

# Opioid Analgesics & Opioid Antagonists

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# Opioid Analgesics

*narcotic → strong Analgesic*

- ❑ **Narcotic analgesics: relieve pain & induce sedation**
- ❑ **Opioids:**
  - **Natural:** morphine, codeine (from opium poppy)
  - **Synthetic:** pethidine, methadone , Fentanyl
  - **Semisynthetic:** heroin → *strenght effect.*
- ❑ **Cultivation of opium poppy (الأفيون, الخشخاش)**  
is restricted & under strict governmental control



# Opioid Receptors

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- Opioid receptors: in the brain & spinal cord
- Involved in transmission & modulation of pain
- **Major opioid receptors:**
  1. mu ( $\mu_1$  &  $\mu_2$ )
  2. Delta ( $\delta_1$  &  $\delta_2$ )
  3. Kappa ( $\kappa_1$ ,  $\kappa_2$  &  $\kappa_3$ )

# Opioid receptor activation

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□ **Spinal & supraspinal sites**

□ **G protein–coupled receptors** [metabotropic]

Post synaptic ■ **Open potassium channels** [hyperpolarization]

Pre synaptic ■ **Prevent opening of calcium channels**

**Therefore:**

□ **Reduce neuronal excitability**

□ **Inhibit release of pain neurotransmitters**  
[mediators]

# Opioid receptor activation

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- **Activation** of opioid receptors leads to:
  - **Reduction of neurotransmitter release (Ach, noradrenaline, serotonin & substance P)**
  - **Inhibition of postsynaptic neurons concerned with pain-transmission in the spinal cord**

# Opioid Receptors

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□ mu-receptors are most important:

■  $\mu_1$ : analgesia, euphoria, physical dependence

[RS, GI] ■  $\mu_2$ : Respiratory depression, inhibition of gut motility

→ Contraindicated: - Asthma (constriction of Airways)  
GI : Constipation

□  $\kappa$ : Analgesia at spinal cord level & dysphoria

□ Delta receptors role is not clear

# Opioid receptor distribution

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- ❑ **Spinal** (dorsal horn neurons) → *transmit Pain sensation*
- ❑ **Supraspinal** regions (medulla, midbrain & Cerebral C)
- ❑ Opioid pain-relief:
  - Activation of opioid receptors
  - Inhibit release of excitatory neurotransmitters
  - Inhibit dorsal horn pain transmission neurons
  - Release of endogenous opioid peptides

# Endogenous Opioid peptides

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- ❑ Opioids act at sites in the brain concerned with pain modulation
- ❑ Sites contain peptides with opioid-like actions
  - Endorphins, dynorphins, enkephalin
- ❑ Precursors present at these sites
- ❑ Also in adrenal medulla & ENS in gut → enteric Nerves
- ❑ Released during stress (pain or anticipation of pain)

# Opioid agonists classification

## □ According to analgesic efficacy:

- Agonist (morphine) *full Agonist.*

Morphine acts primarily on the  $\mu$ -opioid receptor as a full agonist.

- Partial agonist (pentazocine)

Pentazocine acts on both  $\kappa$ - and  $\mu$ -opioid receptors: it is a full agonist at the  $\kappa$  receptor and a partial agonist at the  $\mu$  receptor.

During pentazocine administration in a patient already taking morphine, it can antagonize the effects of morphine, potentially leading to withdrawal symptoms.

## □ High efficacy:

- Morphine, Pethidine, Diamorphine, Methadone

The side effects of pentazocine, such as euphoria or dysphoria, are due to its action on both receptors.

*hensin*

## □ Low efficacy:

- Codeine, Pentazocine, Dextropropoxyphene

# Pharmacokinetics

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- Well absorbed from sites of administration & from MM
- Given **parenterally, orally**
- Some have high **1st pass metabolism** & so **low bioavailability** (morphine) → *Never orally, should parenterally*
- New routes (nasal insufflation, trans-dermal) → *should be avoided during pregnancy*

# Pharmacodynamics

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- ❑ **Morphine is the prototype:**
- ❑ **Acts on  $\mu$ 1 receptors: analgesia, euphoria & dependence**
- ❑ **On  $\mu$ 2 receptors: respiratory depression, constipation**

# Pharmacodynamics of morphine

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## 1. CNS actions:

### □ CNS depression:

- **Analgesia** [high efficacy]
- **Sedation**
- **Respiratory depression**  $\propto$  centers  $\rightarrow$  C.I. in Airway obstructive disease.
- **Cough suppression**  $\propto$  cough centers

# Pharmacodynamics of morphine

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## □ CNS excitation:

*→ slight parasympathatic effect.*

■ N & V (stimulation of brainstem CTZ)

■ Miosis (stimulation of the 3<sup>rd</sup> nerve)

■ Increase reflexes & convulsion: pethedine

□ Loss of appetite [*N, V*]

□ Mood changes (*pentazocine*)

□ Dependence [*Mu 1 receptors, Morphine*]

# Pharmacodynamics of morphine

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## 2. Peripheral NS:

- Analgesia
- Anti-inflammatory actions
- Inhibition of immune system

↳ reduce Activity of NK cells - so There is no cytokines...

# Pharmacodynamics of morphine

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## 3. Smooth muscle stimulation

### □ GIT:

#### ■ Constipation:

- increase segmentation & decreased peristalsis

#### ■ Gastric emptying delayed

#### ■ Increased intracolonic pressure

#### ■ Biliary spasm; increase intrabiliary P. ↑ *Contraction* (spasm of sphincter of Oddi)

# Pharmacodynamics of morphine

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## □ Bronchospasm:

Chronic obstructive airway disease

- Opioids are C/I in asthma & COAD

## □ Ureteric contraction:

- Opioids may worsen ureteric colic [N.V, depression]

## □ Bladder sphincter contraction:

- Urine retention in patients with BPH

Benign Prostatic Hyperplasia

# Pharmacodynamics of morphine

## □ Uterine muscle:

- morphine prolongs labour



Morphine  $\alpha$  [C.I.]

Pethidine ✓

## □ Cardiovascular actions:

- Arteriolar & venular vasodilatation

↓ sympathetic

- Histamine release: vasodilatation

- Bradycardia parasympathetic ↑

## □ Neuroendocrine actions:

- **Stimulate** ADH & prolactin & **Inhibit** LH

↓  
(Luteinizing Hormone)

↓ ovulation

# Clinical Uses of Opioid analgesics

## □ Analgesia:

- Moderate-severe acute pain (PO, labour) *Not chronic [defandeece] Postoperative*
- Chronic pain in dying patients → *عادي لو حاز defandeece لاشه رح يعوت*

## □ Left Ventricular failure: *[acute Pulmonary edema] كوييل':*

- Venodilatation & arteriolar dilatation
- Sedation
- Decreased sympathetic effects on the heart
- Decreased respiratory distress → *↓ sensitive of RS centers.*

# Clinical Uses of Opioid analgesics

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- Premedication in painful conditions → *Before general Anesthesia*
- Anti-diarrhoeal using codeine, diphenoxylate

# Adverse effects

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- ❑ Nausea & vomiting
- ❑ Constipation
- ❑ Respiratory depression
- ❑ Bronchospasm
- ❑ Dependence; physical & psychological

(withdrawal)

[craving] → الرغبة  
التدبيرية .

# Opioid dependence

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□ Physical and psychological

□ **Withdrawal syndrome:** [stop suddenly] <sup>or</sup> [with drug Antagonist]

■ Within 12 hours

■ craving for the drug, rhinorrhoea,

■ Lacrimation, shivering, hyperventilation

■ Nausea, diarrhoea, colic

■ Increase HR & BP, mydriasis, flushing

■ Methadone & clonidine are useful

# Tolerance

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غير مطلوب

- ❑ May occur within days
- ❑ To **analgesic & respiratory depression**
- ❑ Not to **miosis** nor to **constipation**
- ❑ Cross-tolerance occur

# Contraindications

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- ❑ Liver disease [ impair metabolism ]
- ❑ Asthma & COAD
- ❑ Head injury & raised intracranial pressure [ depression, ↑ demand O<sub>2</sub> ]
- ❑ Hypothyroidism & Addison's disease  
[ more Affinity to Morphine, depression, slow metabolism ]  
↑ sensitivity

Drug	t <sub>1/2</sub> / Duration	Main Characteristics	Uses	Notes
Codeine	t <sub>1/2</sub> : 3 h	~10% converted to morphine	Mild–moderate pain, antidiarrhoeal, antitussive	—
Pethidine (Meperidine)	Duration of analgesia: 2–3 h	Lower efficacy, no dependence, does not constipate, less urinary retention, does not prolong labour, less hypnotic, atropine-like effects	Obstetrics	Overdose: CNS stimulation, myoclonus, convulsions; pupil may show miosis or mydriasis
Methadone	t <sub>1/2</sub> : 8 h / Duration: ~24 h	Synthetic, similar to morphine, longer duration	Opioid withdrawal, severe cough	Dependence less severe, slower to develop, milder withdrawal
Diamorphine (Heroin)	t <sub>1/2</sub> : 3 min	Semisynthetic, most potent addicting drug, converted rapidly to morphine	Acute severe pain, chronic pain in dying patients	Illegal manufacturing; parenteral use
Pentazocine (Fortral; Sossegon)	Duration: short	Partial agonist, κ receptor, some μ affinity, less potent, less dependence, less respiratory depression	Moderate–severe pain, chronic pain	Causes dysphoria & withdrawal in morphine addicts; avoided in AMI
Naloxone	t <sub>1/2</sub> : 75 min	Pure competitive antagonist, μ receptor	Opioid overdose	IV; reverses respiratory depression in 2 min; may precipitate withdrawal
Naltrexone	t <sub>1/2</sub> : 10 h	μ opioid receptor antagonist	Chronic addicts	Oral use; clonidine–naltrexone

# Codeine

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- t  $\frac{1}{2}$  of 3 hours
- About 10% of it is converted into morphine
  
- Uses include:
  - **Analgesic:** mild to moderate pains *Not in severe*
  - **Anti-diarrhoeal**
  - **Antitussive**

# Pethidine = (Meperidine)

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- Differs from morphine in being:
  - Lower efficacy *No dependence*
  - Shorter duration analgesia (2-3 hours)
  - Does not constipate → *no Antidiarrhoeal effect*
  - **Less urinary retention**
  - Does not prolong **labour**
  - **Less hypnotic**
  - Has atropine-like effects

# Pethidine

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- Used orally & parenterally => *Never subcutaneous*
- **Metabolism: in the liver & excretion in urine**
- **Widely used in obstetrics** طب التوليد
  
- **Overdose of pethidine**
  - CNS stimulation, **myoclonus & convulsions**
  - Pupil may show **miosis or mydriasis**

# Methadone → high efficacy

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- $t_{1/2}$  is 8 hours
- **Synthetic; similar to morphine**
- **Longer duration of action (24 hours)**
- Used to **cover opioid withdrawal**
- **Dependence:**
  - less severe & slower to develop & withdrawal manifestations are milder
- May be used also for severe cough

⇒ في مقارنته مع Morphine

# Diamorphine (Heroin)

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- ❑ **Semisynthetic, most potent addicting** drug
- ❑ **Illegal manufacturing**
- ❑ **Converted** within minutes into monoacetyl morphine & then to **morphine**
- ❑ Used **parenterally**;  $t_{1/2}$  is **3 min**
- ❑ Uses:
  - **acute severe pain**
  - **chronic pain in dying patients**

# Mixed Agonist-Antagonist opioids;

## Pentazocine (Fortral; sossegon) → الأسماء التجارية

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- ❑ **Partial agonist**
- ❑ At kappa receptors; some affinity to mu receptors
- ❑ May cause **dysphoria & withdrawal precipitation in morphine addicts**
- ❑ **Less potent, shorter duration, less dependence, less respiratory depression**
- ❑ Useful in **moderate to severe pain** and chronic pains
- ❑ **Avoided in AMI**; may **increase blood pressure**  
*+ vascula resistance*

# Opioid receptor antagonists; Naloxone

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- **Pure competitive antagonist**
- Acts on **mu receptors**
- $t_{1/2}$  is **75 min**
- **IV** in opioid overdose toxicity
- **Reverses respiratory depression in 2 min**
- Doses may be repeated as necessary
- **Can precipitate withdrawal in addicts**

# Opioid receptor antagonists; Naltrexone

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- ❑ mu opioid receptor antagonist
- ❑ Can be used orally
- ❑ Longer duration of action ( $t_{1/2}$  10 hr)
- ❑ Useful in chronic addicts
  - as clonidine-naltrexone