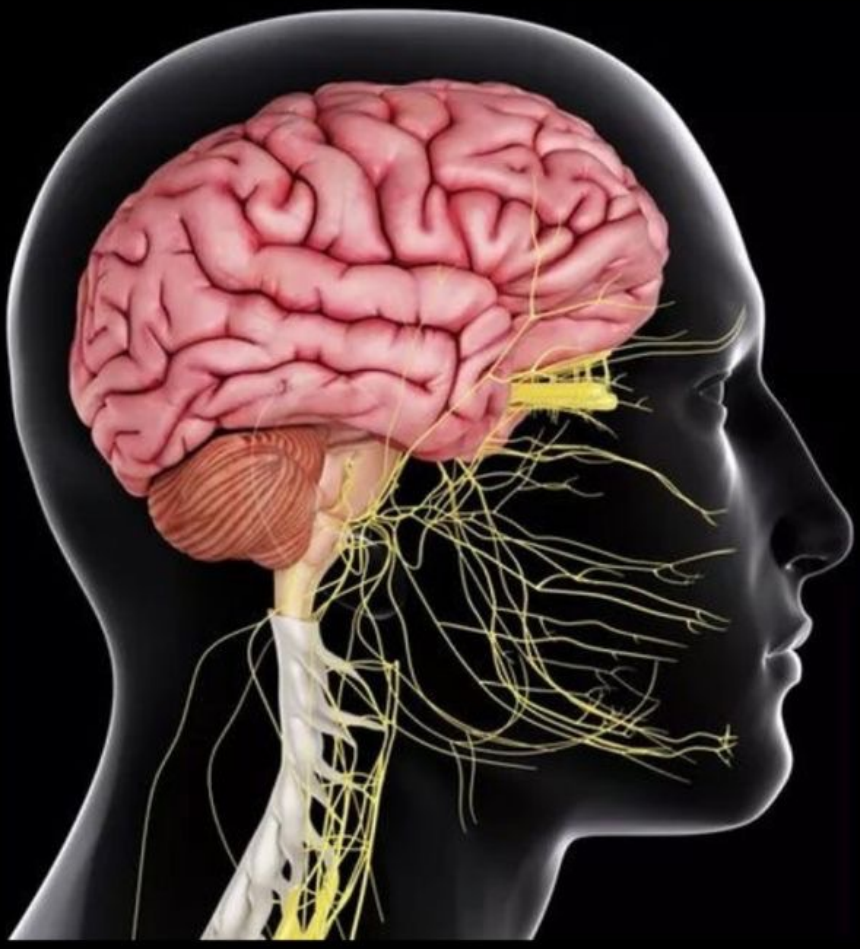
CENTRAL NERVOUS SYSTEM



SUBJECT : Pharmacology

LEC NO. : 2

DONE BY : Batool ALzubaidi

وَقُل رَّبِّ زِدْنِي عِلْمًا

Opioids

Pharmacology and Toxicology

Central Nervous System Module

Third Year Medical Students

Tareq Saleh

Faculty of Medicine

The Hashemite University

Textbook: pp. 180-193

opioids are drugs used to tret pain ال
و الكلمة مشتقة من كلمة opium الي هو
بالعربي افيون ففي الغالب هم naturally
drugs that و هي derived compounds
و اكن carry high liability of abuse
لساتهم يستخدوا to manage pain

pain isn't a simple problem it's a very complicated medical challenge not easy to treat

Pain

pain من الاشياء الي ممكن تسبب level عالي من ال
road traffic accident, big trauma, cancers مثلا

- "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage"
- Acute or chronic

ال chronic لحدا عنده fibromyalgia

- Consequence of complex neurochemical processes in the peripheral and central nervous systems
- Subjective

Pain treatment is wholestic approach that doesn't only involve drugs

Drugs that relieve pain are called analgesics

International Association for the Study of Pain

Pain

The assessment of pain is very difficult because it's subjective to the patient's perception of stimulus

Opioids are used to treat moderate to moderately severe to severe pain, there not used to treat mild pain because they carry high risk for abuse and dependence

Pain

Mild pain that we experience on a daily basis you can prescribe another analgesic like acetaminophen,paracetamol most importantly prescribe non steroidal anti-inflammatory drugs to treat musculoskeletal and back pain, headache, joint pain

Types of pain

- **Nociceptive pain:** pain due to an actual or potentially tissue-damaging injury that is transduced and transmitted via nociceptors.

Pain receptors

Examples: somatic pain, cancer pain, postoperative pain

+ somatic pain like appendicitis which is caused by inflammation, tissue insury and destruction

- **Neuropathic pain:** pain arising as a direct consequence of a lesion or disease of the somatosensory system.

They result from neurological problem in somatosensory system

Examples: carpal tunnel syndrome, chemotherapy-induced peripheral neuropathy, postherpetic neuralgia.

+ Diabetic neuropathy, vitamin D deficiency associated neuropathy

بالعادة ما بكون في physical damage الا اذا كانت
convayes the signals الي sensor nerve بال injusry

- **Others**

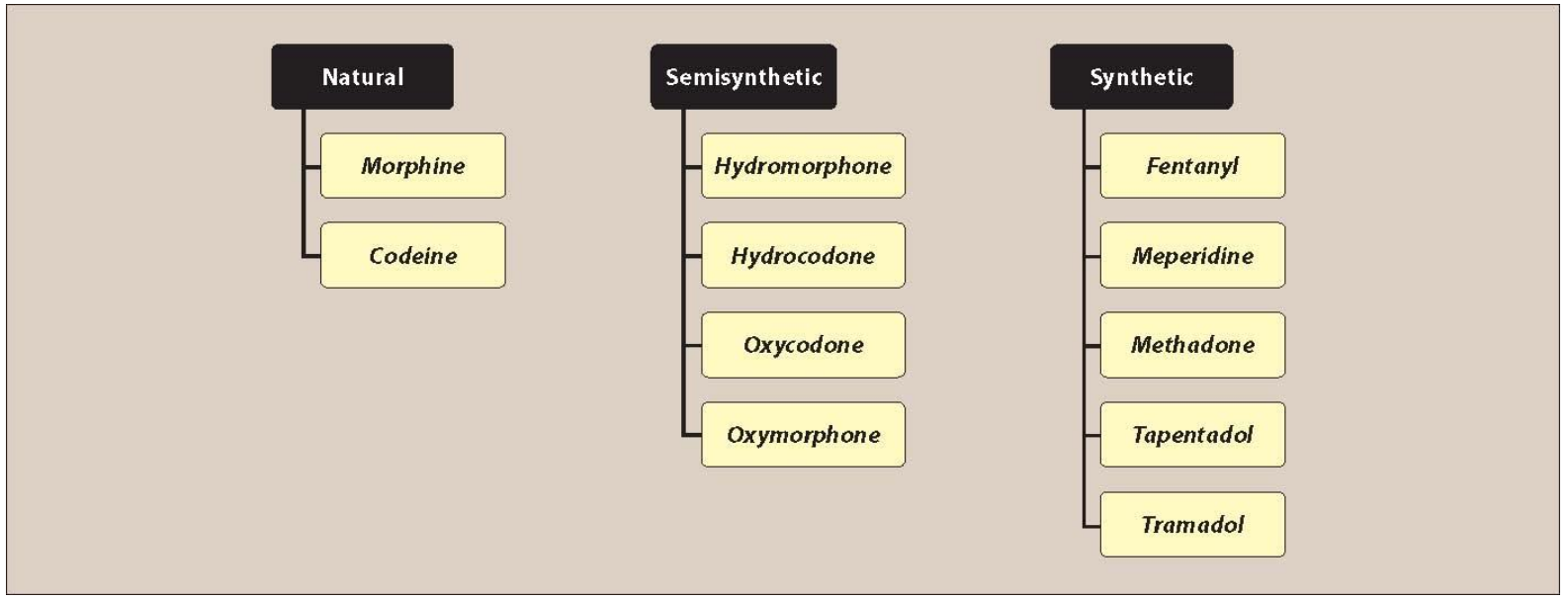
In this case opioids play a very minimal role if any role, there not the drugs good for treating neuropathic pain

Morphine like compounds

Drugs that exert their effect through opioid receptors

Opioids

- *Opioids* are natural, semi-synthetic or synthetic compounds that bind specifically to opioid receptors and share the properties of one or more of the naturally occurring endogenous opioids



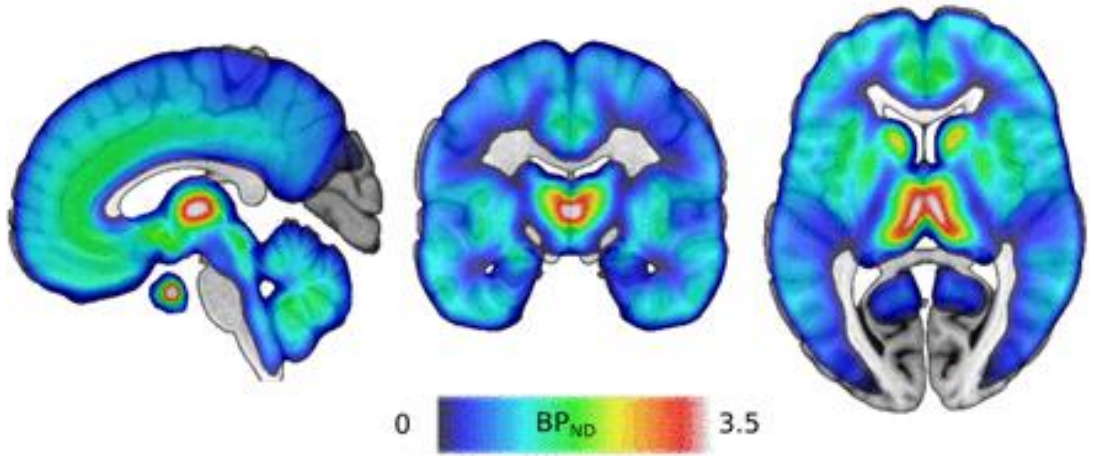
Opioids exert their actions through opioid receptors which are located in different types of neurons in the brain, they have some sort of distinct distribution

Opioid Receptors

- Distributed throughout the CNS
  - Nucleus of tractus solitaries
  - PAG
  - Cerebral cortex
  - Thalamus
  - Spinal cord

  But also….
  - Gut
  - Bladder

Present peripherally



Mean distribution of μ-opioid receptors in the human brain based on the 204 [11C]carfentanil BPND images, *Kantonen et al., 2019*

They're dominant in the peri-aqueductal gray matter, they're present in cerebral cortex (predominant in its sensory part), present in thalamus

Opioid Receptors

Primary receptor that's involved in analgesia and propagates euphoric effects of opioids

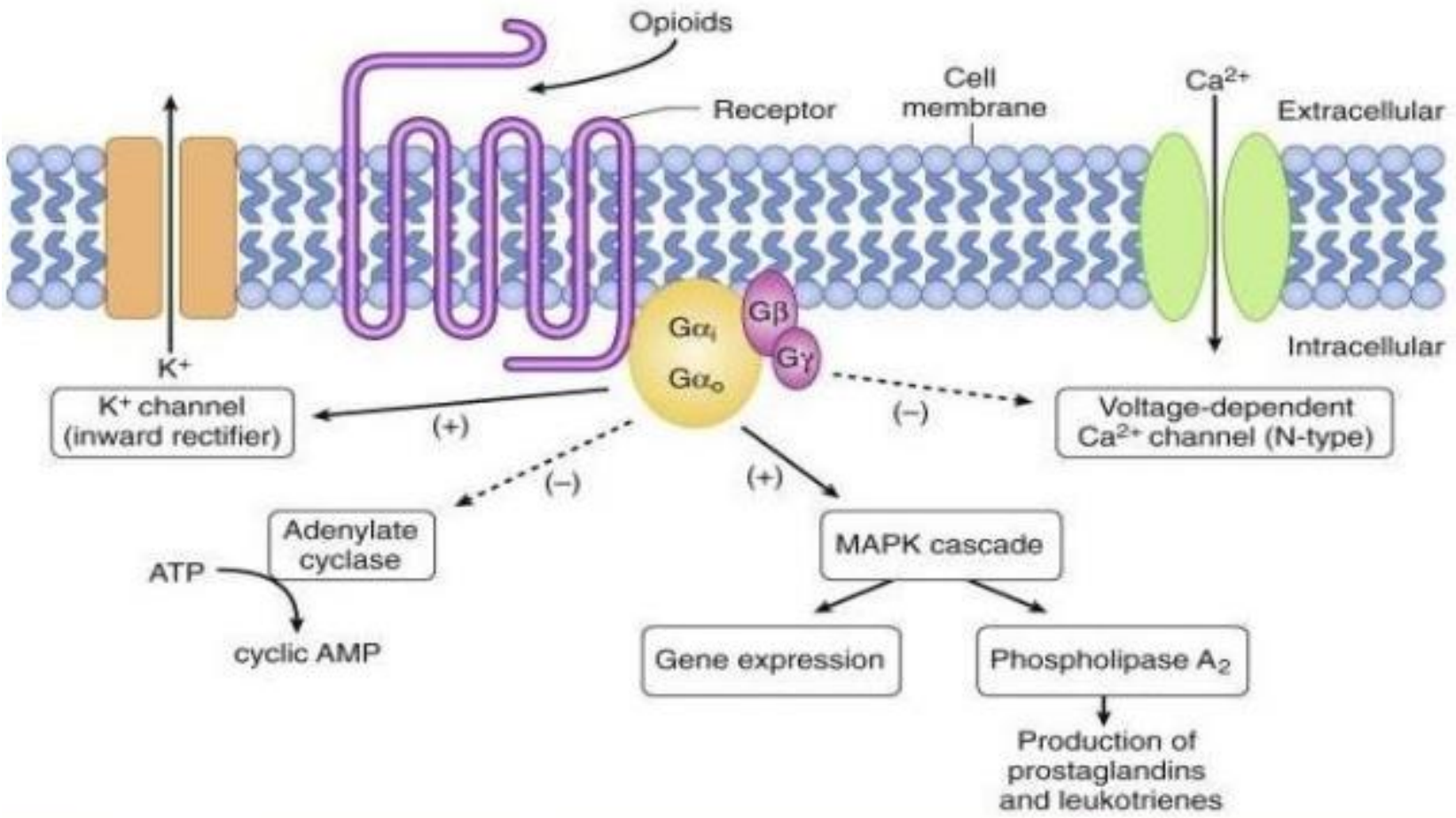
ميو ←

Receptor name → كابا

Opioid Receptor	μ (أهم واحد)	δ (دلتا)	κ (كابا)
Endogenous opioid	*Endorphins*	*Enkephalins*	*Dynorphins*
Effect	Analgesia, euphoria, respiratory depression, constipation, sedation, meiosis	Seizures, analgesia?	Dysphoria, analgesia?

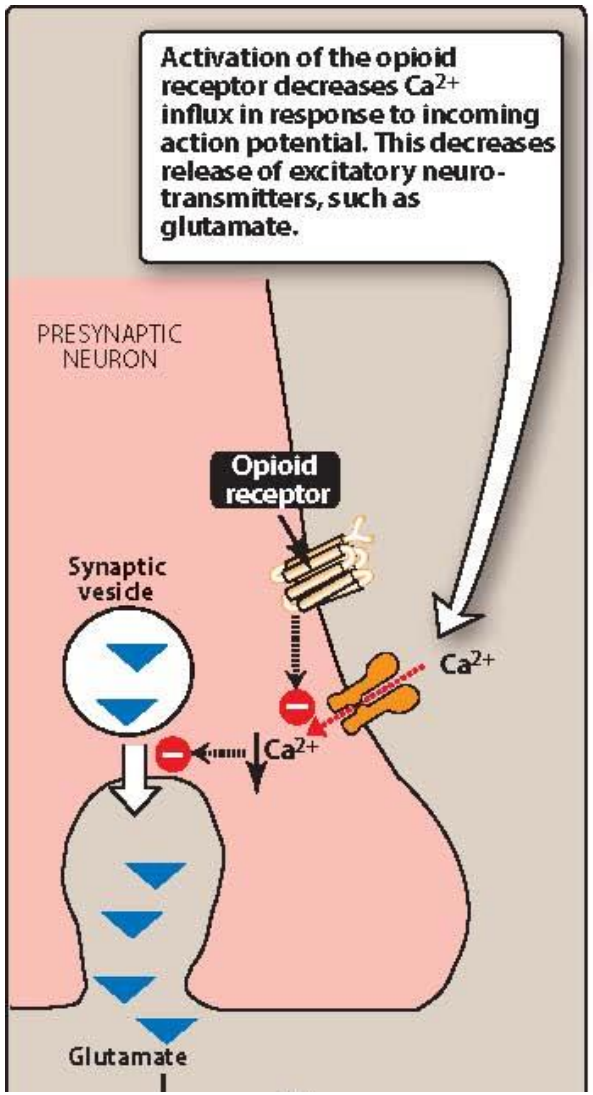
اذا احنا اعتبرنا هدول ال compounds بكونوا naturally derived or semisynthetic يعني يعتبروا external substances ليش الهم بال receptors بال brain؟ ؟
لانه we have our own internal system of endogenous opioids الي حكينا عنهم ال محاضرة الماضية بكونوا inhibitory neurotransmitters

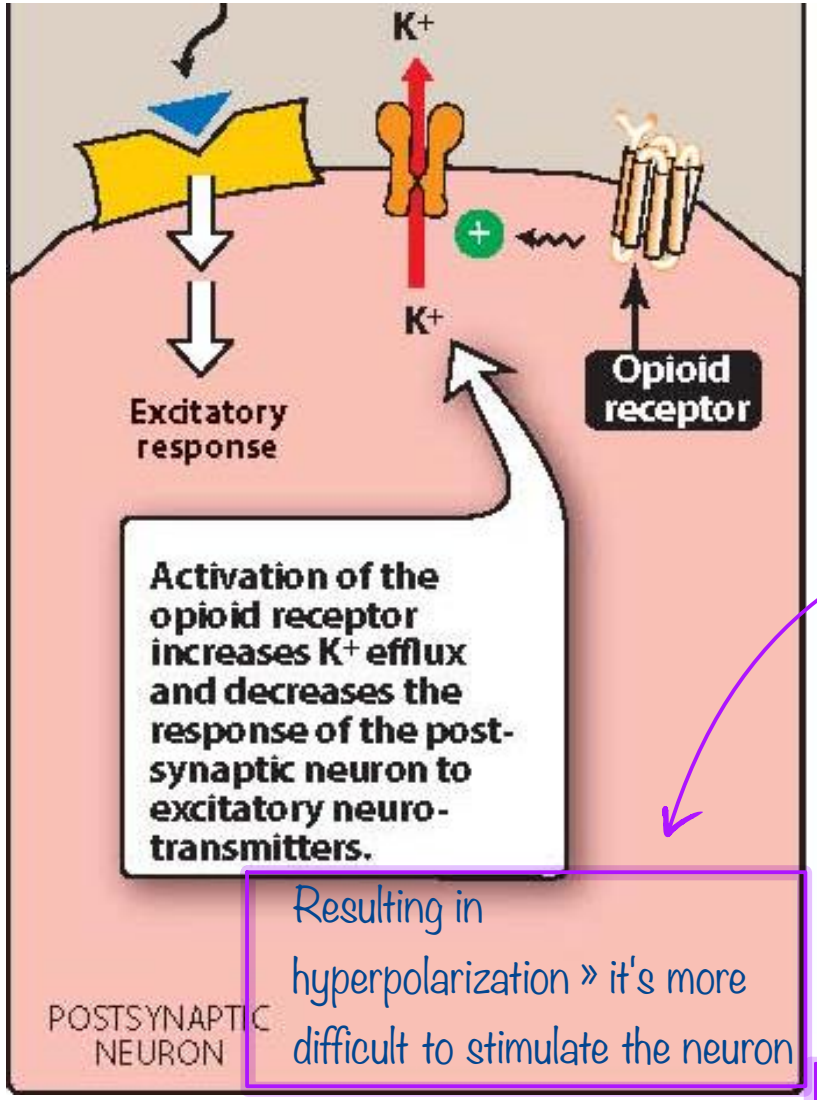
Opioids: Mechanism of Action



Opioids receptors present both pre and post synaptically

Opioids: Mechanism of Action





Resulting in hyperpolarization » it's more difficult to stimulate the neuron

G protein-coupled receptors (GPCRs)
[$G_{i/o}$ (inhibitory)]

Reduce camp production in postsynaptic neuron

Inhibit adenylyl cyclase

Increase *postsynaptic* K^+ efflux

Reduce *presynaptic* Ca^{++} influx

You want to suppress pain » you want to suppress sensory signals propagated through sensory neurons coming from sites of tissue injury

Decreased granulation and release of neurotransmitters

Opioid Agonists

- Morphine
- Codeine
- Oxycodone
- Oxymorphone
- Hydrocodone
- Fentanyl
- Methadone
- Meperidine

Most clinically used

Morphine

- Natural
- Derived from *papaver somniferum*
- After the Greek god of dreams
- " Morpheus"

شو الفرق بين ال analgesia and sedation ؟ ال analgesia يعني pain
ال relief اما ال sedation has to do with awareness ال يعني ال sedative
ال compound بقلل ال awareness و بعمل CNS suppression و ممكن يخليك
تنام فهو اله علا بال consciousness, alertness, awareness بقللهم كلهم

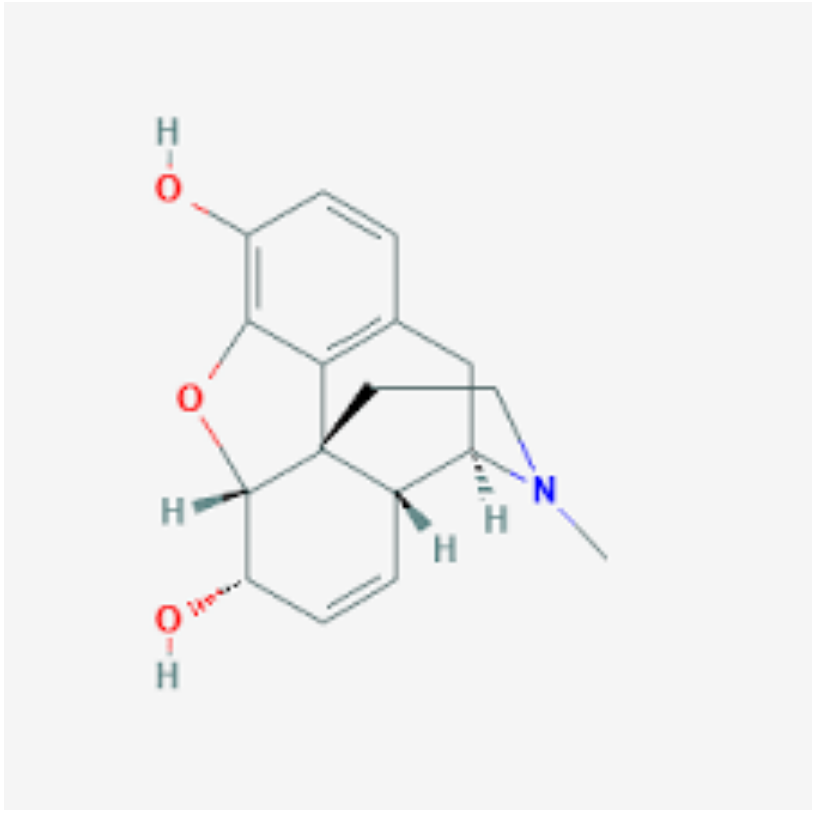
Morphine

Mechanism of action

- Binds to opioid receptors (mainly **μ**)- full agonist

  - CNS, gut, bladder

- Decreases the release of many excitatory transmitters from nerve terminals carrying nociceptive stimuli



Morphine

ال morphine مش انه بعالج ال pain by removing ال tissue damage that causes the pain
مش مثلا انجرحت بالسكينة هو لعالج الجرح ف بروح الوجع لا، هو بغير your perceptionof
pain عن طريق انه يعمل suppression لل pain signals بس ال damage لساته موجود

Morphine

Actions:

- **Analgesia**

sedation ممكن يعمل higher doses اما بال therapeutic doses بال

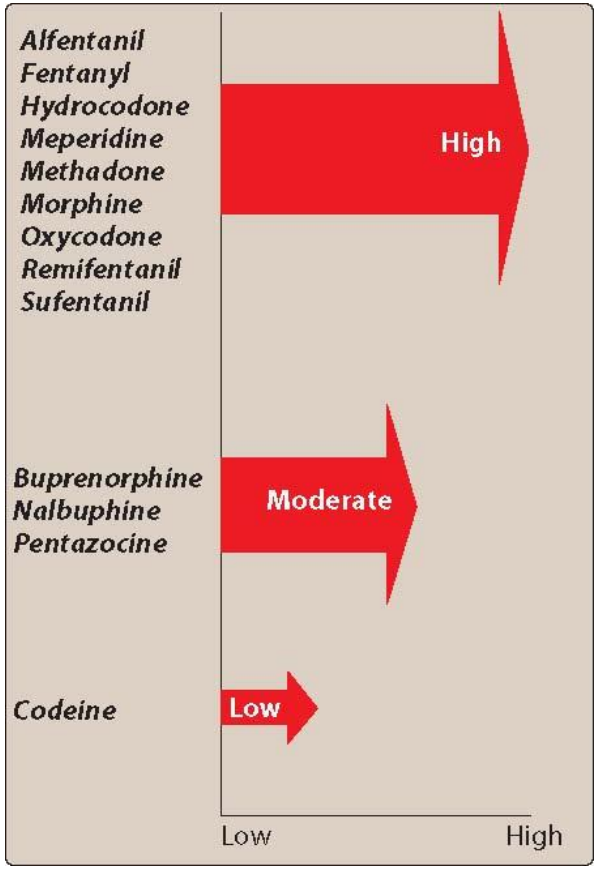
- without loss of consciousness
- raises pain threshold (spinal cord)

يعني ال stimulus الي بالعادة ممكن يعمل pain ببطل

- alters perception of pain (brain)
  - ❖ still aware of pain, but not unpleasant

هو ما بكون في pain بس ال damage موجود

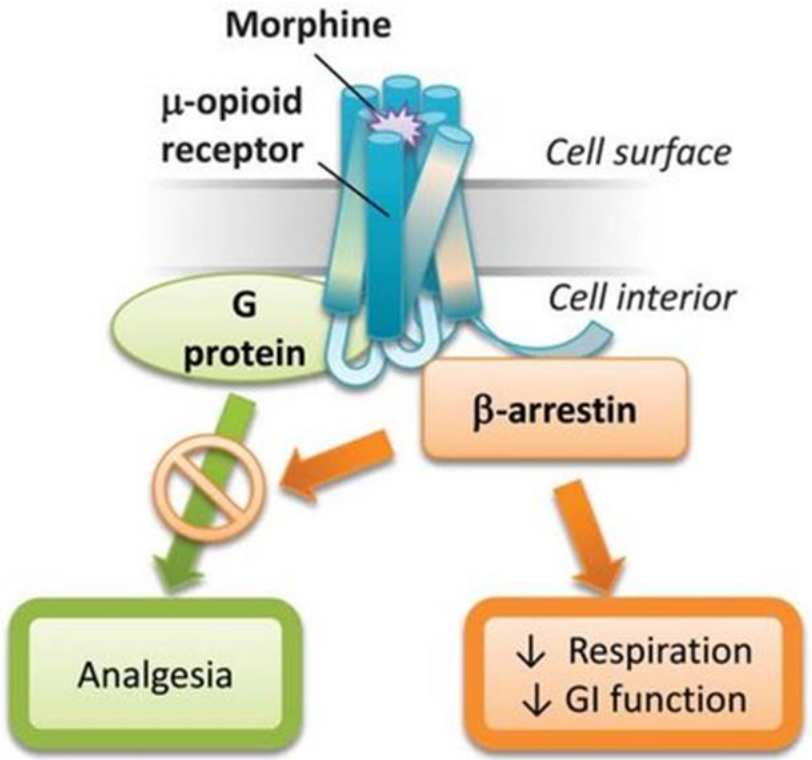
- nociceptive >>> neuropathic



Morphine

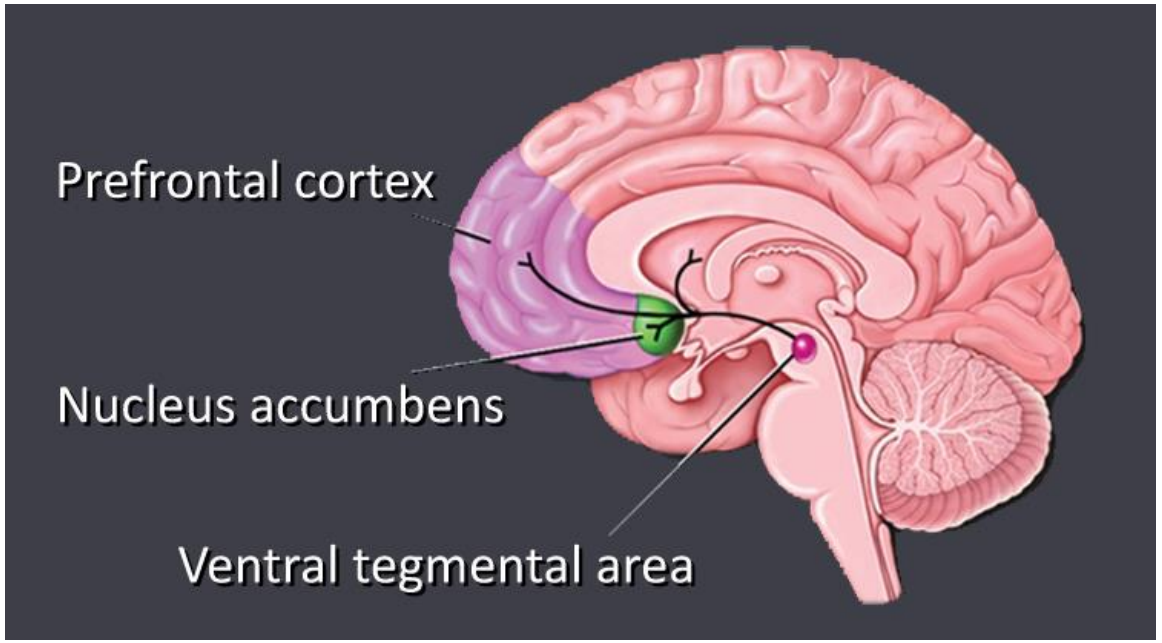
Actions: بالعربي بنحكي بكون مزهزه

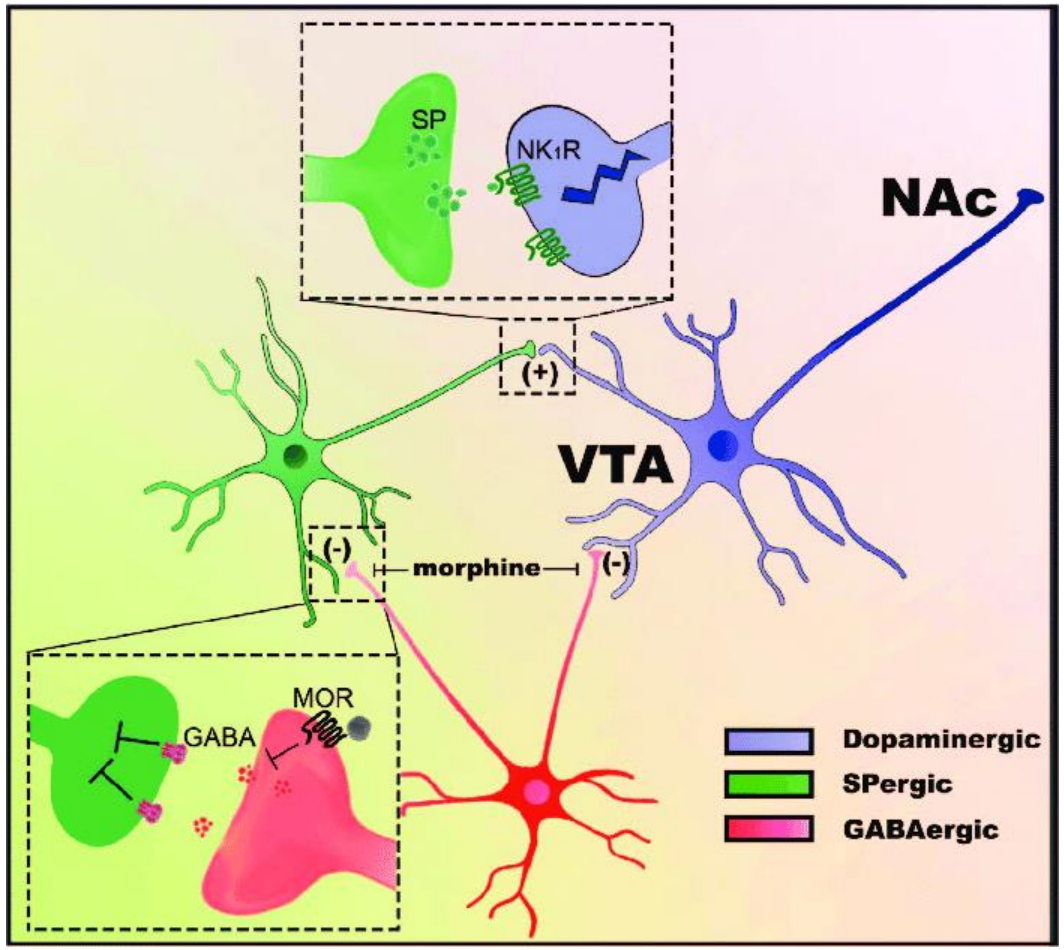
- **Euphoria** Main cause of opioids abuse
  - sense of contentment and well-being
  - caused by the disinhibition of the dopamine-containing neurons of the ventral tegmental area
- **Respiratory depression**
  - reduces the sensitivity of respiratory center to CO_2
  - most common cause of death from opioid overdose.
  - Tolerance develops quickly



With repeatative doses with increasing concentration of morphine the risk of developing respiratory depression reduces because of tolerance

Morphine and the Reward Pathway





ليه بصير عنا euphoria بالمعنى العام هم بعملوا inhibition للاحساس بالالم طيب ليش بنحس بالسعادة ؟ لانه ال opioids activate the reward pathway that results with causing happiness بغض النظر عن ال stimulus يعني مثلا لو اكلت اكلة زاكية او لعبة بلايستيشن مع صحابك كنت مبسوط صار اي اشي منيح معك دخنت سيجارة مثلا ، هاد ال reward feeling اكيد physiological ولكن اله physical basis لانه اله علاقة بال neurons و that project in the ventral segmental area in the midbrain بتروح لل nucleus accumbens بعدين prefrontal cortex فعشان تحس بال euphoria هاد ال pathway لازم يشتغل، طيب احنا حكينا ال opoids suppressive كيف بعملوله activation ؟ بعملوا inhibition لل regulatory neurons لانه دايما هاد ال pathway بكون فيه inhibitory neurons بسكروه و بكونوا فgaba neurons ال morphine بعمللهم inhibition و بحرر ال pathway بنسميها بالاخص disinhibition يعني inhibition ل inhibitory neurons

Morphine

Actions:

- **↓ cough reflex**

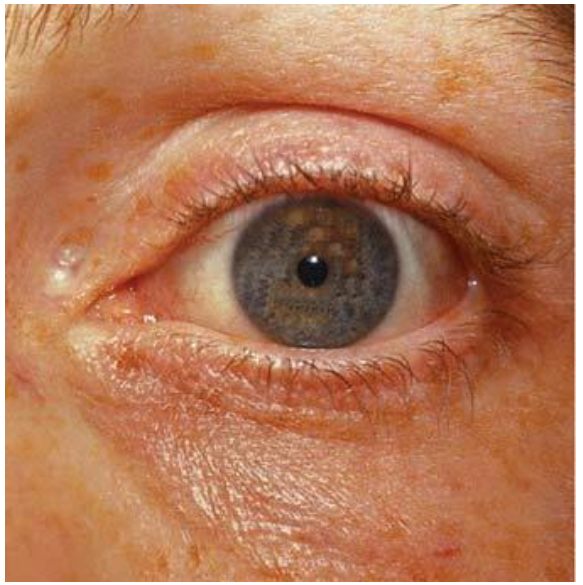
 - both morphine and codeine have *antitussive* effect.

- **Miosis**

 - *pinpoint pupil* — Constriction of pupil

 - results from **μ** and **κ** receptors

 - no tolerance to this effect



meiosis

مهمة لما تكون بال emergency و يجي مريض comatose و تكون بدك تحدد السبب of loss os consciousness ففي حالة ال opoid

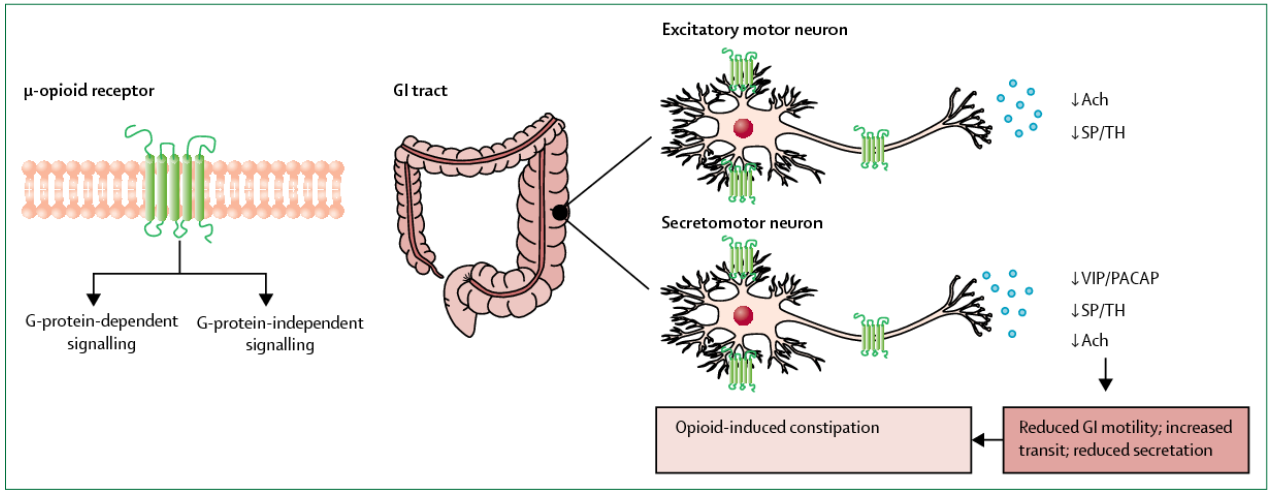
راح يكون عنده pupil constriction لانه معظم اسباب ال coma الاخرى بكون العكس بكون dilation in pupil or unresponsive overdose

Morphine

Actions:

- **Emesis**

- stimulates the chemoreceptor trigger zone in area postrema → vomiting



- **GI tract**

- ↓ gut motility ↑ intestinal smooth muscle tone ↑ anal sphincter tone

- constipation

Most annoying adverse effect for opioids especially when chronically used

- little tolerance to this effect

هل ممكن يكون اشي جيد ؟ هل ممكن استخدم ال morphine عشان اعالج ال diarrhea ؟هو ممكن لانه ممتازين و powerful بس بعمل الخوف من ال abuse

بس مثلا لو بدك تستخدمه بدون ال abuse liability شو تعمل ؟ بعمل modification بحيث ما يعمل لل crossing ل blood brain barrier زي loperamide

Morphine

Actions:

- **Cardiovascular**

Essential component for the treatment of myocardial infarction to treat pain associated with MI, reduced anxiety and reducing preload on cardiac muscle

- Peripheral vasodilation most prominent effect due to histamine release and decreased adrenergic tone

- Very high doses may produce bradycardia and hypotension

- Contraindicated in patients with severe brain/head injury

It causes vasodilation in cerebral veins resulting with increased intracranial pressure and cerebral hypertension

- **Histamine release**

- Enhance the release of histamine from mast cells, causing urticaria, sweating, and vasodilation.

That's why it's contraindicated to be used in patients with allergies or asthma

Morphine

Actions:

- **Urinary retention**:

- Due to contraction of sphincter, inhibition of reflex of urination and increase ADH.

- **OPIAD: opioid-induced androgen deficiency**

And infertility in males

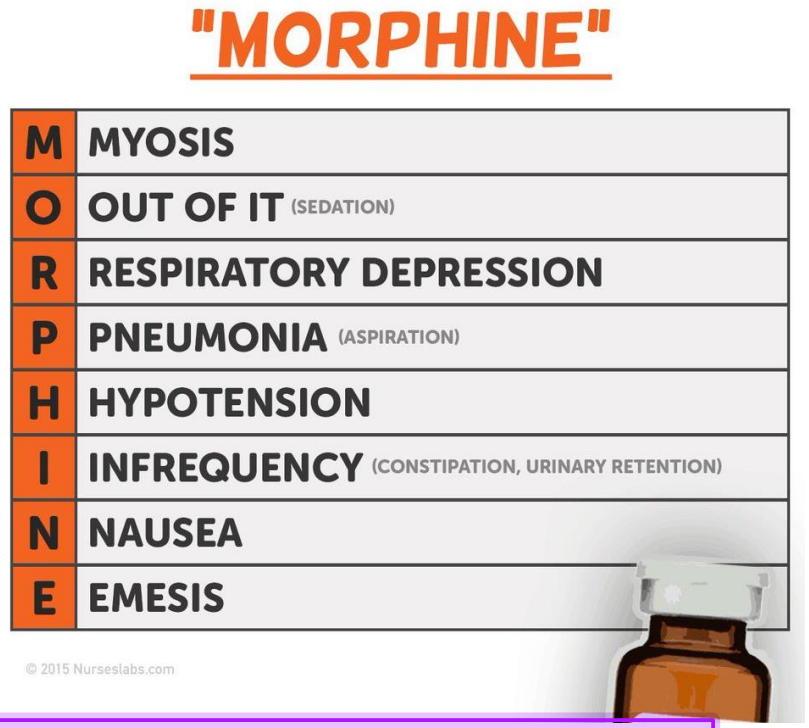
- **Labor**

Delays labour especially second stage

- increases second stage of labor.

How?

Morphine relaxes the muscles including those involved in the contractions of childbirth, this can slow down the progression of labor, potentially prolonging the process.



Pregnant women who are dependent on morphine or they abused morphine at some point usually gibe birth to dependent babies as well that could suffer from severe withdrawal after the moment of birth

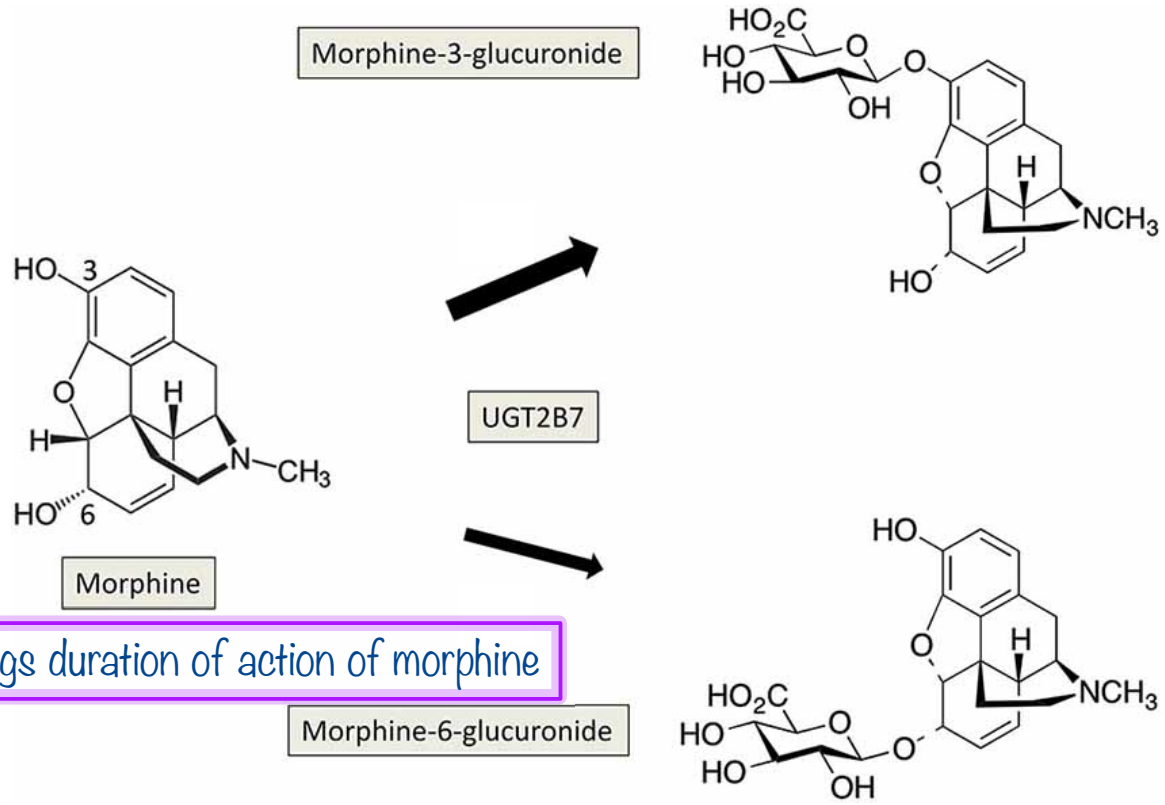
Morphine

Pharmacokinetics

- **Administration:** *IM, IV, SC* – best effect
- **Distribution:** enters all body tissues (including fetus) – contraindicated for analgesia in labor
- **Metabolism**: glucuronidated into 2 metabolites:
  - ❖ Morphine-6-glucuronide: potent analgesic
  - ❖ Morphine-3-glucuronide: not an analgesic

Neuro-exciting compound/metabolite » it prolongs duration of action of morphine

- **Duration of action**: 4-5 h in opioid-naïve patients.



Morphine

Analgesia

- Postoperative pain
- Renal colic
- Cancer-associated pain

MI, Acute Pulmonary Edema (LFV)

- To decrease preload
- Pain

Preanesthetic

Antitussive?

- Codeine is better

Therapeutic Uses

Can you use morphine as antidiarrheal?

Of course not

Morphine

Tolerance:

- Happens to analgesic + respiratory depressant + euphoric + sedative effects
- Not to miotic or constipating effects (problem?) أكيد
- Cross tolerance develops between opioids

Dependence

- Physical
- Psychological

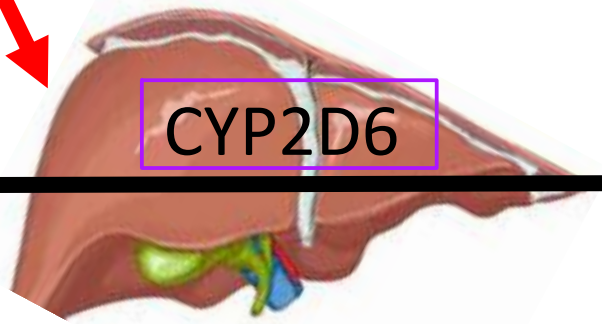
Codeine

Pro-drug

Natural

Weak analgesic

Codeine → CYP2D6 → Morphine



Required for the analgesic effects

Uses:

- mild/moderate pain (+paracetamol)
- Antitussive (dextromorphan preferred)

بينعطى oral على شكل syrup

-used over-the counter??????

اكيد بعمل بس اقل من morphine

Oxycodone

highly abused

semisynthetic

oxycodone >>
morphine (orally)

oxymorphone
>>>>>>>>>>
morphine
(parenterally)

اضعف من ال morphine بال
orally و لكن اقوى parenterally

oxymorphone
>>> morphine
(orally)

semisynthetic

Oxymorphone

Hydrocodone

semisynthetic

Hydrocodone=morphine (orally)

Uses

1. moderate to severe pain (+ibuprofen or paracetamol)
2. antitussive

Fentanyl

Synthetic

Fentanyl 100-folds > morphine

كل اشي بعمله ال morphine من ضاعفه مية مرة risk or effects

very lipophilic اقوى لانه

Uses

- Postoperative pain, epidural analgesia in labor
- Cancer pain
- Anesthesia (sedative)

Contraindicated in opioid-naïve patients

الي ما اخدوا opoid من قبل و ما عندهم tolerance لانه بسهولة بعمل overdose حتى لو استخدمت therapeutic dose

Kinetics

- Rapid onset of action (15-30 mins)
- Short duration of action

Methadone

Synthetic

- Methadone ≠ morphine
- μ agonist
- NMDA antagonist
- SNRI

Glutamatergic pathways

Seretonin epinephrine reuptake inhibitors

Uses

- Analgesia (against nociceptive and neuropathic pain)
- Detoxification of opioids and heroin (treatment of opioid abuse)

V.I

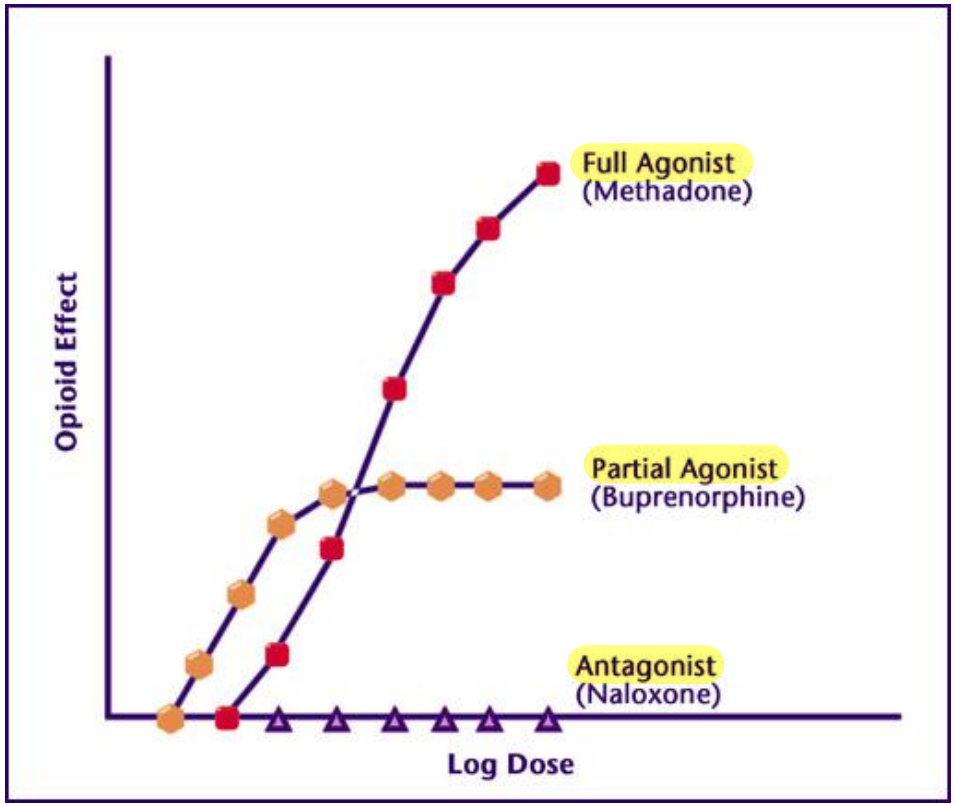
ليش ما بنستخدم الهيروين مع انه it has no clinical utility لانه ؟ opoid

كيف بدي استخدم opioid بمعالجة opioid abuse ؟ اللي بأدي للـ abuse هم الـ withdrawal symptoms
هلا الـ methadone بعمل withdrawal symptoms بس they're milder ،and reward pathway

Opioid Partial Agonists
Mixed Agonist-Antagonist

- Partial opioid agonists bind to opioid receptors but have only partial efficacy relative to full opioid agonists.

- Buprenorphine
- Pentazocine
- Nalbuphine



Less efficacious than morphine because it's a partial agonist, in terms of potency which has to do with the binding affinity it's more potent than morphine it has a higher affinity for binding to opoid receptors

Buprenorphine

Partial agonist at **μ**

Antagonist at **κ**

Lower risk in comparison with full agonist opoid drugs

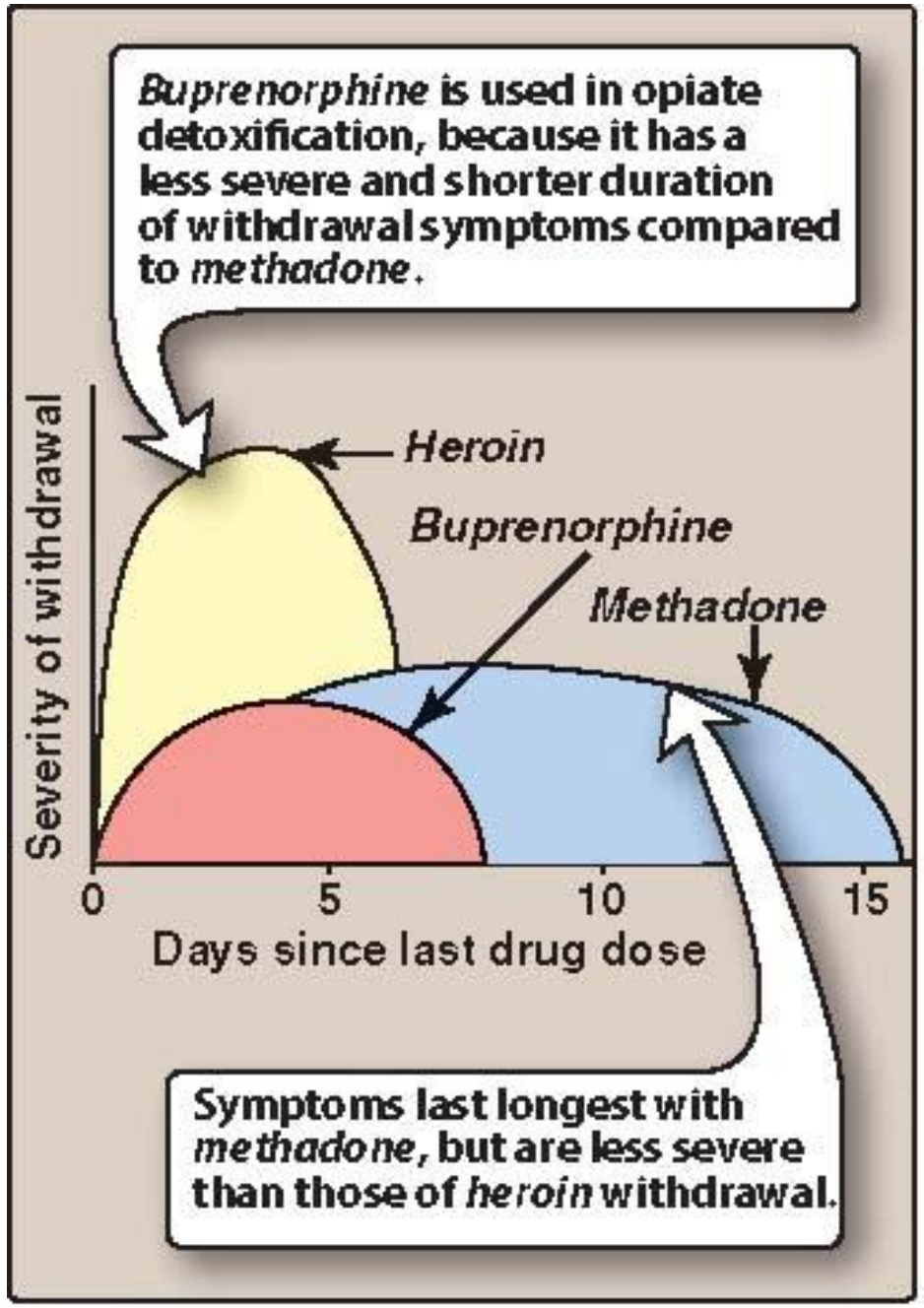
Little sedation, respiratory depression, hypotension

Combined with naloxone (antagonist). Why?

Treatment of opoid dependence, because of its higher affinity it can replace full agonist binding to receptors

Uses

- Used for opioid detoxication
- Moderate to severe pain



Withdrawal symptoms ofbuprenorphine is less than heroin, and can be managedin patients better, it's even better than methadone because it's withdrawal symptoms last less than

Patients using methadone should be rehabilitated and treated under supervision but with buprenophine patient can be treated from home, it requires less frequent dosing because it has a longer half life than methadone

Other Analgesics

- Tapentadol
- Tramadol

Tramadol

Binds and acts on μ

SNRI

Less respiratory depression than morphine

Highly abused

Uses

- Analgesia (moderate to severe pain)

Can be used in oit patients

V.I Opioid Antagonists

- Naloxone
- Naltrexone

Naloxone

Non-selective

Competitive antagonist at μ, κ and δ

Depends on concentration gradient

Administered IV

Half-life: 30-81 minutes

Very fast onset of action

Can precipitate withdrawal

Uses

It can precipitate abrupt withdrawal

- Used to reverse coma and respiratory depression of opioid overdose

Drug of choice to reverse opioid overdose

Opioid Antagonists

- Naloxone
- Naltrexone

Naltrexone

Longer duration of action than naloxone
Oral

Uses

- Used for opioid detoxication (maintenance)
- Used to decrease cravings in patients with alcohol dependence

Activation of μ opioid receptors by morphine can result in which of the following effects?

A) Hyperalgesia
B) Arousal
C) Diarrhea
D) Mydriasis
E) Nausea and vomiting

Morphine is in important component of the treatment of myocardial infarction. The beneficial effect of morphine in the treatment of MI is because of its ability to result in:

A) Decreased venous return (cardiac preload)
B) Increased stroke volume
C) Respiratory depression
D) Reduced peripheral vascular resistance
E) Lowered intracranial pressure

The opioid partial agonist that is indicated for the treatment of heroin and opioid dependence is __Bupernorphine

The opioid antidote is _____Naloxone_____

The opioid agonist used to induce analgesia in labor as a replacement of morphine is _Meperidine_

Metabolism of __Codeine__ by CYP2D6 to morphine is required to produce its analgesic effects.

Which synthetic full-opioid agonist can be used as during anesthesia? __Fentanyl__