Opioids

PHARMACOLOGY LECTURE 2 + 3 😇

Done by : scientific team - hope

Pain

not associated ← وممكن يكون الالم with tissue damage

- "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage"
- Acute or chronic
- Consequence of complex neurochemical processes in the peripheral and central nervous systems → vary from one individual to another
- Subjective measure the severity of the pain → is subjective → depend on the person itself

International Association for the Study of Pain

Pain

[1] to assist the pain

Pain

Types of pain

physical trauma, thermal injury (burns)

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

Examples: somatic pain, cancer pain, postoperative pain

in CNS itself / actual tissue damage

ممكن ما يكون عنا

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

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

injury in median nerve (in pregnant women can suffer from this problem)

follows infection with herpes viruses.

- **Others**

Definitions

Hyperalgesia: abnormally increased sensitivity to pain

Allodynia: pain resulting from an originally non-painful stimulus

↳ in peripheral neuropathy

Hypoalgesia: decreased sensitivity to painful stimuli

Analgesia: reduction or relief of pain sensation without affecting other sensations

↳ specific for pain relief

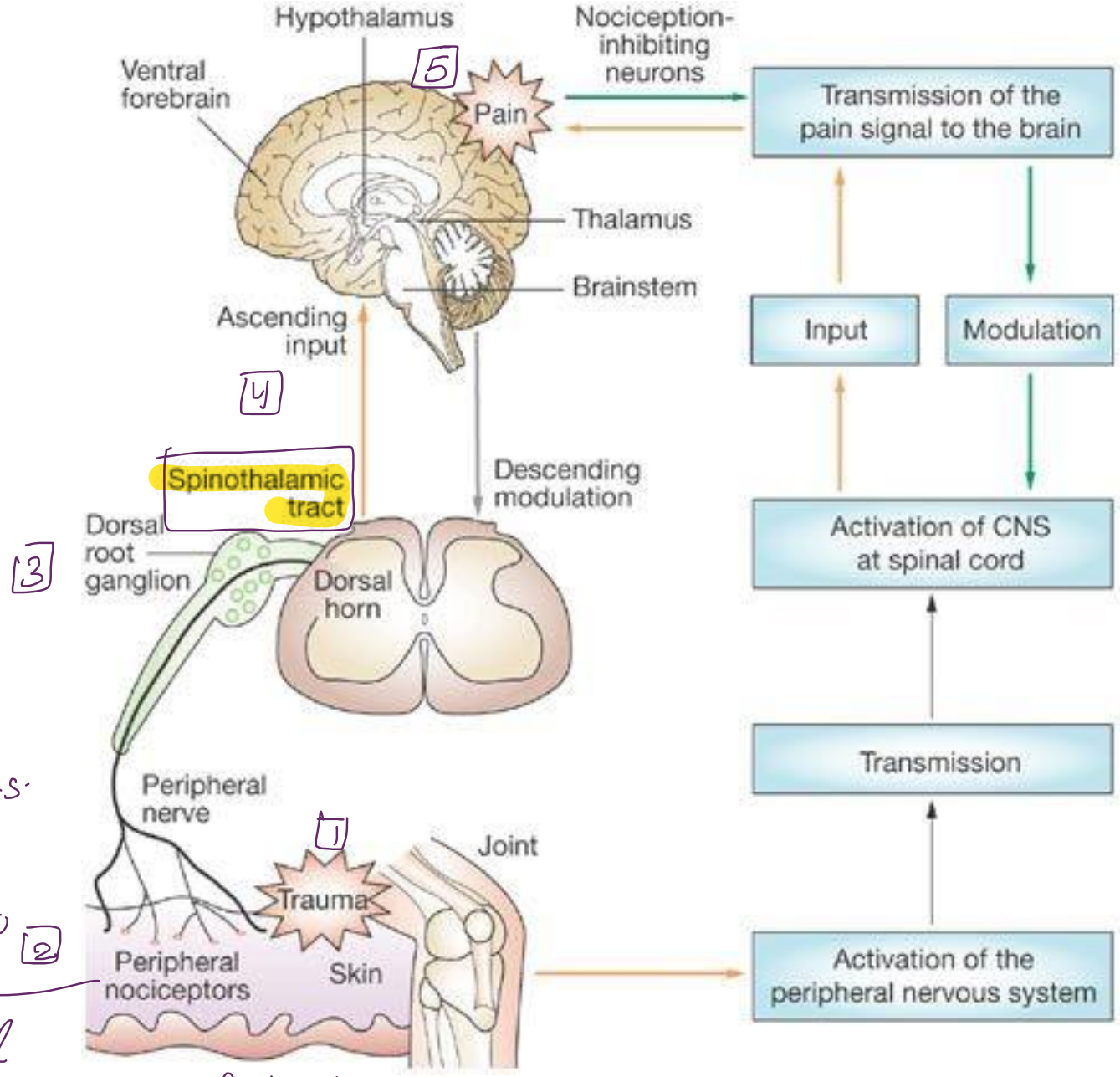
Anesthesia: local or general reduction or absence of all sensations (touch, pain, temperature, …) with or without loss of motor function. This may be accompanied by loss of consciousness

→ more wide suppression of the nervous system

Paresthesia: abnormal or altered sensation of the body (numbness, tingling, or burning)

→ common symptom in neuropathic pain

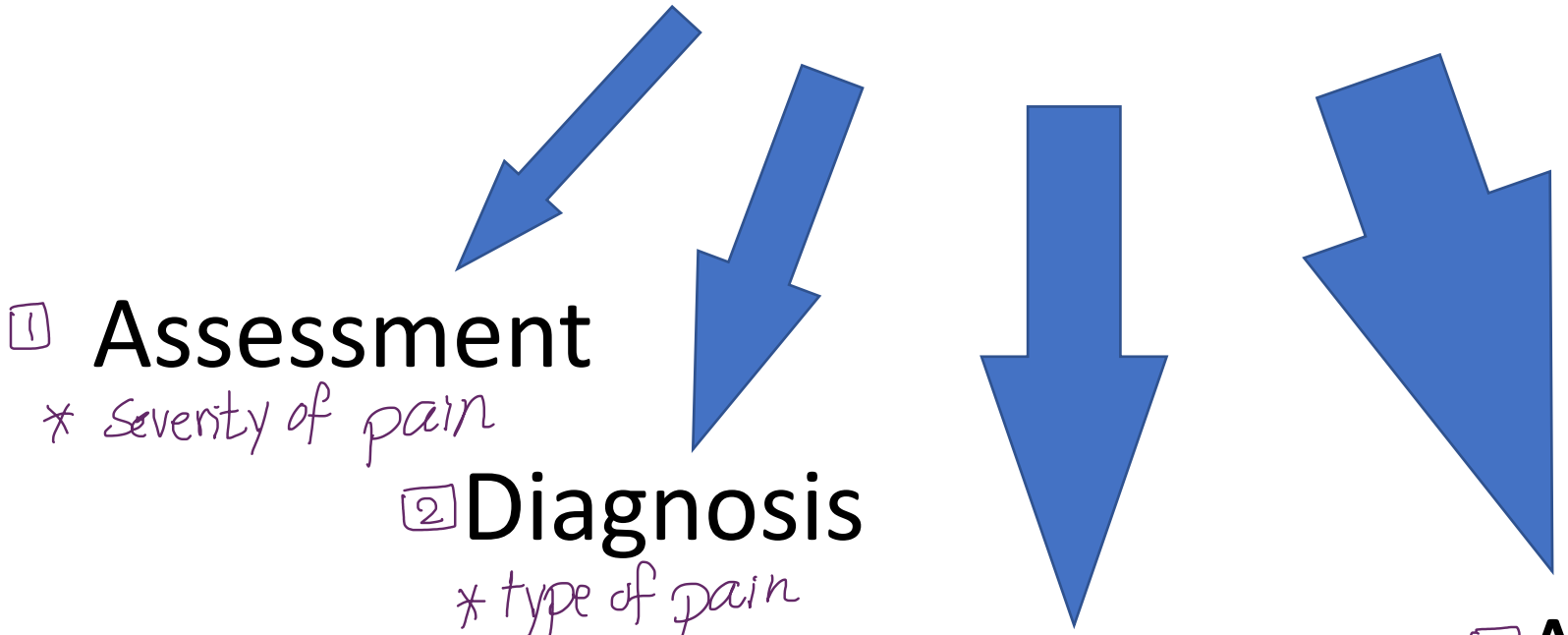
The Pain Pathway



are not receptors.

nociceptors → used to indicate peripheral nerves that indicated in sensing and transmitting painful stimuli

How to manage pain?



1. Assessment
   * Severity of pain
2. Diagnosis
   * type of pain
   chronic or acute
3. Support
4. Analgesics
   - Paracetamol → mild-moderate pain
   - NSAIDs 1st line
   - Opioids (moderate to severe pain)

very potent analgesics

Severe pain

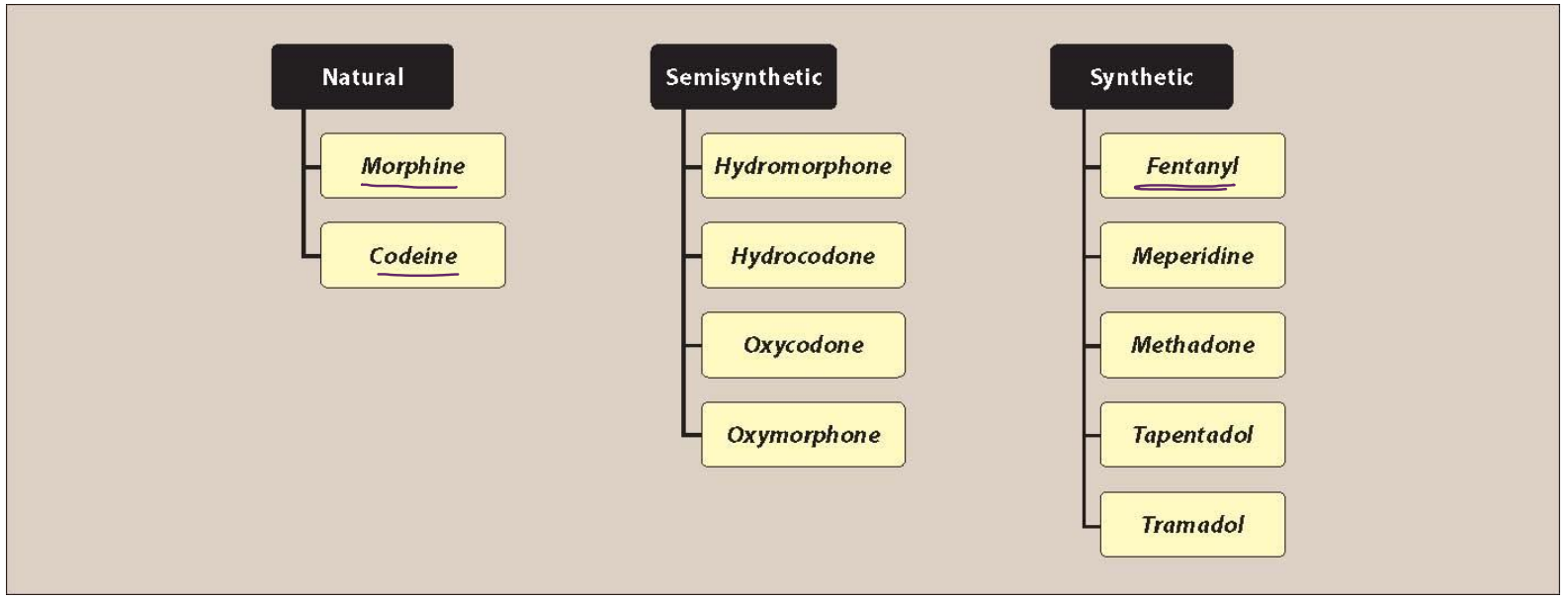
Can you tell the difference between these terms:

- Opium? → original plant source of opioids (الأفيون)
- Opioid? → not only natural derived opium base substances any chemical substance whether natural, semisynthetic or synthetic that has an activity such as [morphine] الدواء الرئيسي في عائلة الـ opioid
- Opiate? → referes to the only natural opioid
- Narcotic? → can be used in exchange with opioid للدلالة مصطلح قديم لا يستخدم حالياً.

Opioids

also have the same characterestic as morphine.

- *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



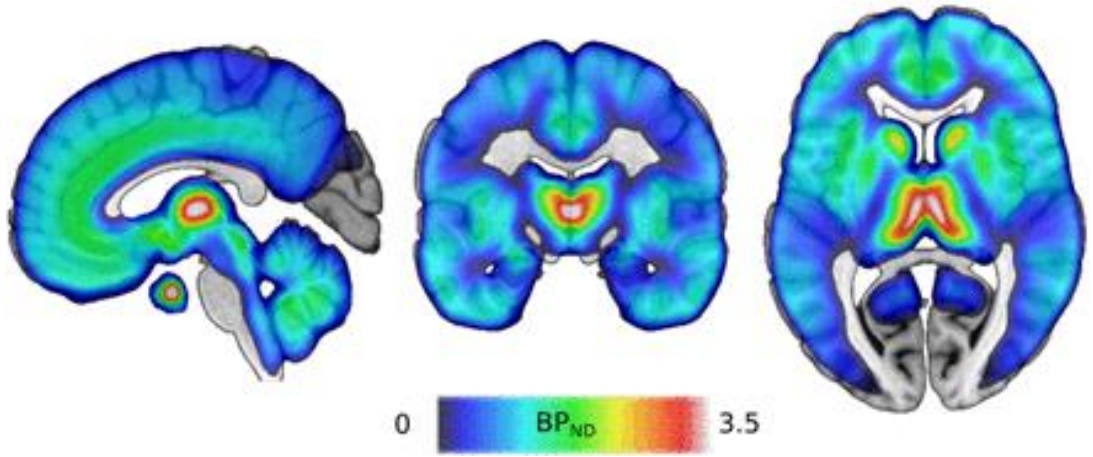
CNS → release an endogenous opioid (NT)
usually have an inhibitory function
→ that is why we have opioid receptors in our CNS

Opioid Receptors

Mu
Kappa
delta

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

  But also….
  - Gut
  - Bladder



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

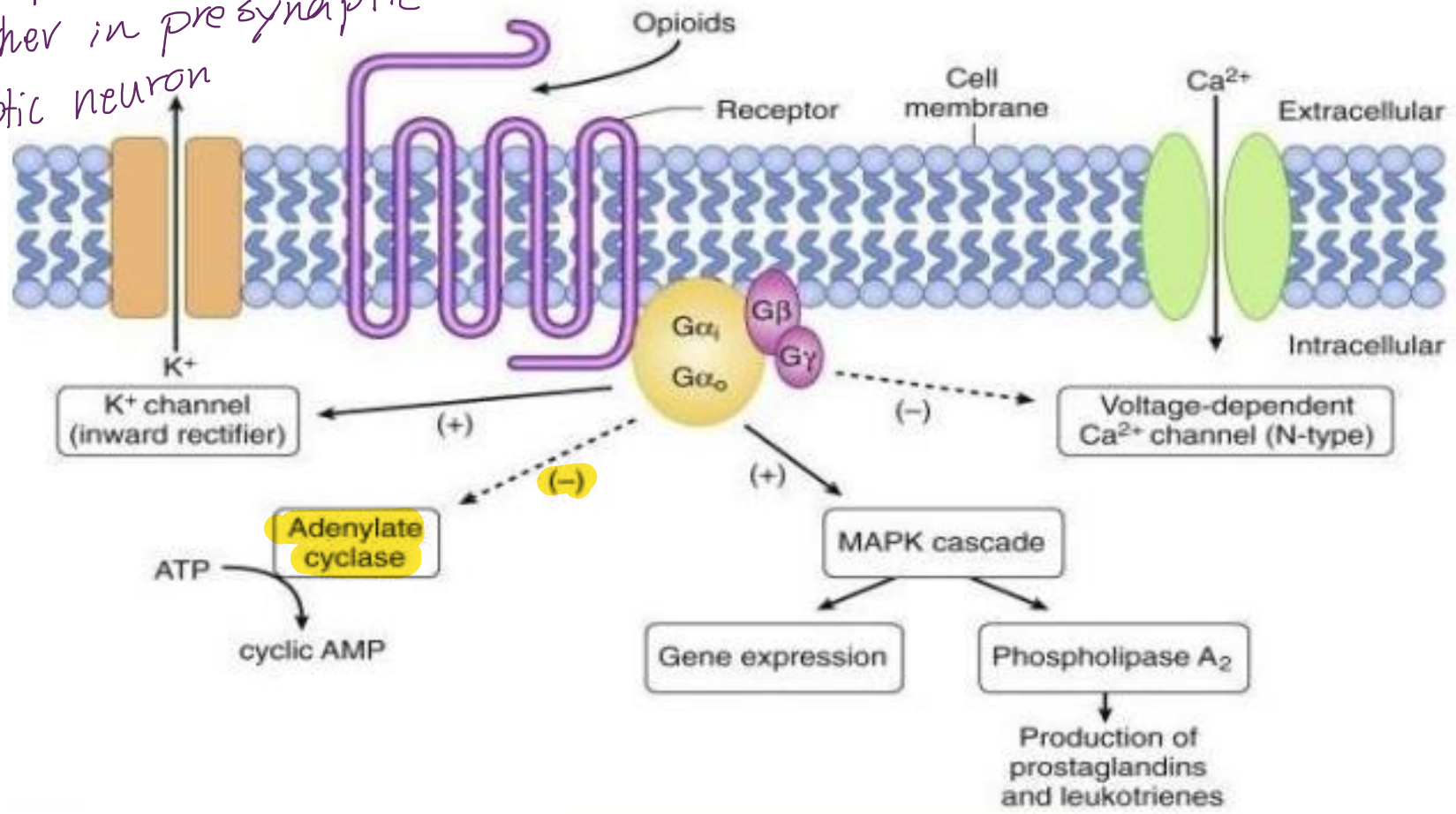
Opioid Receptors

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

Similarity → 1) they able to bind opioid
2) they activated by opioid
3) all are G protein coupled receptors (metapotropic)
all are coupled with Gα inhibitory subunit, and all they inhibit adenylecyclase ↓
↳ responsible for production of 2nd massenger

Opioids: Mechanism of Action

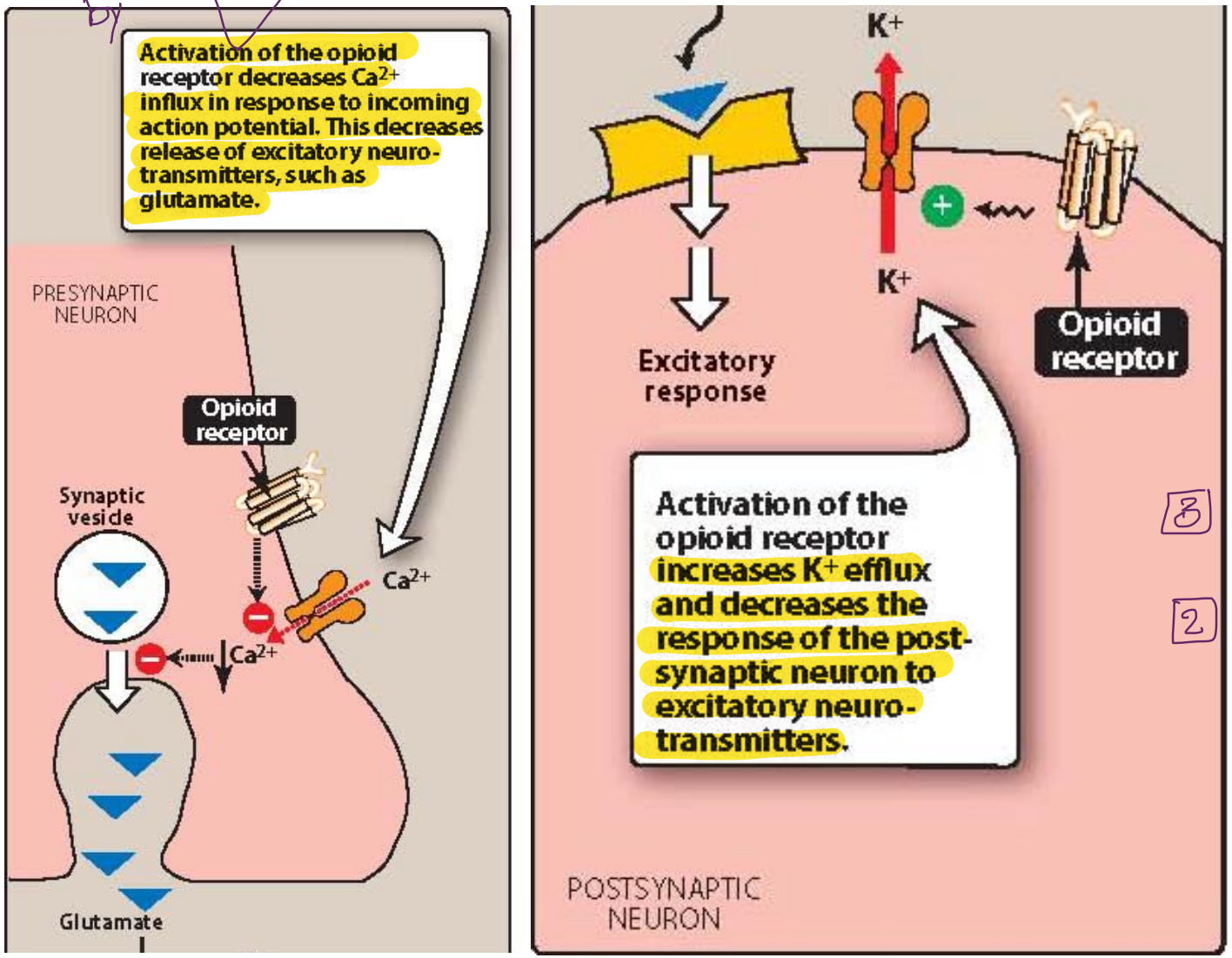
* opioid receptor can be found either in presynaptic or postsynaptic neuron



Opioids: Mechanism of Action

pharmacological opioid

endogenous opioid



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

1. Inhibit adenylyl cyclase
2. Reduce *presynaptic* Ca^{++} influx
3. Increase *postsynaptic* K^+ efflux

Opioids

Phenanthrenes	Action on Opioid Receptors
Morphine	Agonist
Codeine	Agonist
Oxycodone	Agonist
Oxymorphone	Agonist
Hydromorphone	Agonist
Hydrocodone	Agonist
Buprenorphine	Partial agonist
Nalbuphine	Mixed Agonist/Antagonist
Butorphanol	Mixed Agonist/Antagonist

Benzmorphan	
Pentazocine	Mixed Agonist/Antagonist
Phenylpiperidines	
Fentanyl	Agonist
Alfentanil	Agonist
Sufentanil	Agonist
Meperidine	Agonist
Diphenylheptane	
Methadone	Agonist

1 Opioid Agonists

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

Morphine

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

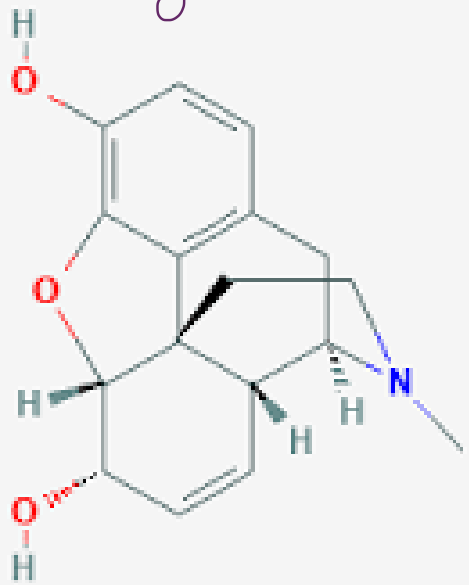
because morphine has a very intense sedative effect

Morphine

↳ activate delta and kappa but it acts mainly on μ

Mechanism of action

- Binds to opioid receptors (mainly **μ**)- full agonist
  - CNS, gut, bladder
- Decreases the release of many excitatory transmitters → specially those on the sensory pain pathway from nerve terminals carrying nociceptive stimuli



Morphine

* inhibitory effect

Morphine

Actions:

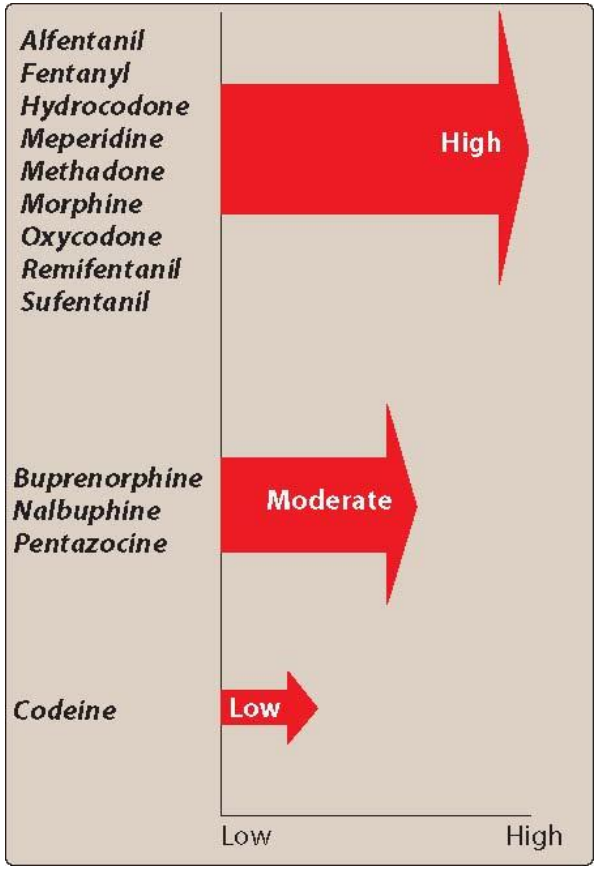
main theraputic use as analgesic

- **Analgesia**
  - without loss of consciousness
  - raises pain threshold (spinal cord)
  - alters perception of pain (brain)
    - ❖ still aware of pain, but not unpleasant
  - nociceptive >>> neuropathic

why

pain associated with tissue damage

morphine has a very little activity on neuropathic pain (not used for peripheral neuropathy, diabetic ...)



Euphoria مش كل الأدوية الي بتسكن الالم بتعمل *

opioids are highly abused drug

Morphine

لانه ممكن بدل ما الواحد ياخد ال morphine عشان ال analgesic effect ياخده عشان ال Euphoria → drug abuse

Actions:

2 • **Euphoria** the feel of happiness / bad effect

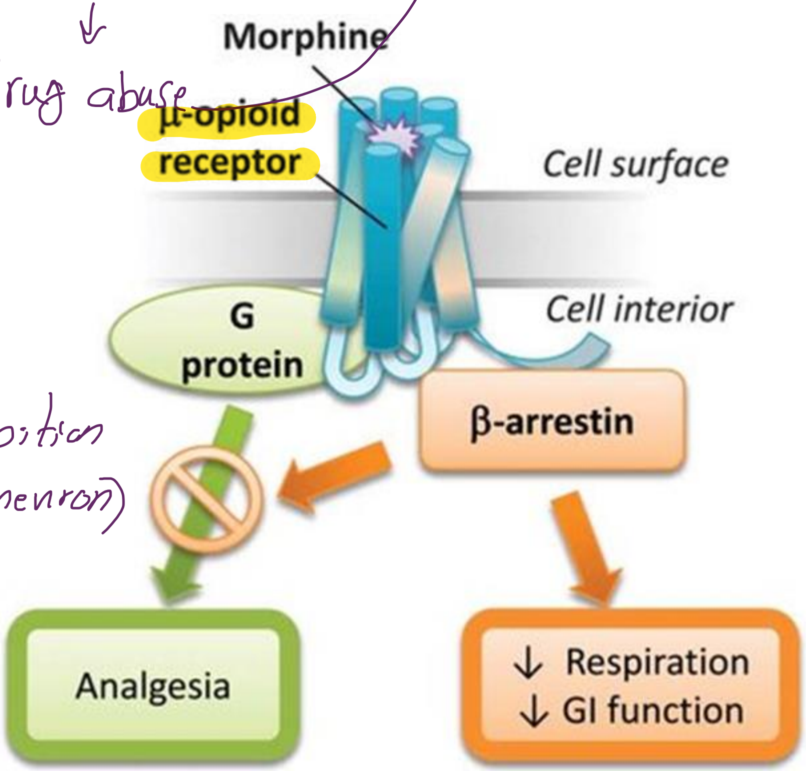
- sense of contentment and well-being
- caused by the disinhibition of the dopamine-containing neurons of the ventral tegmental area

inhibition of inhibition (inhibit interneuron)

3 • **Respiratory depression**

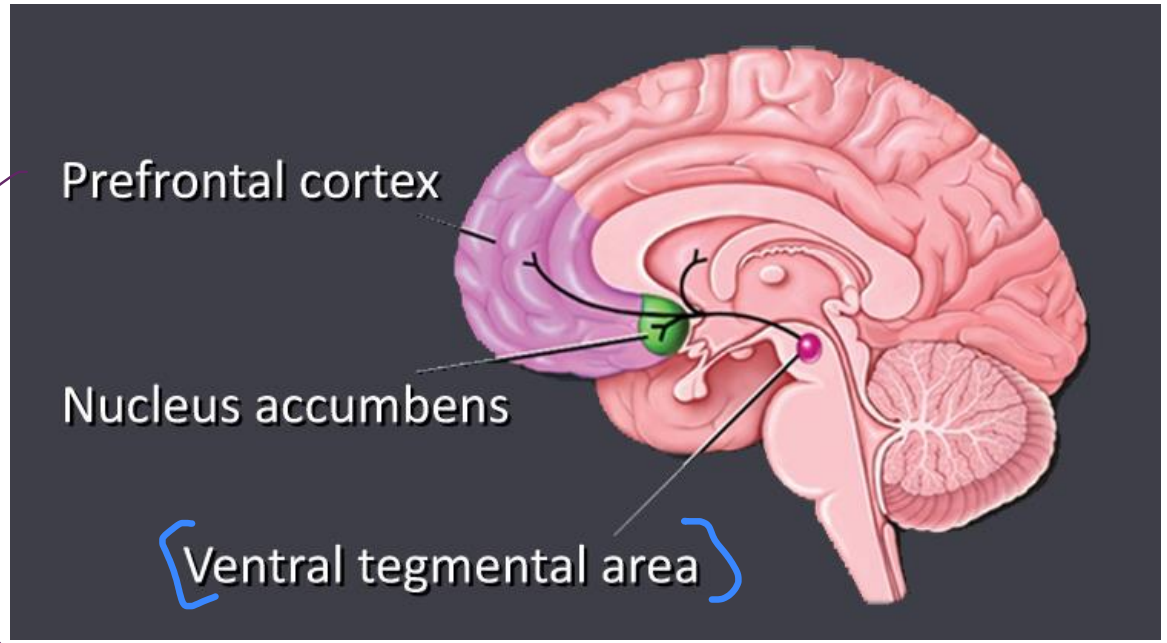
- reduces the sensitivity of respiratory center to CO_2 لما نزيد ال CO_2 في جسم مارح نزيد ال ventilation
- most common cause of death from opioid overdose.
- Tolerance develops quickly

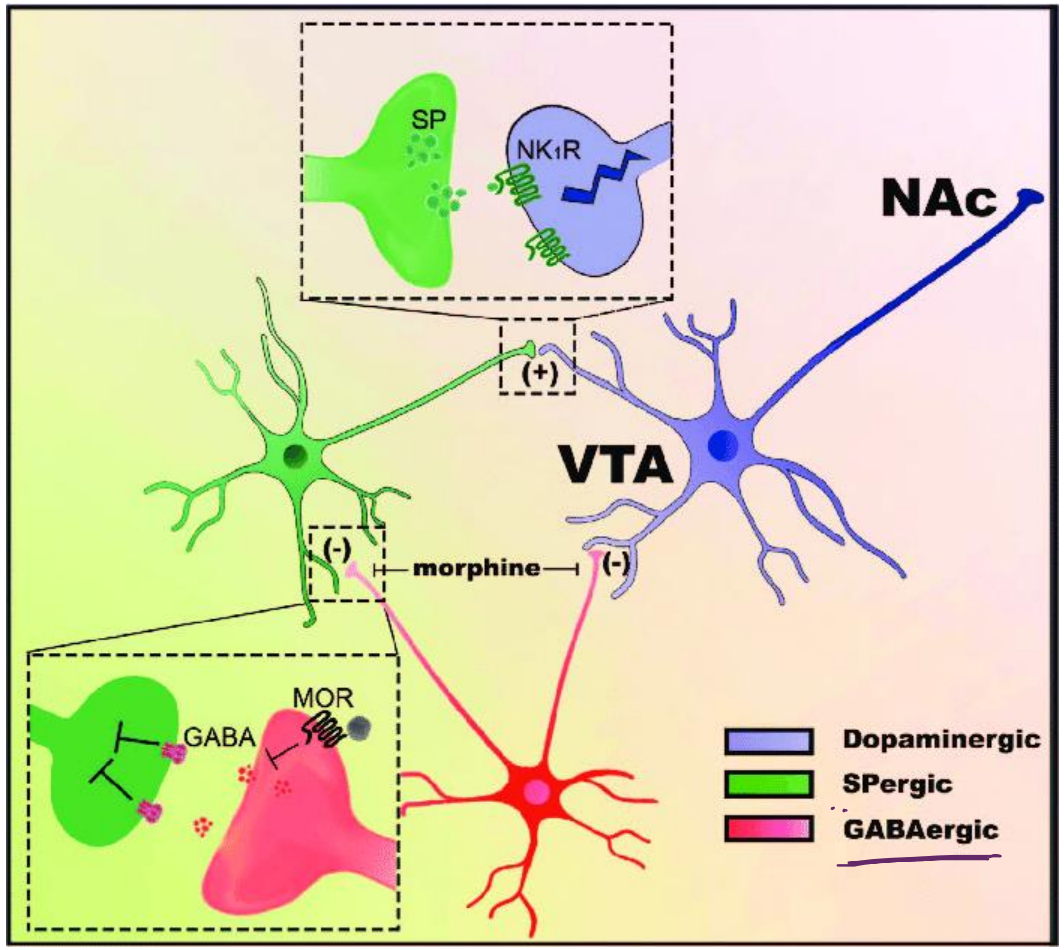
the action of morphine on Respiratory center with repeated dose will decrease / ما رح يستجيب



Morphine and the Reward Pathway

meso limbic pathway.





dopaminergic pathway.

↳ dopamine released into BG

Morphine

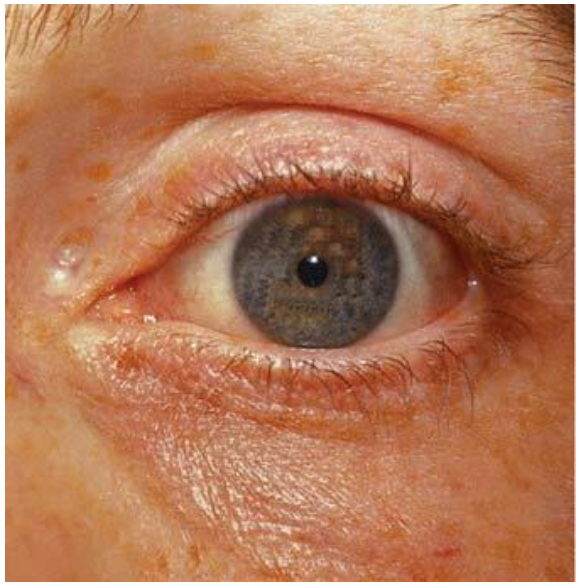
Actions:

4 • **↓ cough reflex**

- both morphine and codeine have *antitussive* effect.

5 • **Miosis** constriction of pupis → this action is very useful diagnostically

- pinpoint pupil
- results from **μ** and **κ** receptors
- no tolerance to this effect



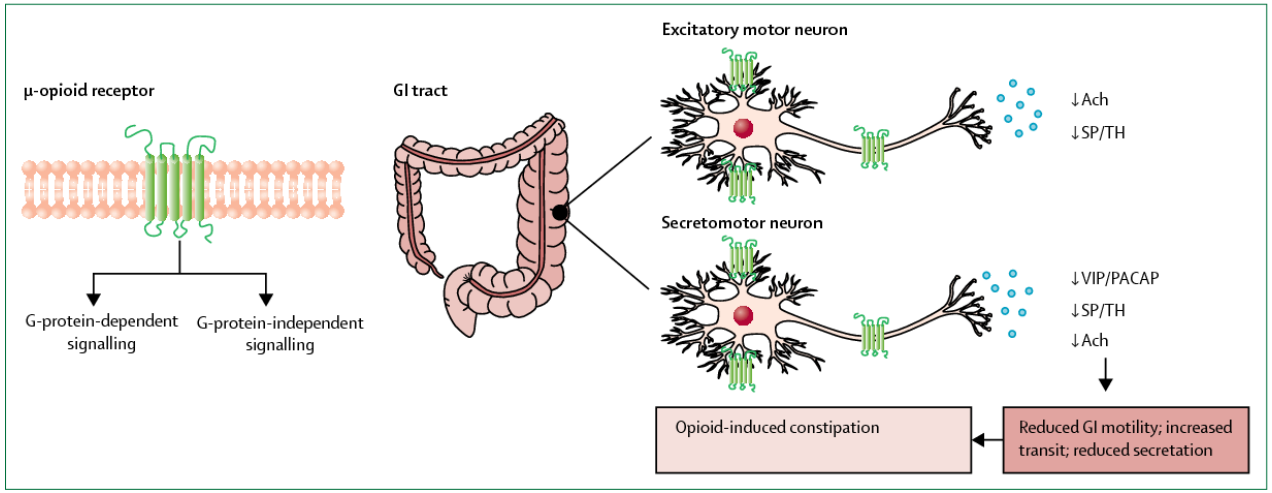
meiosis

Morphine

Actions:

6 • **Emesis** N/V

- stimulates the chemoreceptor trigger zone in area postrema → vomiting



7 • **GI tract**

- ↓ gut motility ↑ intestinal smooth muscle tone ↑ anal sphincter tone
- constipation most common AE of opioid use.
- little tolerance to this effect → bad

Morphine

Actions:

- **Cardiovascular**

- 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

- **Histamine release**

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

Morphine

Actions:

10 • **Urinary retention**:

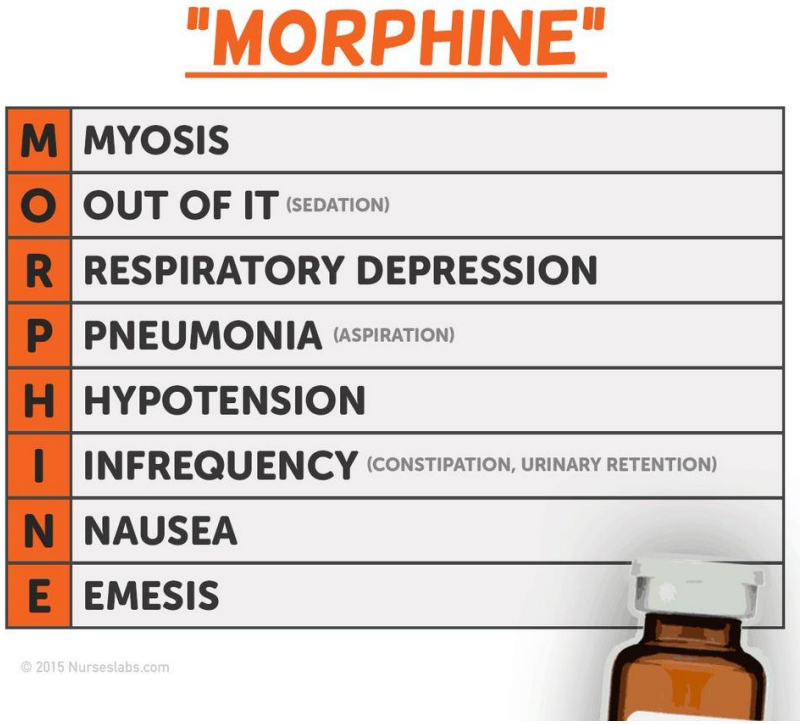
- Due to contraction of sphincter, inhibition of reflex of urination and increase ADH.

11 • **OPIAD: opioid-induced androgen deficiency** (with chronic use of opioid)

12 • **Labor**

- increases second stage of labor.

How? by inhibiting the contractility of the uterus



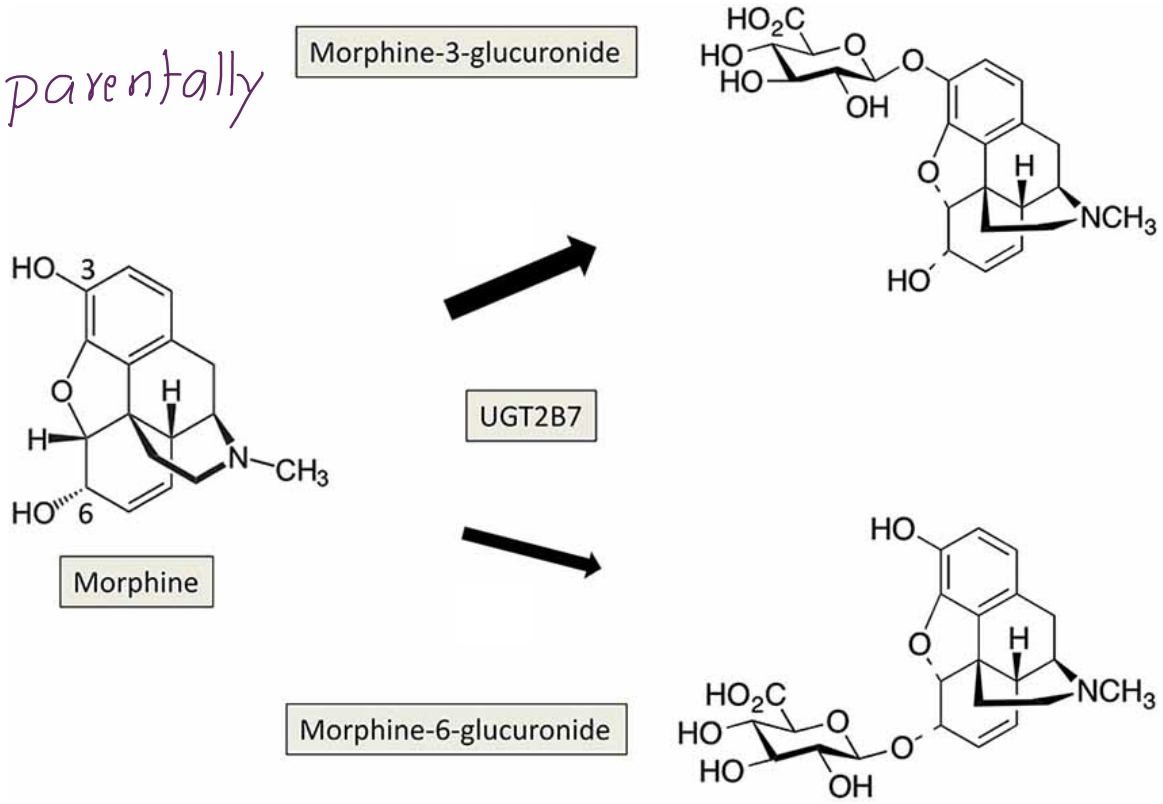
Morphine is used with caution/contraindicated in patients with bronchial asthma. WHY?

Morphine

the least lipophilic drug

Pharmacokinetics [never given orally]

- **Administration:** *IM, IV, SC* – best effect always parentally
- **Distribution:** enters all body tissues (including fetus) – contraindicated for analgesia in labor
- **Metabolism**: glucuronidated into 2 metabolites:
  - ❖ Morphine-6-glucuronide: potent analgesic (prolonged 1/2t of morphine)
  - ❖ Morphine-3-glucuronide: not an analgesic
- **Duration of action**: 4-5 h in opioid-naïve patients.



morphine لـ بعض هم ما استخدموا ال

in morphine dependent users (Chronic use) → the duration ↓

Morphine

somatic nocciceptive pain

1 Analgesia

- Postoperative pain
- Renal colic
- Cancer-associated pain

2 MI, Acute Pulmonary Edema (LFV)

to reduce anexity and pain.

- To decrease preload → because of VD action.
- Pain

3 Preanesthetic

4 Antitussive?

morphine is not strong as antitussive

- Codeine is better

Therapeutic Uses

Can you use morphine as antidiarrheal? No we can use anothe opioid act on gut specifically

like loperamide

Summary of Morphine's Therapeutic Uses

Therapeutic Use	Comments
Analgesia	*Morphine* is the prototype opioid agonist. Opioids are used for pain in trauma, cancer, and other types of severe pain.
Treatment of diarrhea	Opioids decrease the motility and increase the tone of intestinal circular smooth muscle. [Note: Agents commonly used include *diphenoxylate* and *loperamide* (see Chapter 31).]
Relief of cough	*Morphine* does suppress the cough reflex, but *codeine* and *dextromethorphan* are more commonly used.
Treatment of acute pulmonary edema	Intravenous *morphine* dramatically relieves dyspnea caused by pulmonary edema associated with left ventricular failure, possibly via the vasodilatory effect. This, in effect, decreases cardiac preload and afterload, as well as anxiety experienced by the patient.
Anesthesia	Opioids are used as preanesthetic medications, for systemic and spinal anesthesia, and for postoperative analgesia.

Morphine

Tolerance:

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

Dependence

- Physical
- Psychological

Opioid Agonists

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

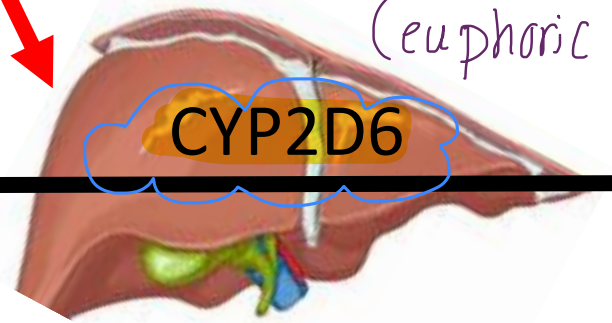
Codeine

→ could be abused and that is why we use dextromorphan instead of it ... (euphoric effect)

Natural

Weak analgesic

compared with morphine



Codeine → Morphine

Required for the analgesic effects

Uses:

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

-used over-the counter?????? Now it is not used OTC

Opioid Agonists

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

Oxycodone

highly abused

semisynthetic

(codeine معدل) oxycodone >> morphine (orally)

يستخدم في علاجات الأسنان

as tablet

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

(morphine معدل) oxymorphone >>> morphine (orally)

semisynthetic

Oxymorphone

Opioid Agonists

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

Hydrocodone

semisynthetic

Hydrocodone=morphine (orally)

Uses

- moderate to severe pain (+ibuprofen or paracetamol)
- antitussive

NSAID

VICODIN

Opioid Agonists

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

natural

Semi synthetic

Fentanyl

Synthetic

Fentanyl 100-folds > morphine

* it is very potent analgesic (very strong)

* used for severe pain

Uses

- Postoperative pain, epidural analgesia in labor
- Cancer pain
- Anesthesia (highly sedative and very potent) (sedative)

Contraindicated in opioid-naïve patients

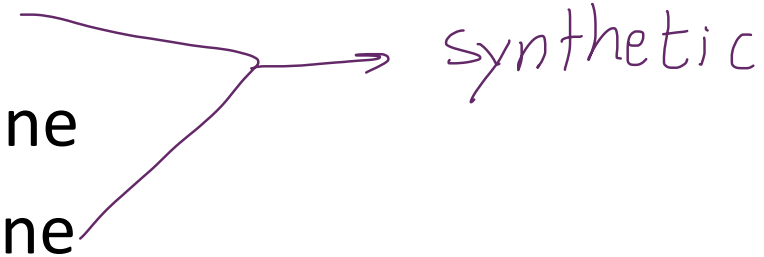
over dose effect * لدين عالج يعمل

Kinetics (prefered in people are already tolaranced)

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

Opioid Agonists

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



Methadone

Synthetic

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

Uses

1. Analgesia (against nociceptive and neuropathic pain)
2. Detoxification of opioids and heroin (treatment of opioid abuse)!!!

other opioid are bad for neuropathic pain

الي قبل هيك كانوا تحفظ μ agonist

serotonin norepinephrin reuptake inhibitor

glutamate receptors

most predominance excitatory NT in the CNS

NMDA AMPA

heroin = أفيون abuse

opioid and has an analgesic effect, but it is highly abusive drug

Opioid Agonists

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

induces high dependence

(dependence > analgesic effect)

even with very low dose

so it is not used as therapeutic drug.

Meperidine (Pethidine)

Synthetic

- κ agonist — full agonist
- Some μ agonist activity
- anticholinergic → many AE

Uses

- Used only for short-term analgesia management
- Preferred over morphine during labor ← is not used in labor

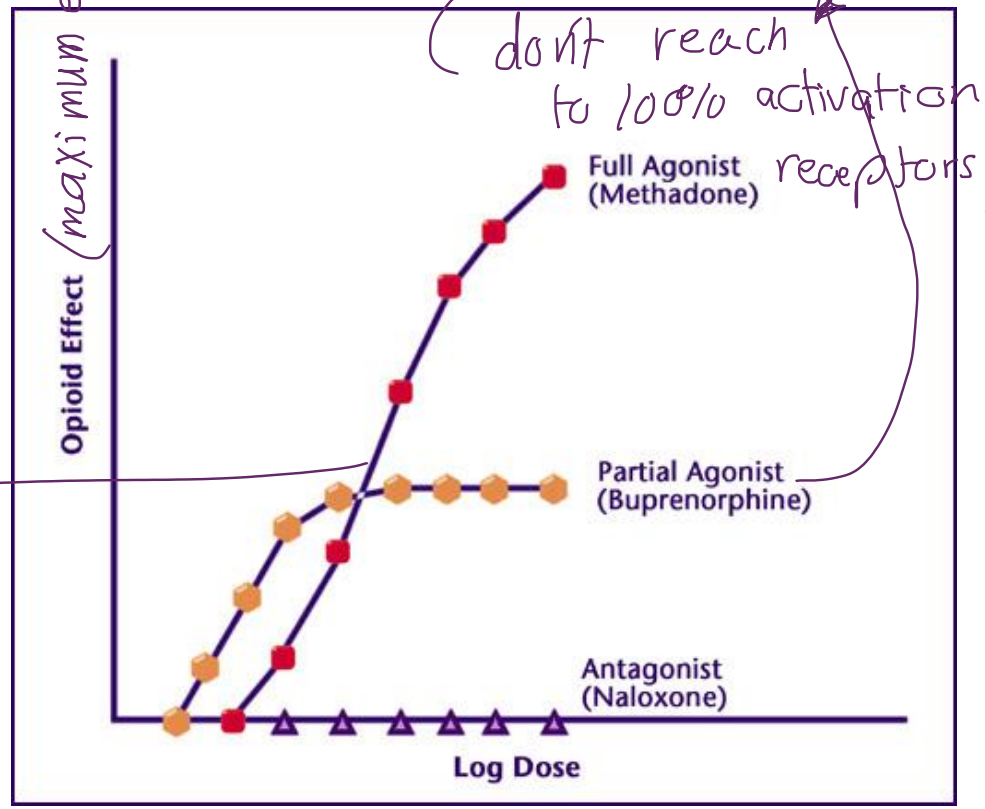
Opioid Partial Agonists Mixed Agonist-Antagonist

can also activate the receptors but they have a ceiling effect (no matter how much increasing the concentration after a certain limit → plateau (don't reach to 100% activation of receptors)

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

- Buprenorphine
- Pentazocine
- Nalbuphine

do not reach the maximal effect of full agonist



(full agonist)

with increasing concentration is capable for reaching 100% activation of receptors

Buprenorphine

- Partial agonist at **μ** (very tight binding to μ)
- Antagonist at **κ**

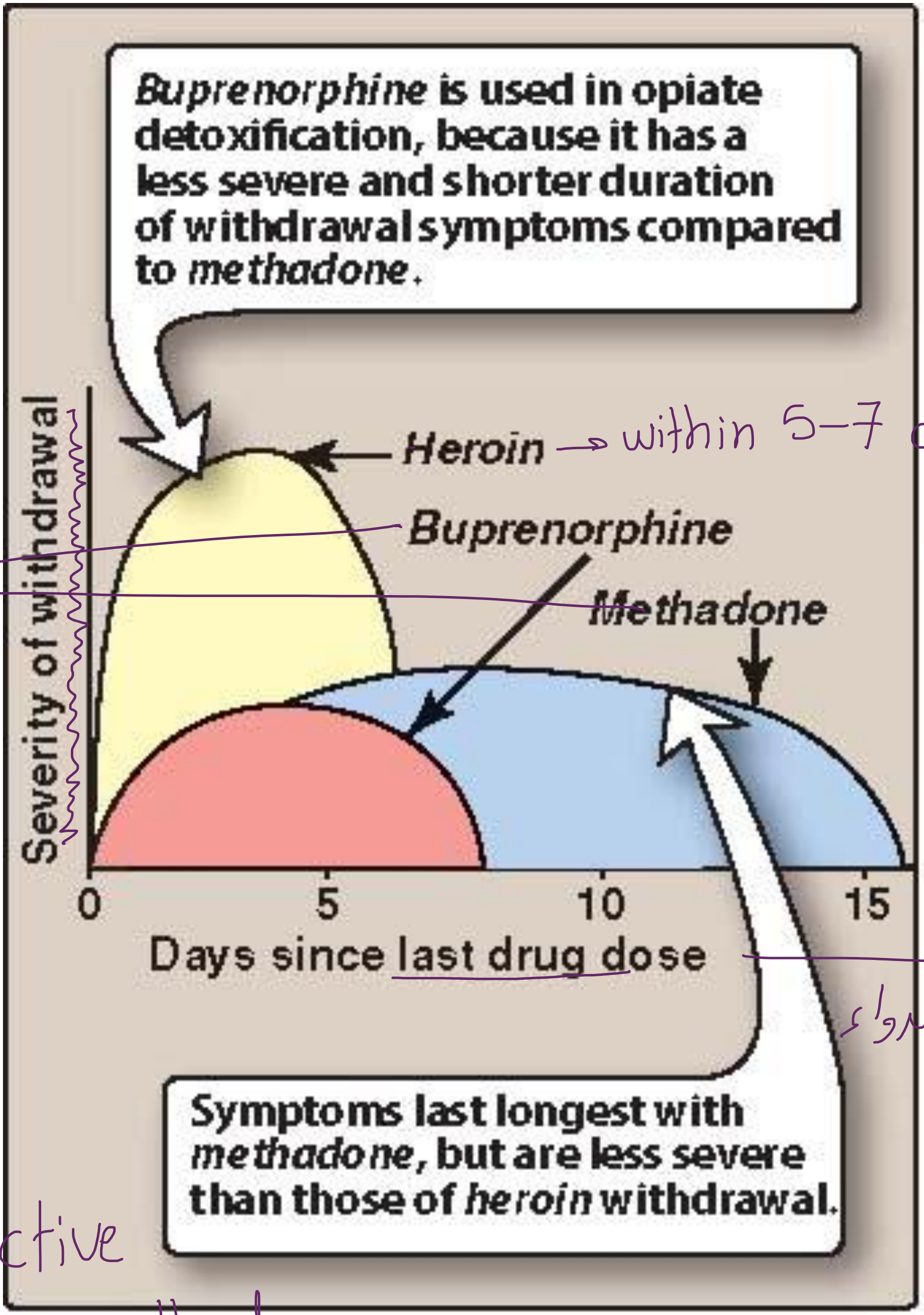
Little sedation, respiratory depression, hypotension

Combined with naloxone (antagonist). Why? (OD)

Uses

- Used for opioid detoxication like methadone.
- Moderate to severe pain

How we use methadone and buprenorphine for opioid detoxification?



Heroin → within 5–7 days (very sever withdrawal symptoms within short time)

peak happens very quickly

1. the withdrawal symptoms of them are not severe as heroin
2. very long duration to reach the peak (the duration not very fast)

so we can replace the addictive opioid with burprenorphine or methadone.

Days since last drug dose → * تقلل عدد الايام من بعد اخر dose من الدواء

* heroin لازم اوقف ال... مباشرة

Opioid Partial Agonists

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

- Buprenorphine
- Pentazocine
- Nalbuphine

Pentazocine

Partial agonist at κ

Antagonist at μ and δ

Less euphoria

Contraindicated in patients with coronary artery disease

Uses

- Analgesia (limited use because of side effects)

Other Analgesics

- Tapentadol
- Tramadol

Chemically are not opioid but they bind to opioid receptors (μ)

Tramadol

→ available orally

Binds and acts on μ

SNRI

Highly abused

- Less respiratory depression than morphine

Uses

- Analgesia (moderate to severe pain)

Opioid Antagonists

- Naloxone
- Naltrexone

Naloxone

مهم *

Competitive antagonist at μ, κ and δ

Administered IV
Half-life: 30-81 minutes

Can precipitate withdrawal with chronic use of opioid...

Uses

- Used to reverse coma and respiratory depression of 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

High-Yield Terms to Learn

Opiate	A drug derived from alkaloids of the opium poppy
Opioid	The class of drugs that includes opiates, opiopeptins, and all synthetic and semisynthetic drugs that mimic the actions of the opiates
Opioid peptides	Endogenous peptides that act on opioid receptors
Opioid agonist	A drug that activates some or all opioid receptor subtypes and does not block any
Partial agonist	A drug that can activate an opioid receptor to effect a submaximal response
Opioid antagonist	A drug that blocks some or all opioid receptor subtypes
Mixed agonist-antagonist	A drug that activates some opioid receptor subtypes and blocks other opioid receptor subtypes

التفريغ شامل لأهم ما ذُكر في المحاضرة وليس تفريغ حرفي

اللهم اغفر لموتانا وموتى المسلمين ، اللهم أكرمهم بجنة عرضها السماوات والارض
يخيرون بين أبوابها واجعل قبورهم باردة طيبة بطيب الجنة

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__

You decide to partake in a research project on opioid development. The main theme of the project is to design the PERFECT opioid analgesic. In a meeting, you were asked by your adviser to formulate ideas on the characteristics of that perfect drug. Which of the following statements will be your best answer?

A) The drug should be a non-selective opioid agonist.

B) The drug should bind differentially to opioid receptors in the CNS but not in the gut.

C) The drug should have an extremely short half-life.

D) The drug should be only available intramuscularly.

E) The drug should be a mixed agonist-antagonist at opioid receptors