Opioids

Pharmacology and Toxicology

Central Nervous System Module

Third Year Medical Students

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In the Book

- Chapter 14: Opioids

Pain

- “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
- Subjective

International Association for the Study of Pain

Pain

Pain

Types of pain

- **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

- **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.

- **Others**

Definitions

Hyperalgesia: abnormally increased sensitivity to pain

Allodynia: pain resulting from an originally non-painful stimulus

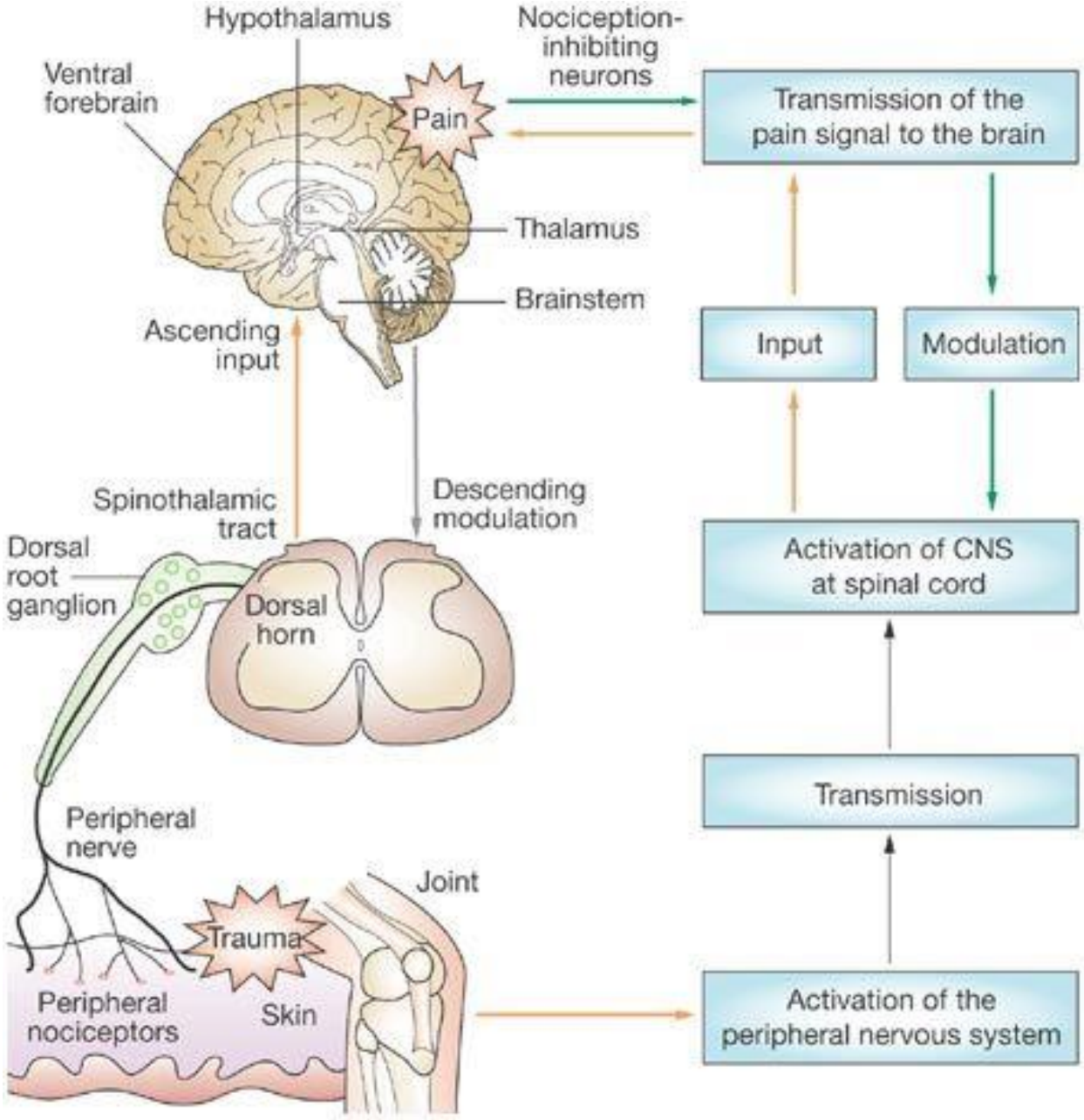
Hypoalgesia: decreased sensitivity to painful stimuli

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

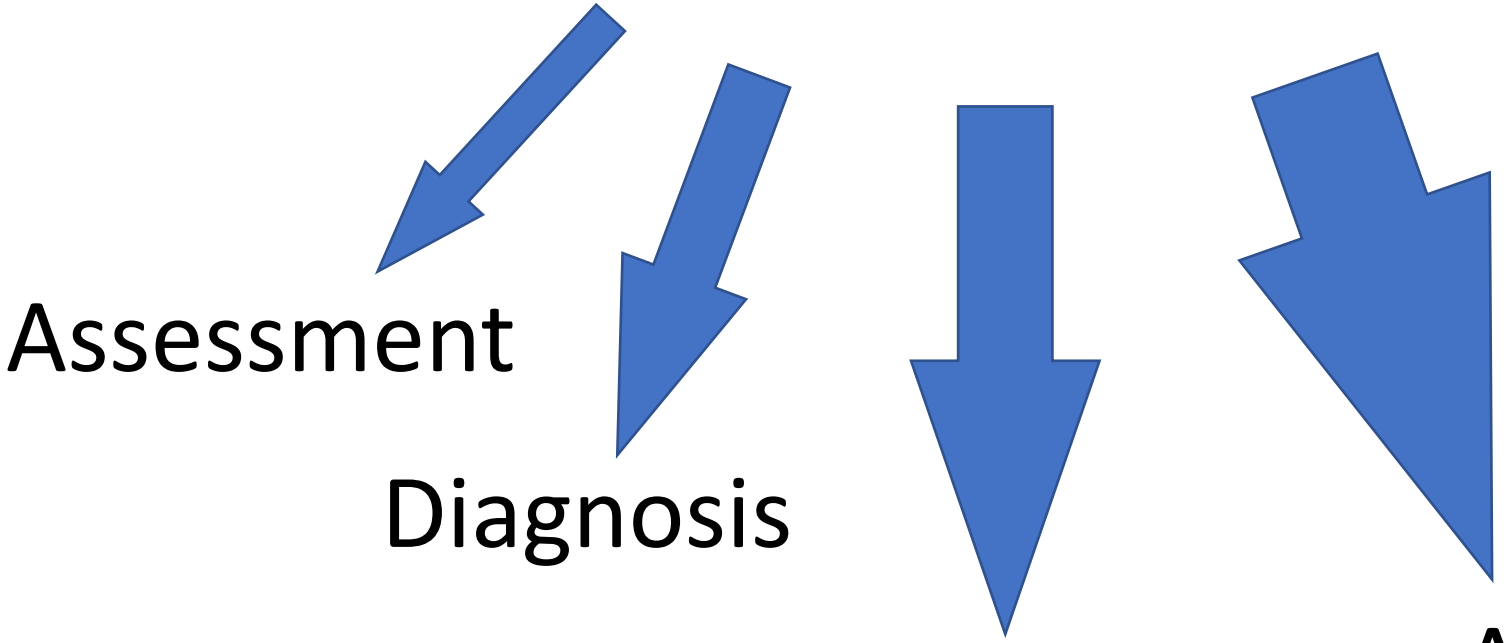
Anesthesia: local or general reduction or absence of all sensations (touch, pain, temperature, …) with or without loss of motor function. This may be accompanied by loss of consciousness

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

The Pain Pathway



How to manage pain?



Analgesics

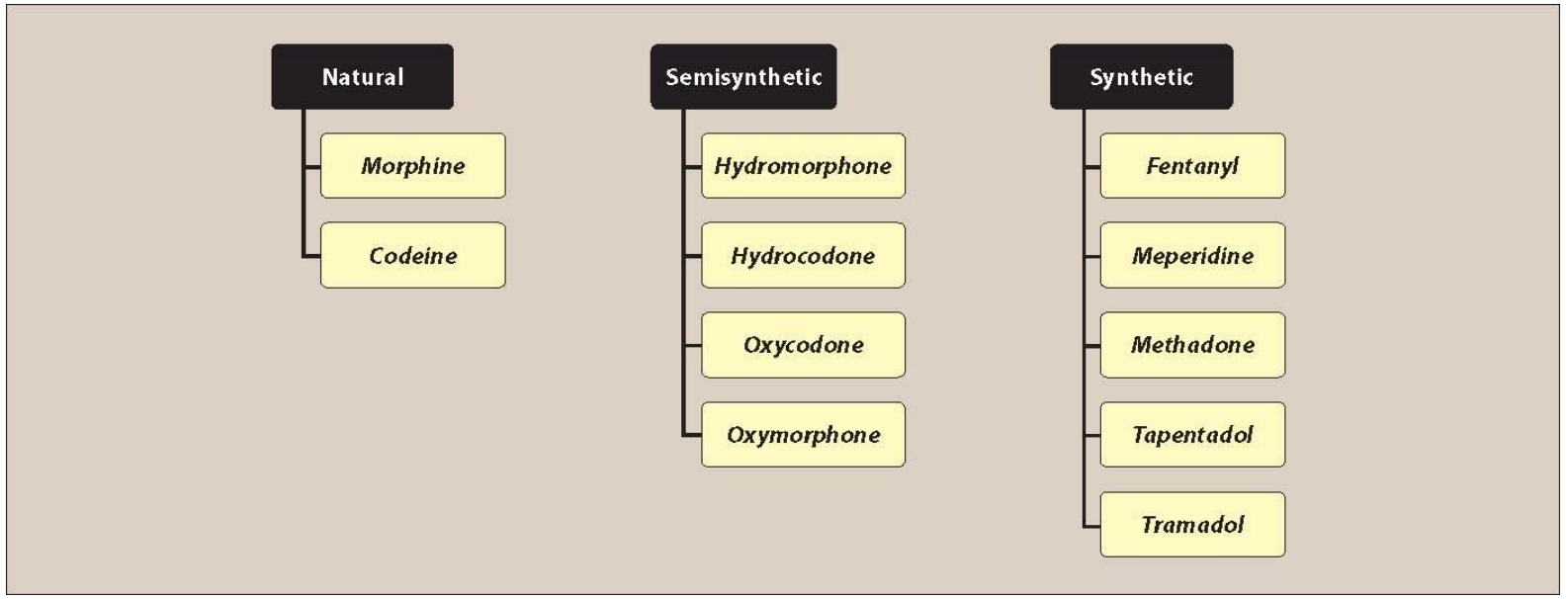
- Paracetamol
- NSAIDs
- Opioids

Can you tell the difference between these terms:

- Opium?
- Opioid?
- Opiate?
- Narcotic?

Opioids

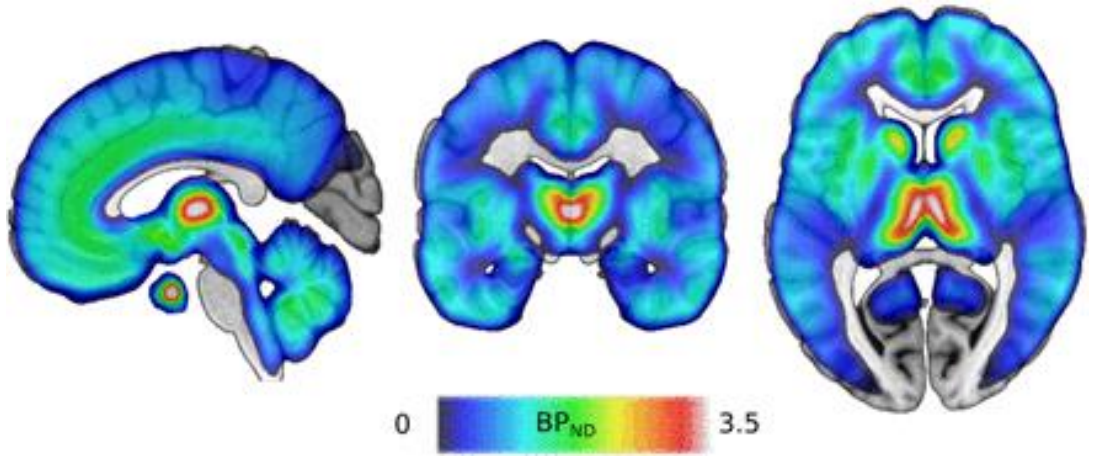
- *Opioids* are natural, semi-synthetic or synthetic compounds that bind specifically to opioid receptors and share the properties of one or more of the naturally occurring endogenous opioids



Opioid Receptors

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

  But also….
  - Gut
  - Bladder

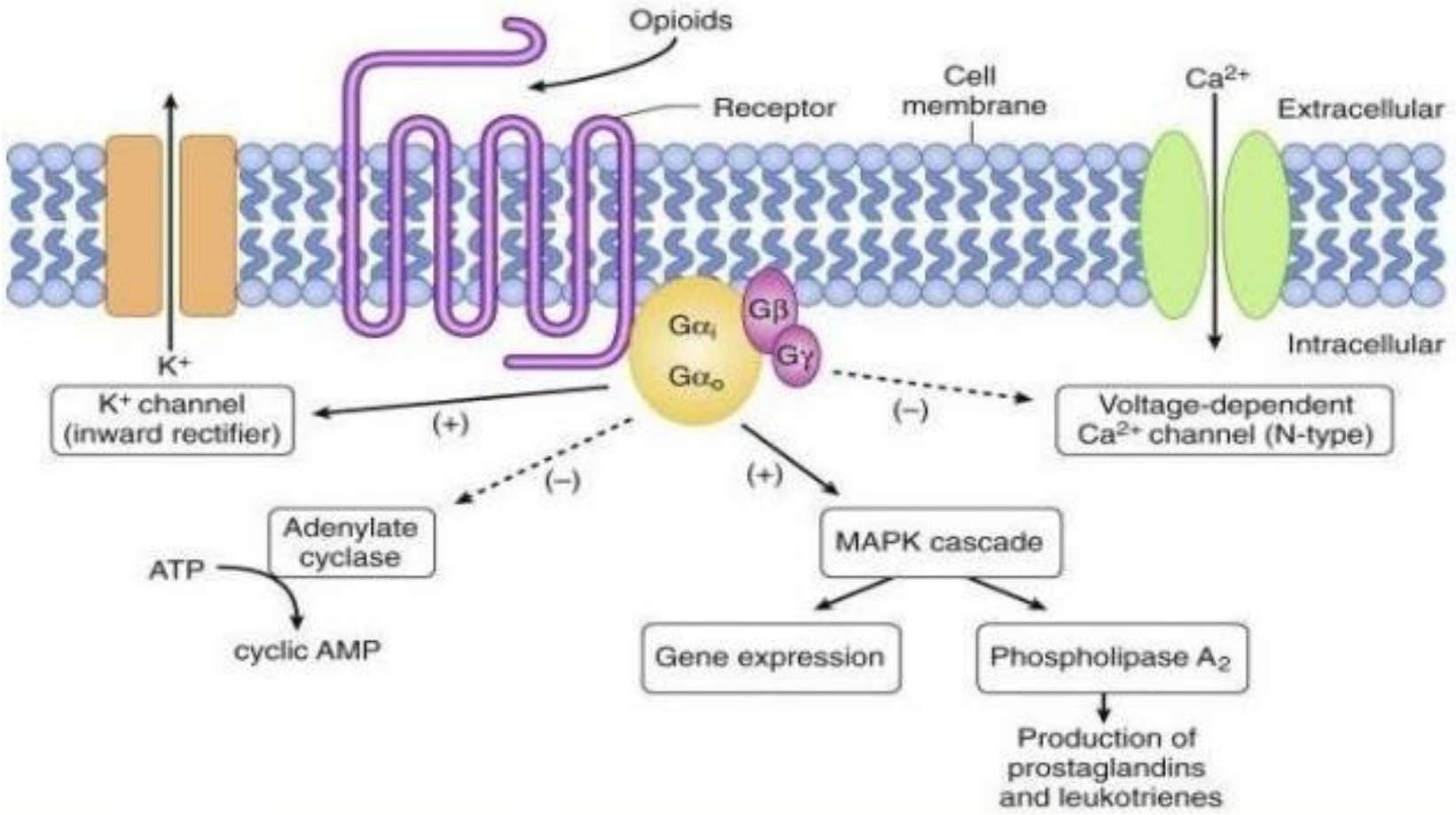


Mean distribution of μ-opioid receptors in the human brain based on the 204 [11C]carfentanil BPND images, *Kantonen et al., 2019*

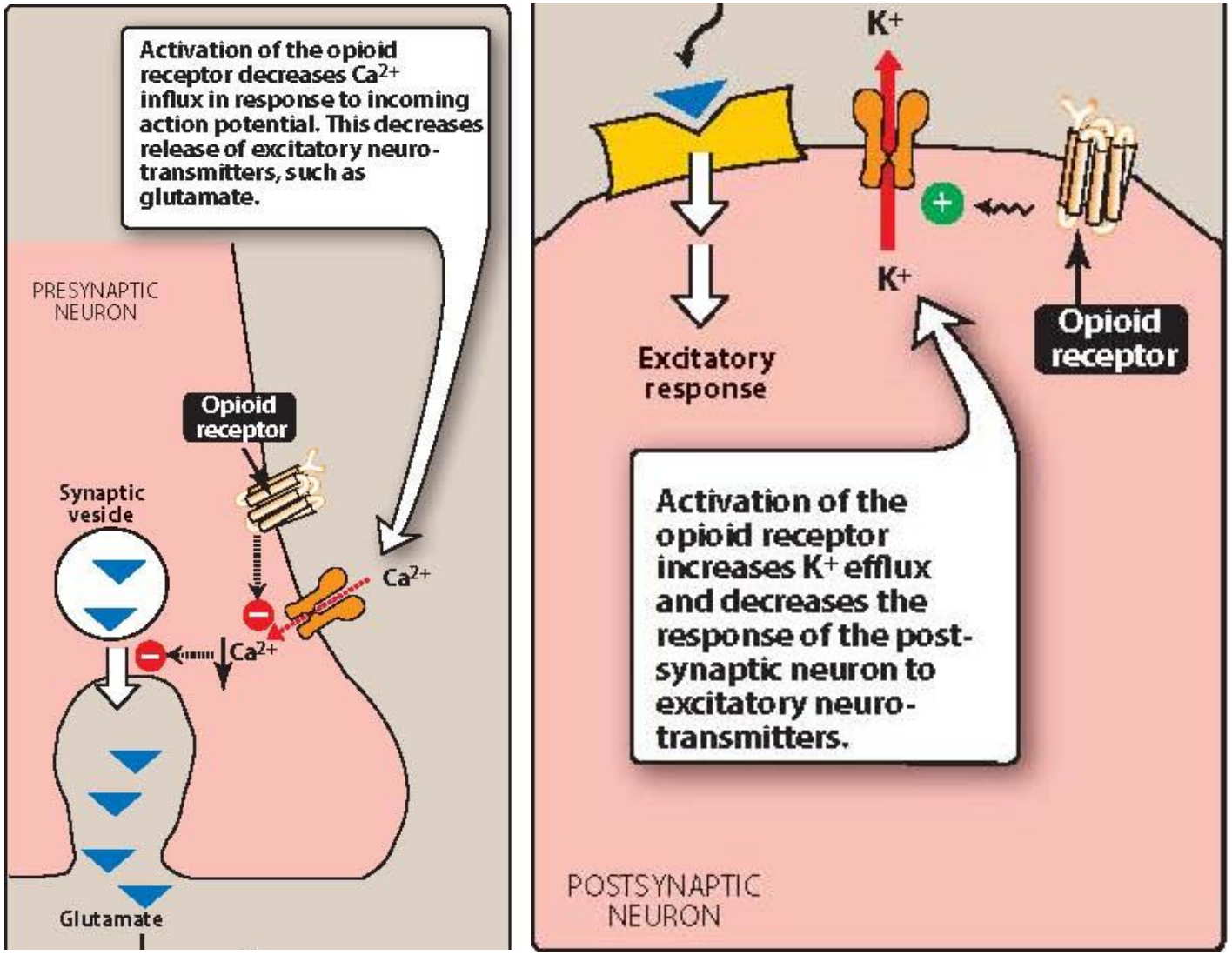
Opioid Receptors

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

Opioids: Mechanism of Action



Opioids: Mechanism of Action



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

Inhibit adenylyl cyclase

Increase *postsynaptic* K^+ efflux

Reduce *presynaptic* Ca^{++} influx

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

Opioid Agonists

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

Morphine

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

“ Morpheus”

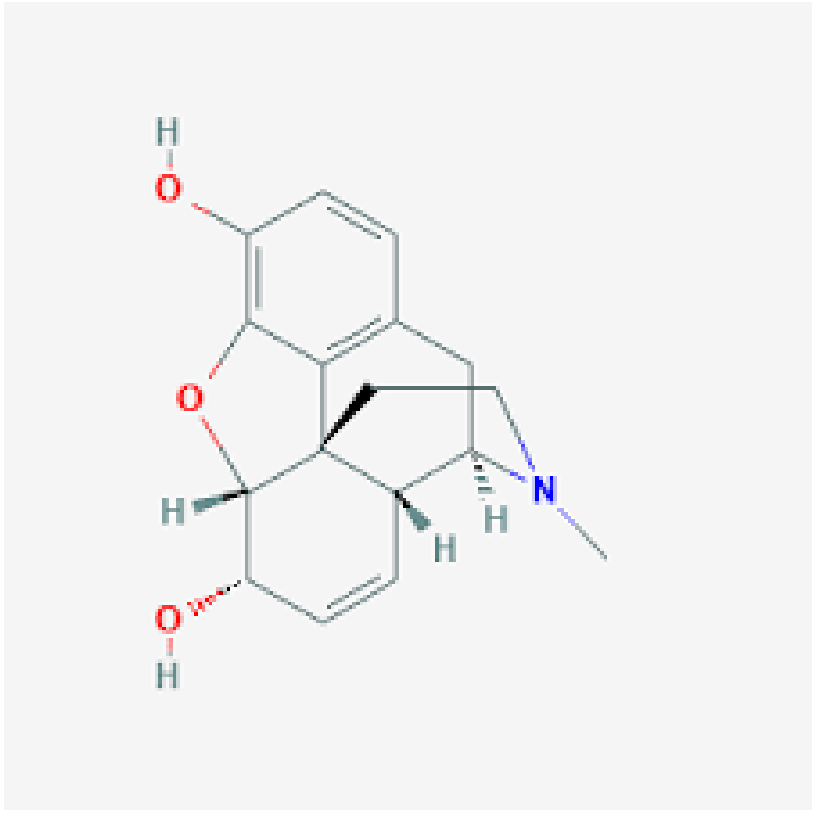
Morphine

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

Morphine

Actions:

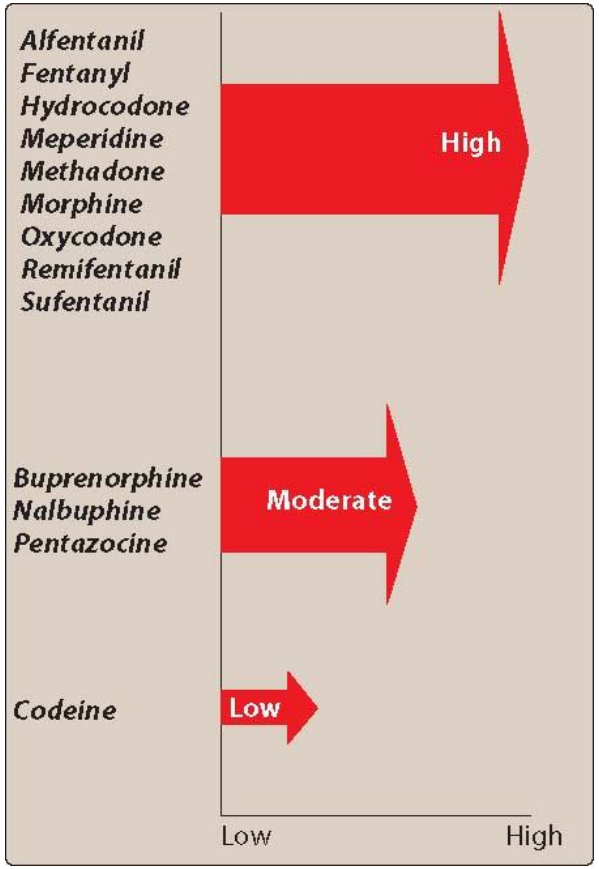
- **Analgesia**

- without loss of consciousness

- raises pain threshold (spinal cord)

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

- nociceptive >>> neuropathic



Morphine

Actions:

- **Euphoria**

- sense of contentment and well-being

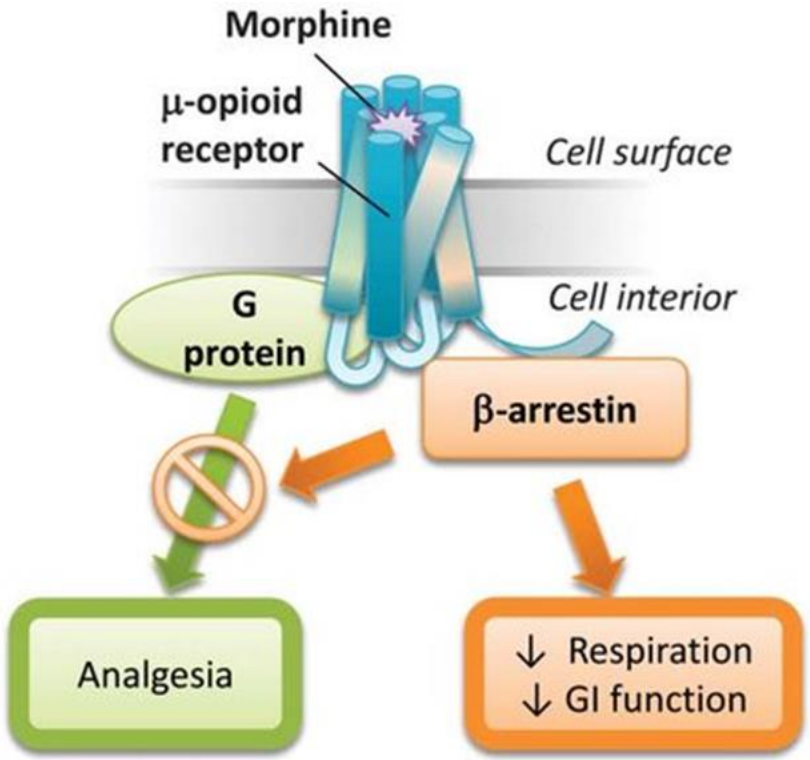
- caused by the disinhibition of the dopamine-containing neurons of the ventral tegmental area

- **Respiratory depression**

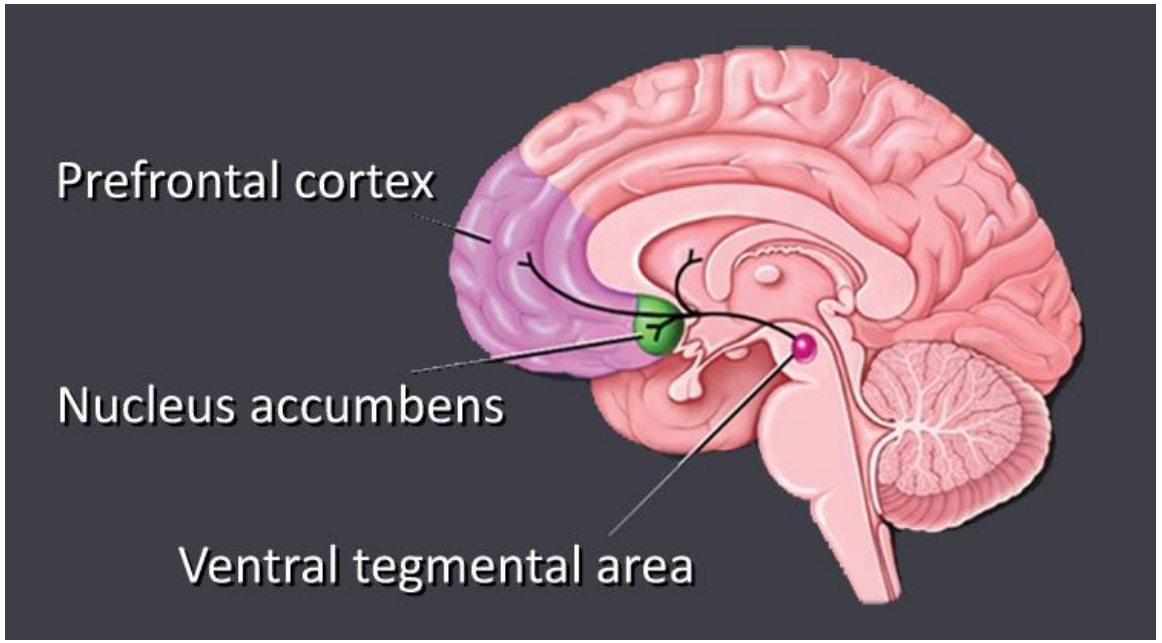
- reduces the sensitivity of respiratory center to CO_2

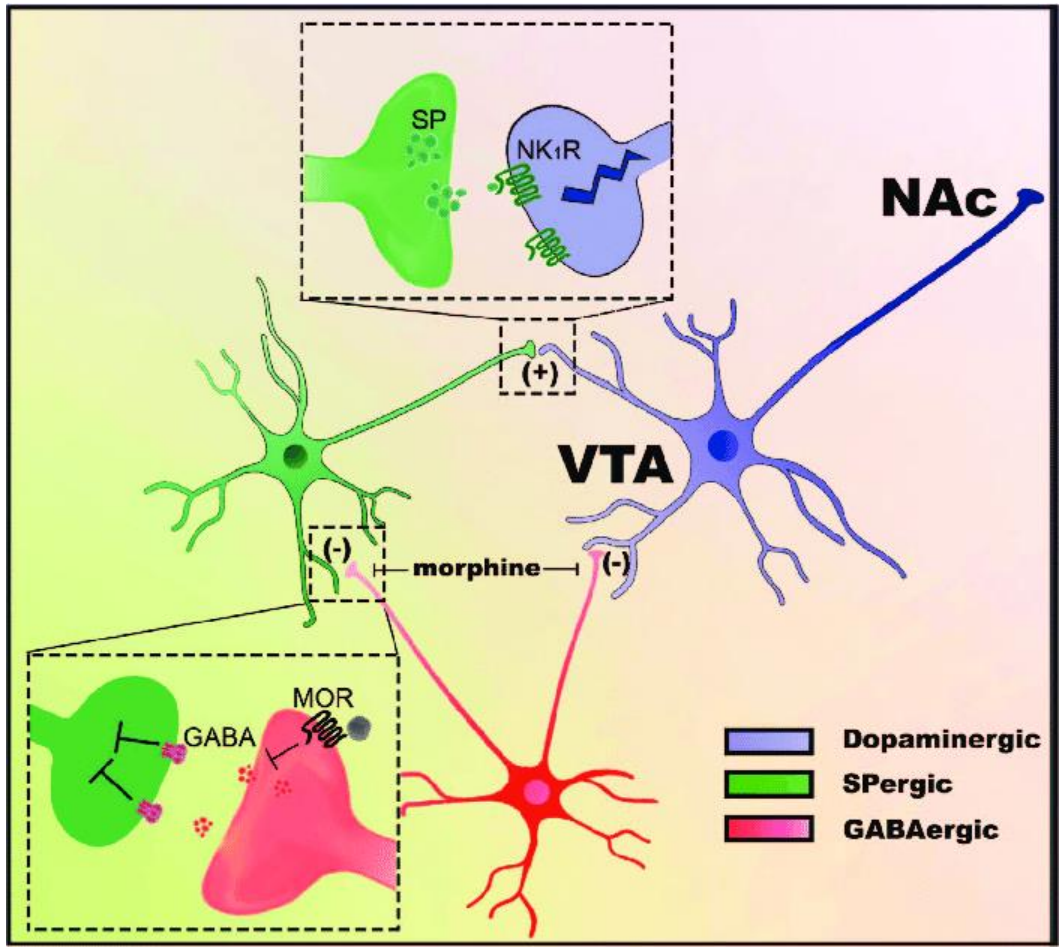
- most common cause of death from opioid overdose.

- Tolerance develops quickly



Morphine and the Reward Pathway





Morphine

Actions:

- **↓ cough reflex**

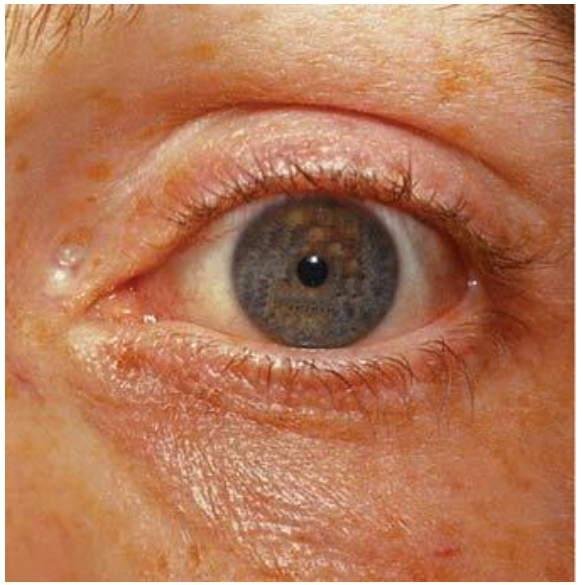
 - both morphine and codeine have *antitussive* effect.

- **Miosis**

 - pinpoint pupil

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

 - no tolerance to this effect



meiosis

Morphine

Actions:

- **Emesis**

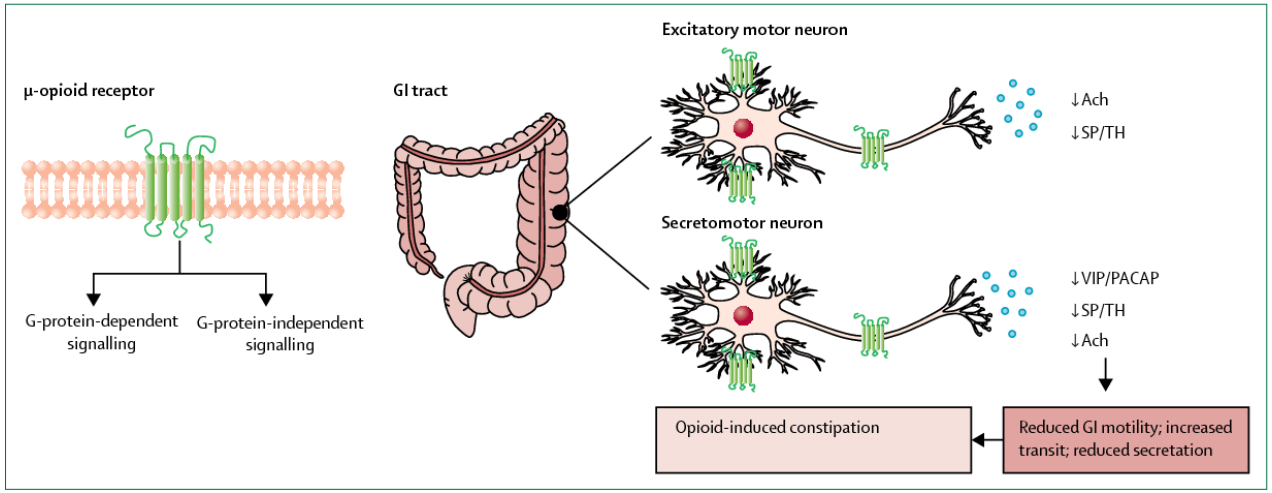
- stimulates the chemoreceptor trigger zone in area postrema → vomiting

- **GI tract**

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

- constipation

- little tolerance to this effect



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:

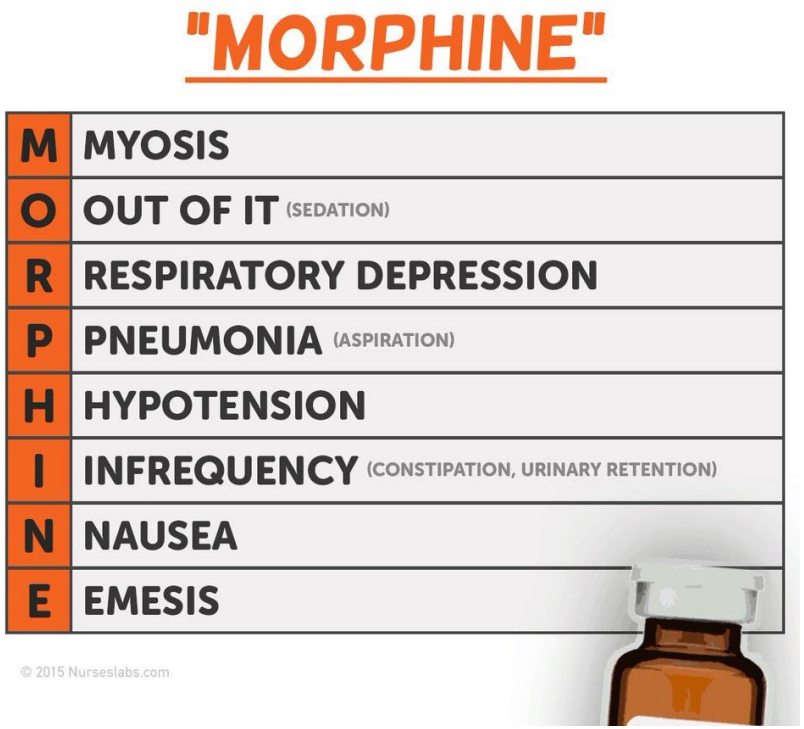
- **Urinary retention**:

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

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

- **Labor**

- increases second stage of labor. How?

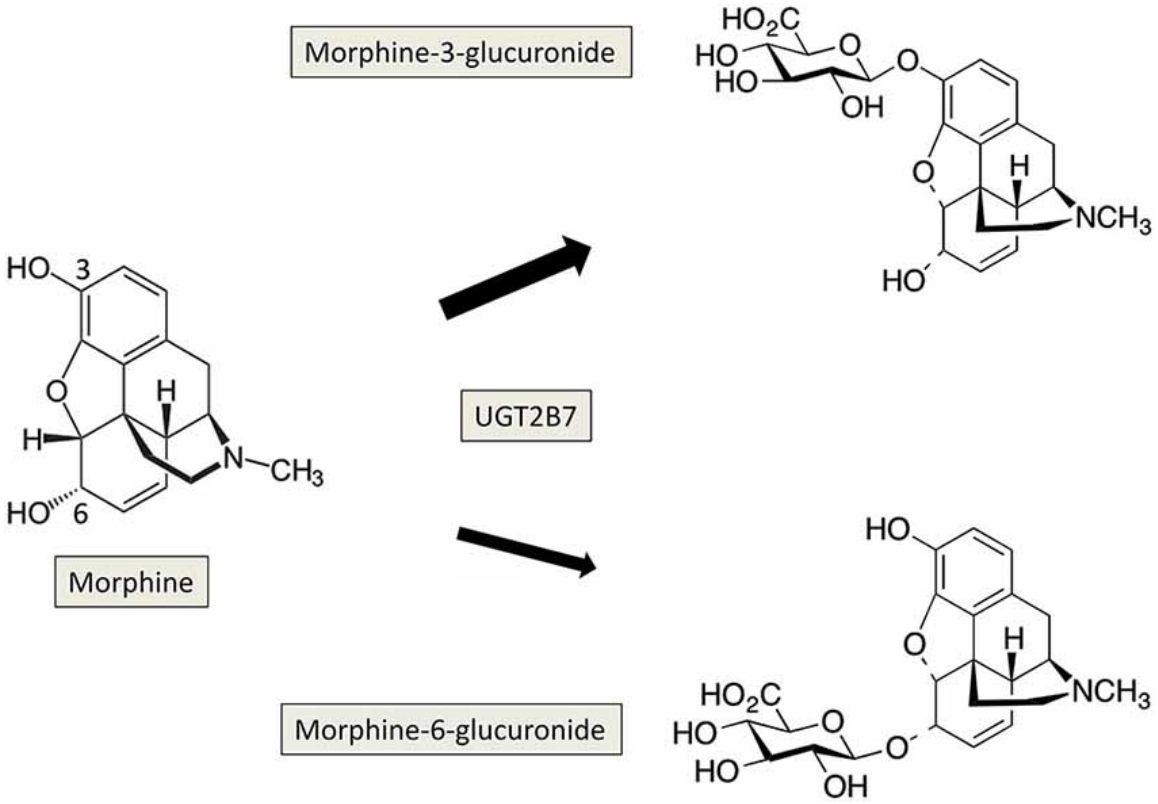


Morphine is used with caution/contraindicated in patients with bronchial asthma. WHY?

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
- **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

Can you use morphine as antidiarrheal?

Therapeutic Uses

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

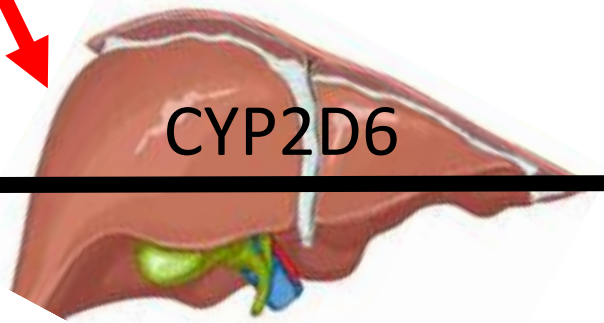
Opioid Agonists

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

Codeine

Natural

Weak analgesic



Codeine → Morphine

Required for the analgesic effects

Uses:

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

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

Opioid Agonists

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

Oxycodone

highly abused

semisynthetic

oxycodone >>
morphine (orally)

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

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

Opioid Agonists

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

Fentanyl

Synthetic

Fentanyl 100-folds > morphine

Uses

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

Contraindicated in opioid-naïve patients

Kinetics

- 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

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

Opioid Agonists

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

Meperidine (Pethidine)

Synthetic

- κ agonist
- Some μ agonist activity
- anticholinergic

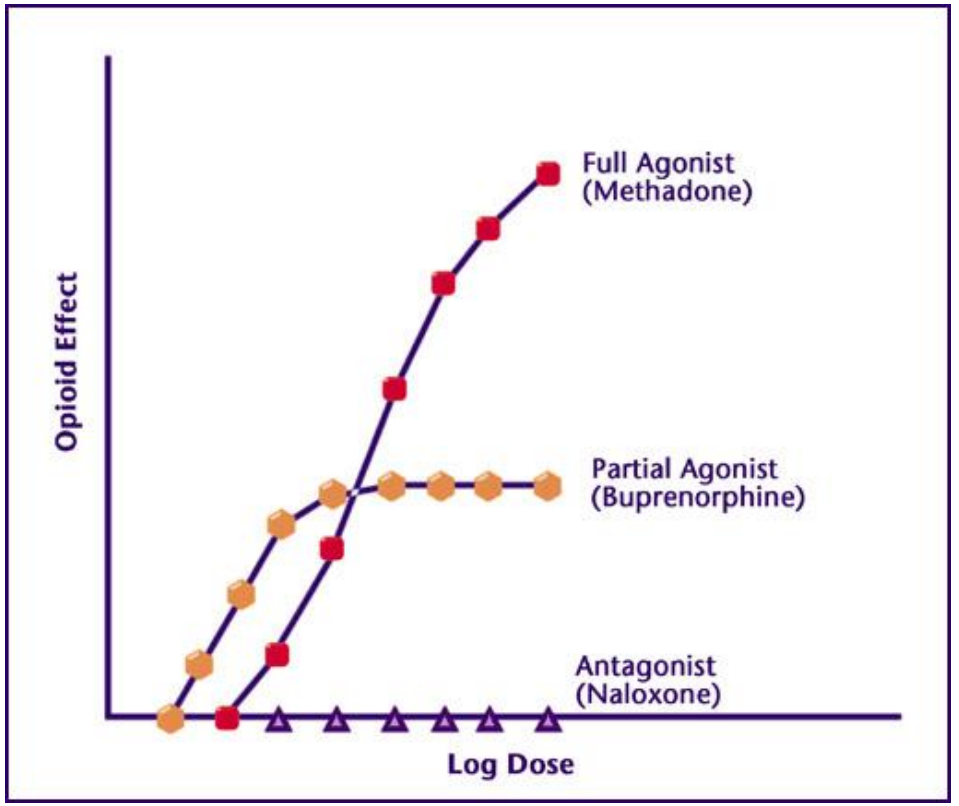
Uses

- Used only for short-term analgesia management
- Preferred over morphine during <u>labor</u>

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



Buprenorphine

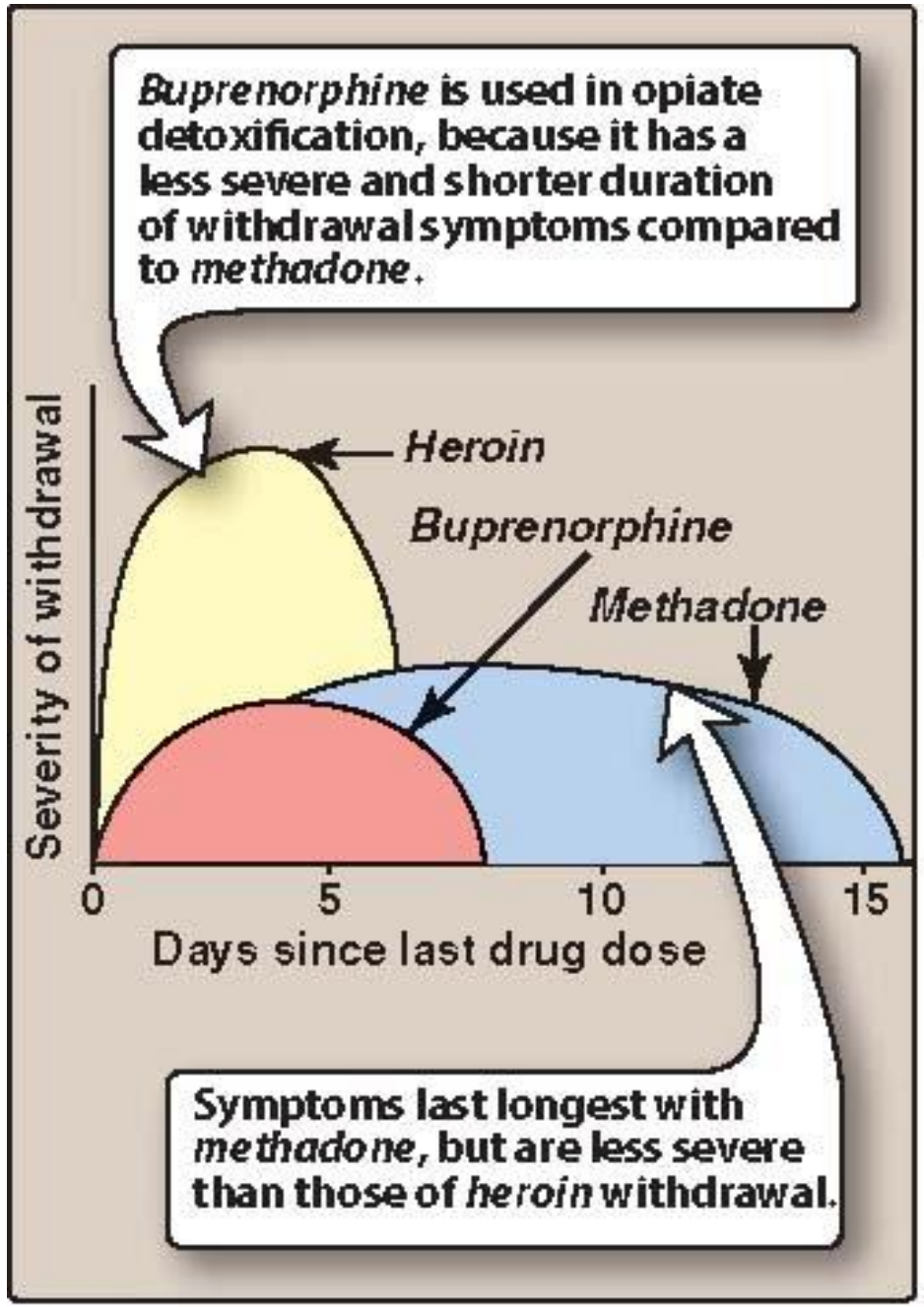
Partial agonist at **μ**
Antagonist at **κ**

Little sedation, respiratory depression, hypotension

Combined with naloxone (antagonist). Why?

Uses

- Used for opioid detoxication
- Moderate to severe pain



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

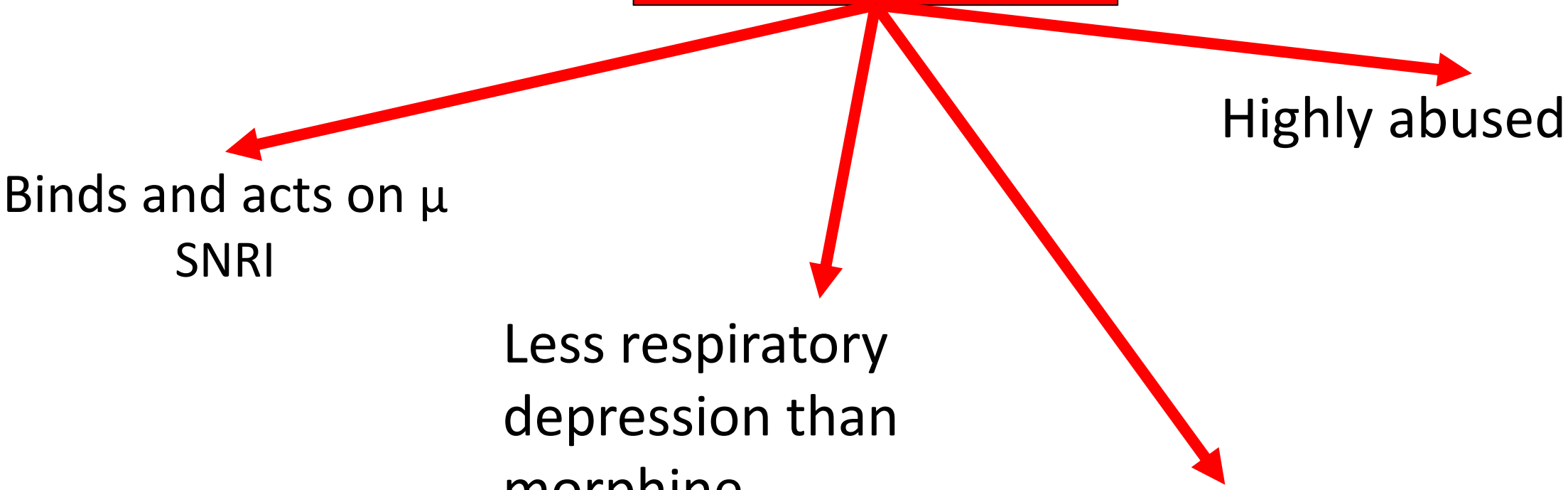
Uses

- Analgesia (limited use because of side effects)

Other Analgesics

- Tapentadol
- Tramadol

Tramadol



Binds and acts on μ
SNRI

Less respiratory depression than morphine

Highly abused

Uses

- Analgesia (moderate to severe pain)

Opioid Antagonists

- Naloxone
- Naltrexone

Naloxone

Competitive antagonist at μ, κ and δ

Administered IV
Half-life: 30-81 minutes

Can precipitate withdrawal

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

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