
- Pain suppression response that occurs during or following exposure to a stressful or fearful stimulus.
- It's a well known phenomenon seen when the soldier is wounded in battle field but feels no pain until the battle is over.
- The cause is not known may be it is similar to gate control hypothesis.

Phantom pain sensations

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

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

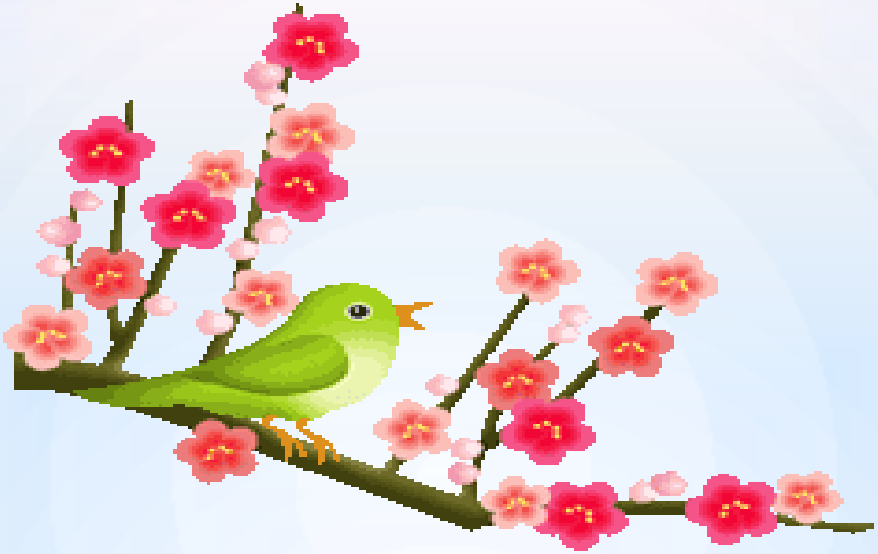
- It is excruciating intermittent pain by stimulation of trigger area in the face.
- e.g. Washing of face, combing hair, blast of air on face.
- It results from compression of trigeminal nerve root by blood vessels.

Neuropathic pain (NP)

- 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.



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