Pharmacology

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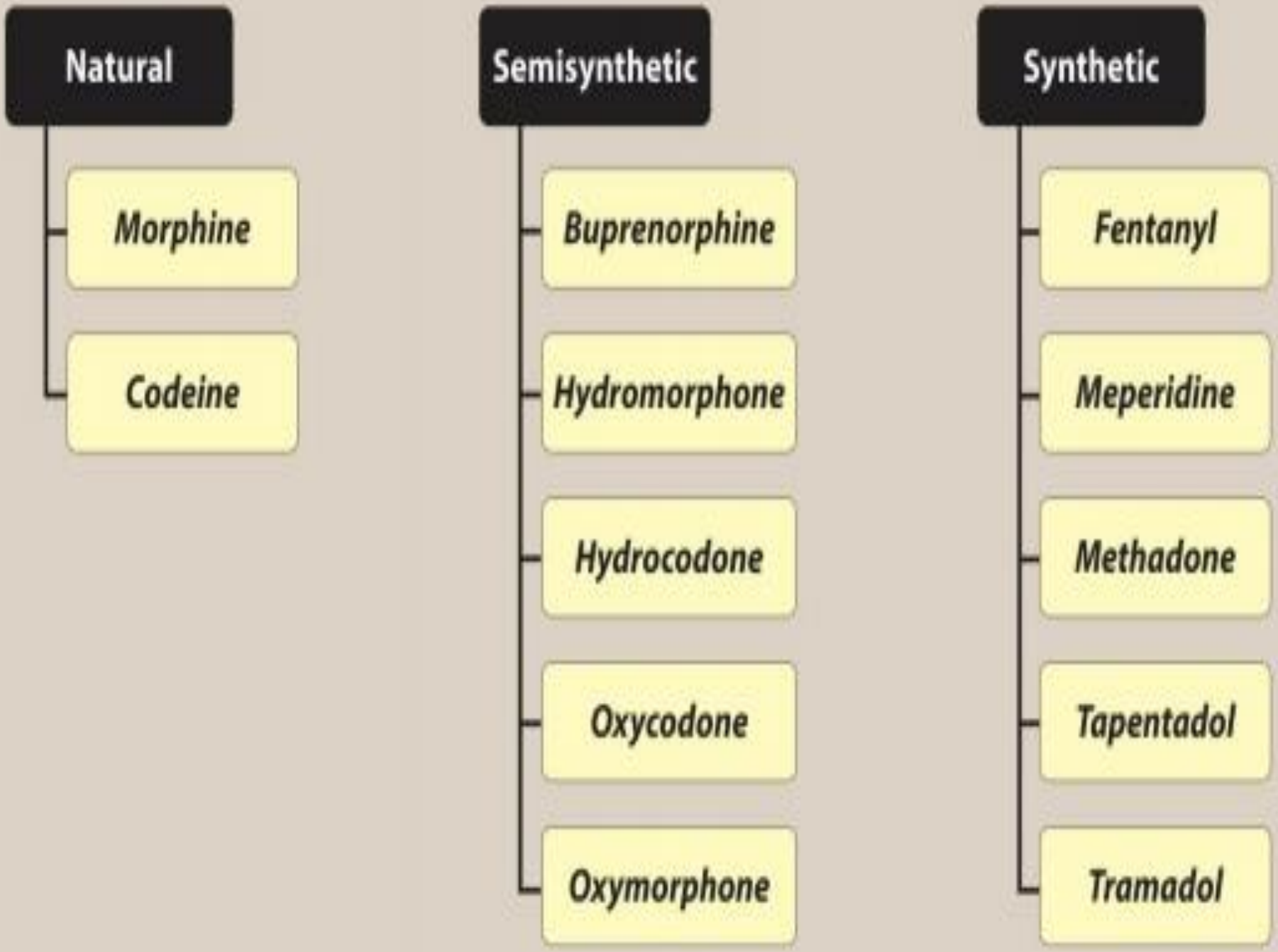
Lab. 8


OPIOIDS
PAIN
PAIN RELIEF
PRESCRIPTION
EPIDEMIC
PAINKILLERS
PILLS
CRISIS
TRAUMA
OVERDOSE
ADDICTIVE
ADDICT
DEATH
PTSD
PHARMACEUTICALS

Opium Poppy-*Papaver somniferum*

Overview:

- Opioids are natural, semisynthetic, or synthetic compounds that produce morphine-like effects.
- All opioids act by binding to specific opioid receptors in the CNS to produce effects that mimic the action of endogenous peptide neurotransmitters (for example, endorphins, enkephalins, and dynorphins).
- Although the opioids have a broad range of effects, their primary use is to relieve intense pain that results from surgery, injury, or chronic disease.
- Unfortunately, widespread availability of opioids has led to abuse of agents with euphoric properties.
- Antagonists that reverse the actions of opioids are also clinically important for use in cases of overdose.

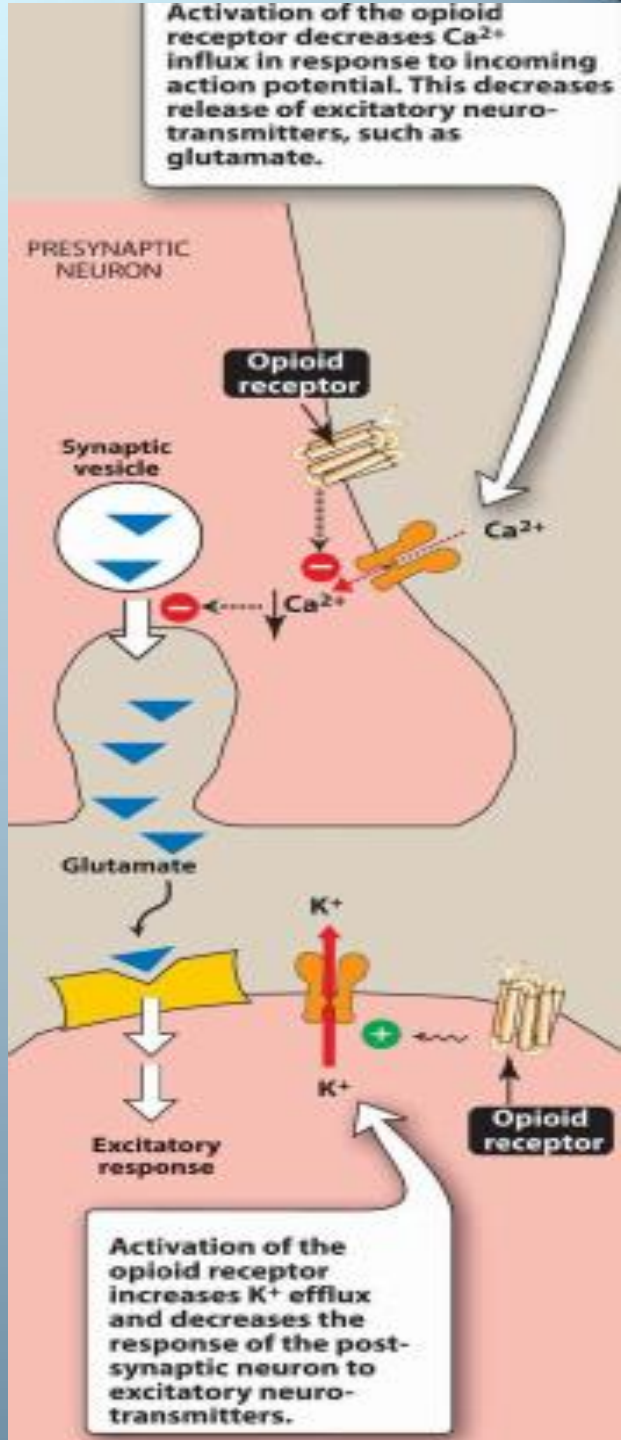

Natural
Morphine
Codeine
Semisynthetic
Buprenorphine
Hydromorphone
Hydrocodone
Oxycodone
Oxymorphone
Synthetic
Fentanyl
Meperidine
Methadone
Tapentadol
Tramadol

Opioid Receptors

- The major effects of the opioids are mediated by three main receptor families, commonly designated as μ (mu, MOR), κ (kappa, KOR), and δ (delta, DOR).
- Each receptor family exhibits a different specificity for the drug(s) it

  binds.
- The analgesic properties of the opioids are primarily mediated by the mu receptors that modulate responses to thermal, mechanical, and chemical nociception.
- The κ receptors in the dorsal horn also contribute to analgesia by modulating the response to chemical and thermal nociception.
- The enkephalins interact more selectively with δ receptors in the periphery.

- All three opioid receptors are members of the G protein–coupled receptor family and inhibit adenylyl cyclase.
- They are also associated with ion channels, increasing postsynaptic K+ efflux (hyperpolarization) or reducing presynaptic Ca2+ influx, thus impeding neuronal firing and transmitter release in the spinal dorsal horn



Morphine

- Morphine and other opioids exert analgesic effects by interacting with opioid receptors on the membranes of neuronal cells in the CNS and other anatomic structures, such as the smooth muscles of the gastrointestinal (GI) tract and the urinary bladder.
- Morphine is somewhat selective to the μ opioid receptor but has some affinity for the κ and δ receptors.
- Morphine also inhibits the release of many excitatory transmitters from nerve terminals carrying nociceptive (painful) stimuli.

Morphine has a linear pharmacokinetic profile; however, absorption of morphine after oral administration is slow and erratic. Extended-release oral preparations provide more consistent plasma levels. Because significant first-pass metabolism of morphine occurs in the liver, subcutaneous and intravenous (IV) injections produce the most reliable response.

Actions:

a. Analgesia:Morphine and other opioids relieve pain.

b. Euphoria: Morphine produces a powerful sense of contentment and well-being.

c. Morphine causes respiratory depression.

d. Depression of cough reflex: Both morphine and codeine have antitussive properties.

e. Miosis: The pinpoint pupil characteristic of morphine use results from stimulation of μ and κ receptors. There is little tolerance to this effect. [Note: This is important diagnostically, because many other causes of coma and respiratory depression produce dilation of the pupil.]

f. Emesis: Morphine directly stimulates the chemoreceptor trigger zone that causes vomiting.

g. GI tract: Morphine relieves diarrhea by decreasing the motility and increasing the tone of the intestinal circular smooth muscle. Morphine also increases the tone of the anal sphincter. Morphine and other opioids produce constipation, with little tolerance developing. Morphine can also increase biliary tract pressure due to contraction of the gallbladder and constriction of the biliary sphincter.

h. Cardiovascular: Morphine has no major effects on blood pressure or heart rate at lower dosages, but hypotension and bradycardia may occur at higher doses. Because of respiratory depression and carbon dioxide retention, cerebral vessels dilate and increase cerebrospinal fluid pressure. Morphine is usually contraindicated in individuals with head trauma or severe brain injury.

i. Histamine release: Morphine releases histamine from mast cells causing urticaria, sweating, and vasodilation. Because it can cause bronchoconstriction, morphine should be used with caution in patients with asthma.

j. Hormonal actions: Prolonged use of morphine may lead to opioid-induced androgen deficiency due to suppression of the hypothalamic–pituitary–gonadal axis (HPA). This results in decreased production of sex hormones, especially testosterone, resulting in many clinical symptoms like sexual dysfunction, fatigue, hot flashes, depression, weight gain, decreased muscle mass and osteoporosis.

Morphine

Pharmacology Mnemonics

M	• **M**iosis (pin point pupil)
O	• **O**rthostatic hypotension
R	• **R**espiratory depression
P	• **P**hysical dependency
H	• **H**istamine release
I	• **I**ncreased ICP
N	• **N**ausea
E	• **E**uphoria
S	• **S**edation

Codeine: is a naturally occurring opioid and a weak analgesic compared to morphine. It is used for mild to moderate pain. The analgesic actions of codeine are derived from its conversion to morphine by the CYP2D6 enzyme . CYP2D6 activity varies among patients, and ultra-rapid metabolizers may experience higher levels of morphine, leading to possible overdose and toxicity. Life-threatening respiratory depression and death have been reported in children who received codeine, mostly following tonsillectomy and/or adenoidectomy. Codeine is commonly used in combination with acetaminophen for management of pain. The drug exhibits good antitussive activity at doses that do not cause analgesia.

Dextromethorphan: is a synthetic cough depressant that has relatively no analgesic action and much lower potential for abuse in usual antitussive doses. It is preferred over codeine in most situations where cough suppression is needed.

- ***Oxycodone and oxymorphone :*** are orally active, semisynthetic analogs of morphine and codeine, respectively. Oxymorphone given parenterally is approximately ten times more potent than morphine, but when administered orally, the potency drops to about three times that of morphine.
- Oxymorphone is available in both immediate-release and extended-release oral formulations.
- Oxycodone is approximately two times more potent than morphine and is available in an immediate-release formulation, alone or in combination with acetaminophen, aspirin, or ibuprofen. An extended-release formulation is also available.

- Hydromorphone and hydrocodone are orally active, semisynthetic analogs of morphine and codeine, respectively.
- Oral hydromorphone is approximately 4 to 7 times more potent than oral morphine. It is preferred over morphine in patients with renal dysfunction due to less accumulation of active metabolites.
- Hydrocodone is a weaker analgesic than hydromorphone, with oral analgesic efficacy comparable to that of morphine. This agent is often combined with acetaminophen or ibuprofen to treat moderate to severe pain. It is also used as an antitussive.

Fentanyl: is a synthetic opioid.

- Fentanyl has 100-fold the analgesic potency of morphine .
- It is used for anesthesia and acute pain management.
- The drug is highly lipophilic and has a rapid onset and short duration of action (15 to 30 minutes).
- It is usually administered IV, epidurally, or intrathecally. Fentanyl is combined with local anesthetics to provide epidural analgesia for labor and postoperative pain. IV fentanyl is used in anesthesia for its analgesic and sedative effects.
- Many fast-acting transmucosal and nasal fentanyl products are available for cancer-related breakthrough pain in opioid-tolerant patients. The transdermal patch creates a reservoir of the drug in the skin and has a delayed onset of at least 12 hours and a prolonged offset. The patch is used for management of chronic severe pain.
- It is contraindicated in opioid-naïve patients and should not be used in management of acute or postoperative pain.

Sufentanil, alfentanil, remifentanil, and carfentanil:

They are synthetic opioid agonists related to fentanyl.

Methadone: is a synthetic, orally effective opioid . Methadone is a μ agonist, an antagonist of the N-methyl-D-aspartate (NMDA) receptor, and a norepinephrine and serotonin reuptake inhibitor. Therefore, it is useful in the treatment of both nociceptive and neuropathic pain. Methadone may also be used for opioid withdrawal and maintenance therapy in the setting of prescription opioid and heroin abuse. The withdrawal syndrome with methadone is milder but more protracted (days to weeks) than that with other opioids. Methadone induces less euphoria and has a longer duration of action than morphine. Unlike morphine, methadone is well absorbed after oral administration. Methadone is also constipating, but less so than morphine.

Meperidine: is a lower-potency synthetic opioid.

It is used for acute pain and acts primarily as a κ agonist, with some μ agonist activity.

Meperidine is very lipophilic and has anticholinergic effects, resulting in an increased incidence of delirium compared with other opioids. Meperidine has an active metabolite (normeperidine), which is potentially neurotoxic. Due to the short duration of action and the potential for toxicity, meperidine should only be used for short-term (≤48 hours) management of pain.

Meperidine should not be used in elderly patients or those with renal insufficiency, hepatic insufficiency, preexisting respiratory compromise, or concomitant or recent administration of MAOIs.

Serotonin syndrome has been reported in patients receiving both meperidine and selective serotonin reuptake inhibitors (SSRIs).

Tramadol: is a centrally acting analgesic that binds to the μ opioid receptor. In addition, it weakly inhibits reuptake of norepinephrine and serotonin.

It is used to manage moderate to severe pain.

Tramadol has less respiratory-depressant activity compared to morphine. Administration of naloxone can only partially reverse tramadol toxicity and has been associated with an increased risk of seizures. Anaphylactoid reactions have been reported. Tramadol should be used with caution in patients with a history of seizures.

As with other agents that bind the μ opioid receptor, tramadol has been associated with misuse and abuse.

Antagonists : The opioid antagonists bind with high affinity to opioid receptors, but they fail to activate the receptor-mediated response. Administration of opioid antagonists produces no profound effects in individuals not taking opioids. In opioid-dependent patients, antagonists rapidly reverse the effect of agonists, such as morphine or any full μ agonist, and precipitate the symptoms of opioid withdrawal.

- Naloxone: Naloxone can be administered intravenously, intramuscularly, subcutaneously, and intranasally.
- Naltrexone: has actions similar to those of naloxone, but it has a longer duration of action and can be given orally.

Thank You