



Pharmacology

Modified (1)

Writer: Zaid Alabsi & Abdullah Mohammad

Corrector: Zaid Alabsi & Abdullah Mohammad

Doctor: Malik Zuhluf

Pain

- Brings patients to the DRs
- Fear can keep the patient from going to the Drs at appropriate time
- Treatments are often done on the inflamed, hypersensitive tissues of a patient
- Pain is a symptom of a pathologic condition that needs to be taken care of:
 - no treatment, still pain.
 - Induced by the release of histamine, serotonin, prostaglandins, bradykinins, etc. that activate pain signaling.

Introduction

- Pain will bring the patient to the doctor, and the doctor's optimum objective must be to reduce the pain.
- There are many types of pain such as inflammatory pain (mild to moderate) , post-surgery pain (moderate to severe) and cancer pain (severe chronic pain).
- Mild to moderate pain can be alleviated by NSAIDs such as diclofenac and ibuprofen, or by paracetamol, however, these drug aren't effective in case of moderate to severe pain or cancer pain .
- Hence, the need for opioid use has become necessary despite their adverse effects .
- You must differentiate between two concepts "opiates" & "opioids"
"Opiates" refer specifically to naturally occurring substances derived from the opium poppy plant, On the other hand, "opioids" encompass a broader category that includes both natural opiates and synthetic or semi-synthetic substances .

WHO analgesic ladder

Pain persists or increases → Pain persists or increases → Pain

1. Non-opioid
± adjuvant

2. Weak opioid
± non-opioid
± adjuvant

3. Strong opioid
± non-opioid
± adjuvant

If mild to moderate postoperative pain is expected



Acetaminophen



If 1,000 mg of acetaminophen is insufficient
(i.e., for moderate to severe pain)

If no contraindication



NSAID



If more analgesia is required



Add codeine to NSAID, acetaminophen or ASA
or
Add oxycodone with acetaminophen or ASA

If concerns regarding
gastric bleeding
or if elderly



rofecoxib

If NSAIDs contraindicated



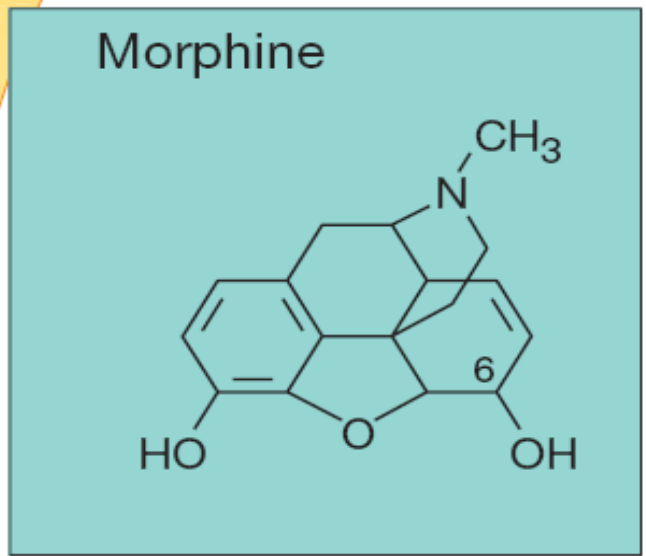
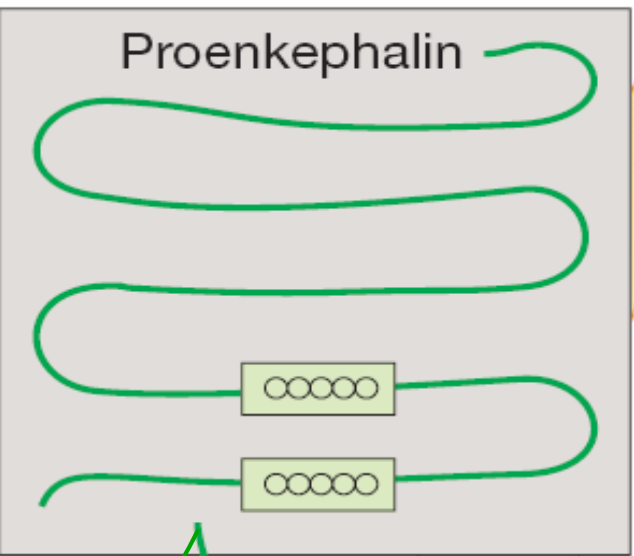
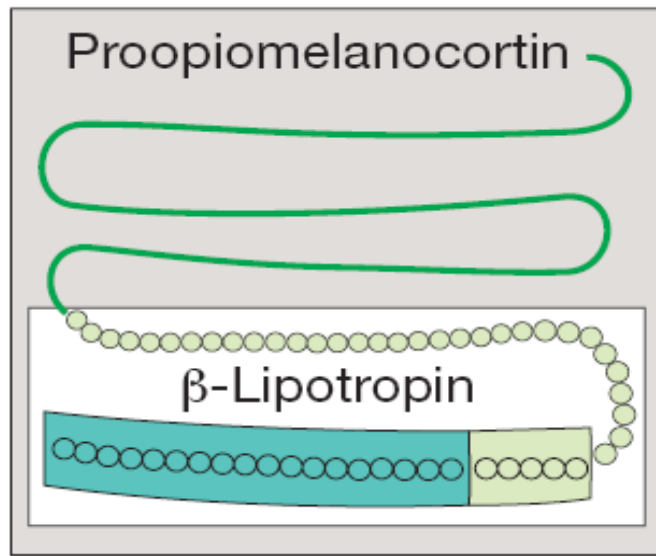
Add codeine to acetaminophen
or
add oxycodone with acetaminophen

Opioid analgesics

- All drugs in this category act by binding to specific Opioid receptors in CNS to produce effects that mimic the action of naturally occurring substances, called *endogenous opioid peptides* or *endorphins*.
- Exert their major effect by interacting with Opioid receptor in the CNS, and in other places such as GI tract and urinary bladder.
- Opioids cause hyperpolarization of nerve cells, inhibiting nerve firing, and presynaptic inhibition of transmitter release.
- Morphine causes analgesia, and patients treated with morphine are still aware of the presence of pain, but sensation is not unpleasant.

Opioid Analgesics: Indications

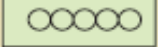
- Main use: to alleviate moderate to severe pain
- Cough centre suppression
- Treatment of diarrhea
- Balanced anaesthesia



β -Endorphin

Endogenous opioids

Exogenous opioids



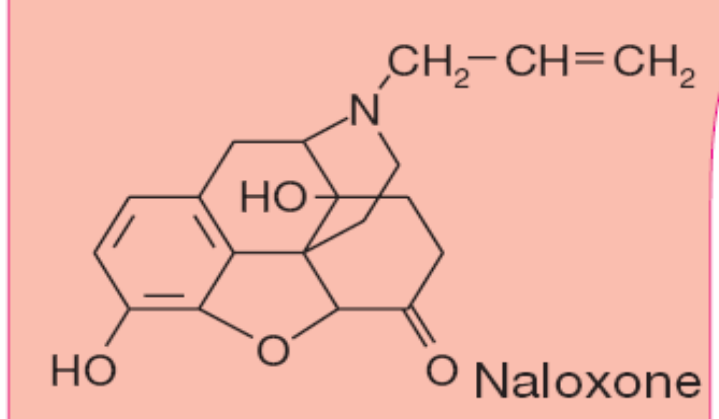
Enkephalin



Opioid receptors

K⁺-permeability \uparrow
Excitability \downarrow

Ca²⁺-influx \downarrow
Release of transmitters \downarrow



- Opioids can be classified to endogenous opioids (produced naturally within the body) and exogenous opioids (such as morphine or heroin) .

Both of them bind to opioid receptors in CNS, leading to analgesic (pain-relieving) effects.

- Endorphins and enkephalins are endogenous opioids, meaning they are opioids naturally produced within the body. They function as neurotransmitters and play a role in pain relief and pleasure.

- There are three main types of opioid receptors: mu, delta, and kappa receptors .

- When mu receptors are activated by endorphins and enkephalins, it leads to a cascade of events (decrease in calcium ions influx & increase in potassium ions permeability, thus hyperpolarization). This activation inhibits the release of neurotransmitters such as substance P and glutamate, which are involved in transmitting pain signals. As a result, the transmission of pain signals is reduced, leading to analgesia or pain relief. Additionally, the activation of mu receptors may also enhance the release of other neurotransmitters such as dopamine, which contributes to feelings of pleasure and reward (euphoria) .

This is the MOA for all opioids, we will study some of them in this lecture .

- Very important 

Naloxone is an opioid antagonist used to rapidly reverse opioid overdose in emergency.

Mediated by opioid receptors

Stimulant effects

Vagal centers,
Chemoreceptors of area postrema
Oculomotor center
(Edinger's nucleus)

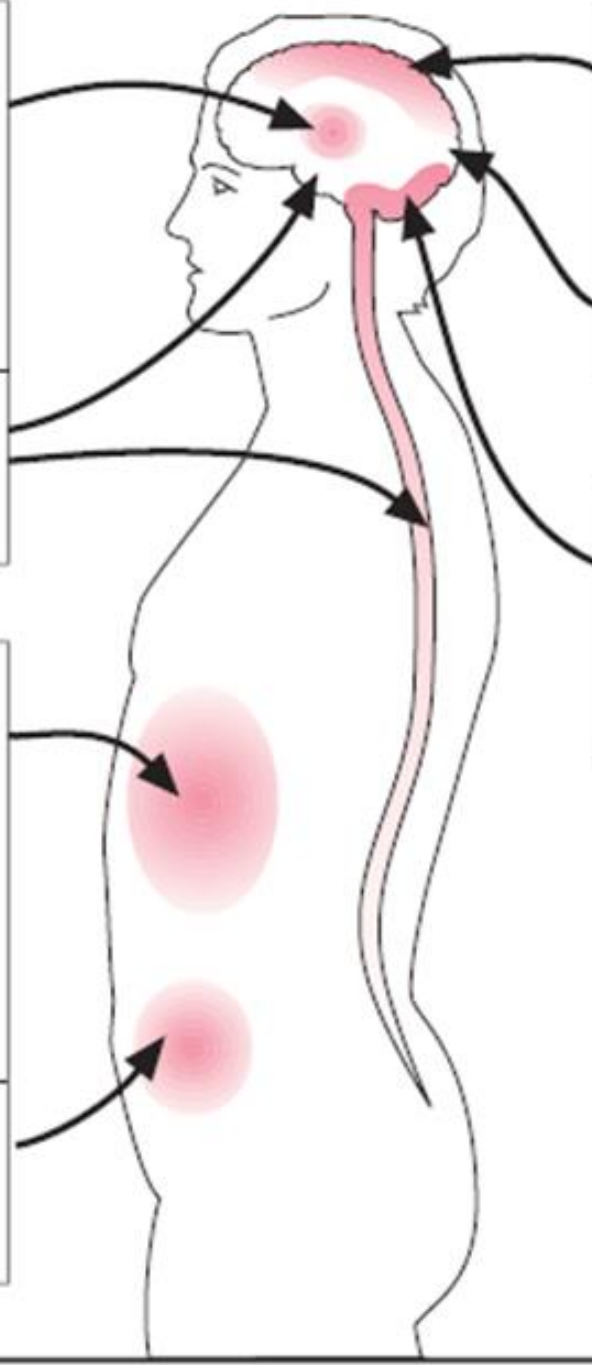
Antinociceptive system

Analgesic

Smooth musculature
stomach
bowel
→ spastic constipation

Antidiarrheal

Ureter
bladder
bladder sphincter



Dampening effects

Pain sensation

Analgesic

Mood
alertness

Respiratory center
Cough center

Antitussive

EFFECTS MEDIATED BY OPIOID RECEPTORS:

1- Dampening effects on:

A- Pain sensation causing analgesic effect (used for moderate to severe pain).

B- Mood alertness, because they inhibit norepinephrine release in the brain .

- Methadone is an exception here .

C- cough center (antitussive effect), such as codeine .

2- Stimulant effects on:

A- Antinociceptive system causing analgesic effect .

B- Smooth muscles of stomach and bowel causing spastic constipation (antidiarrheal effect) such as Loperamide which works peripherally (can't cross BBB).

Therefore, healthcare providers may recommend the use of laxatives for cancer patients who experience constipation.

C- Opioids also causes contraction of the detrusor muscle along with closure of the sphincter in the urinary bladder (urinary retention).

Therefore, opioids are contraindicated for patients with prostate hyperplasia .

D- Vagal Centers, chemoreceptor trigger zone (CTZ), and the parasympathetic nucleus of the oculomotor nerve .

🚫 Most crucial side effect :-

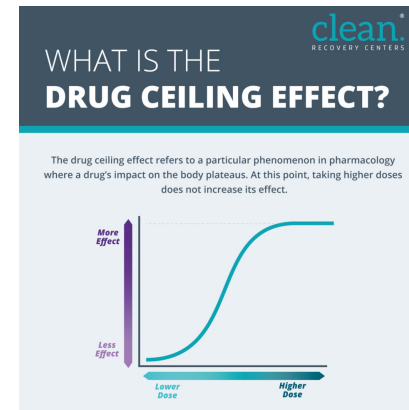
Dampening effects on the respiratory center .

More clarification

As mentioned earlier , there are different thresholds of pain: mild, moderate, moderate-severe, and severe pain . On the other hand, the drugs have different E max .

In the case of cancer pain, which is a very bad chronic severe pain, or post-surgery pain which is acute moderate-severe pain, we cannot rely on NSAIDs (that are indicated for moderate inflammatory pain), even at their maximum tolerated doses, because the pain exceeds their ceiling effect. Hence, the idea of a drug that enters the brain and pain center to INTERRUPT THE PERCEPTION OF PAIN has emerged, which are OPIOIDS.

These are MAGICAL drugs that don't have a ceiling effect and can treat strong pain, no matter how intense it is. Severe pain doesn't respond to neither NSAIDs nor steroids.



Opioid Analgesics: Side Effects


- Euphoria
- CNS depression
- Nausea and vomiting
- Respiratory depression
- Urinary retention
- Diaphoresis and flushing
- Pupil constriction (miosis)
- Constipation
- Itching

1- Euphoria (Happiness الزهزة)

As mentioned above, this feeling is associated with increased dopamine release in response to rewarding stimuli. The reward system is under the control of gamma-aminobutyric acid (GABA), which is influenced by mu, delta, and kappa opioid receptors.

When agonists bind to these receptors, they inhibit GABA neurons, leading to a reduction in GABA release within the dopaminergic system of the reward pathway. This reduction in GABA release ultimately results in an increase in dopamine release, contributing to the experience of reward.

- The most common drug that causes this feeling is heroin فوق النجوم بوديك

فاصل اعلاني من الدكتور  ٩٩٪ من المرضى الي يوخذو المورفين لعلاجات العلاج (بمركز الحسين للسرطان مثلا) ما بصيرو مدمنين رغم انهم يوخذوه لاشهر و يمكن حتى لسنوات ، على العكس تام كل الي اخذو المورفين لغاية الوصول لحالة الزهزة (وهم يلعبو طرنيب طبعاً) صارو مدمنين ولو اخذو one shot , ليش ؟؟؟؟؟ علما انو الفتتين صارت عندهم قصة الدوبامين

2-CNS depression because they inhibit norepinephrine release in the brain.

3-N&V because they stimulate the chemoreceptor trigger zone (CTZ) in the brain.

In cases of anesthesia, it is not preferable to administer morphine to the patient due to its relatively long half-life of four hour. Patients may become very nauseated. Instead, we give Fentanyl, which has a shorter half-life (0.5-1 hour).

6-Diaphoresis and flushing

9-Itching

because they cause the release of histamine. Accordingly these medications are contraindicated in asthma patients.

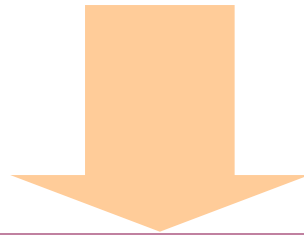
- Histamine also causes hypotension .

7-Pupil constriction (miosis) due to activation of the parasympathetic nucleus of oculomotor nerve . It's called pinpoint pupil.

● Constipation & pinpoint pupil are persistent side effects of morphine that may continue to occur as long as the medication is being taken, even if drug tolerance occurs.

++ 10-Bradycardia due to vagal stimulation

Repeated use of Morphine



- Psychological dependence
 - Physical dependence
 - Tolerance
- Withdrawal syndrome
- Hyperalgesia????????

Repeated use of Morphine

These three concepts may appear similar, but they actually have totally distinct meanings :-

1-Tolerance

- Physiologic phenomenon resulting in progressive decline in the potency of an opioid with continued use.
- Continuous use results in downregulation (desensitization) of the receptors.
- Agonists lead to downregulation, while antagonists lead to upregulation.
- Overusing the Ventolin/Salbutamol inhaler by asthma patients leads to downregulation of beta 2 receptors, resulting in reduced effectiveness at the regular dose.
- The same concept happens with mu receptor agonists (opioids, morphine)
- What can we do to overcome tolerance ?
Increase the dose (gradually).

2-Dependence (physical dependence)

- Physiologic state characterized by withdrawal symptoms upon abrupt discontinuation/ reduction of narcotic therapy.
- Abstinence syndrome
- Independent of tolerance
- As mentioned before, tolerance involves the downregulation of receptors. However, the levels of normal endogenous substances do not decrease. When a drug is abruptly discontinued (let's say morphine), these endogenous substances (enkephalins and endorphins) function on the limited number of remaining receptors, resulting in diminished effectiveness (the normal physiological function is no longer exist).
- This concept also applies to antidepressants, even though they don't actually work on a receptor, they work on a transporter (change the physiology (connectivity) of the brain).
- What can we do to overcome dependence ? Tapering
- What is tapering? Tapering refers to the gradual reduction of a medication dosage over time instead of abruptly stopping it. This approach helps to minimize withdrawal symptoms and potential adverse effects associated with sudden discontinuation of the drug.

3-Addiction (Psychological Dependence)

- Psychological & behavioral syndrome manifested by drug-seeking behavior, loss of control of drug use, and continued use despite adverse effects.
- Related to abuse, (NOT misuse).
- Patient Know the drug is harmful but take it anyway because they believe it makes them happy, helps them to sleep, etc...
- It's really psychological more than the drug's actual effects, some patients become addicted to placebos!!!

الحل الحقيقي ؟ تطبيق حدود الله

الحل للـ USMLE بنقعد مع المريض و بنحكيه كلمتين حلوات

- Cannabis can lead to addiction, even though it doesn't involve tolerance or dependence..
- Morphine and opioids can lead to tolerance, dependence and addiction 😊

Tolerance and Dependence

