Narcotic analgesics

Opioid

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MSc Pharmacology & Toxicology

Pain

Definition:

An unpleasant sensory & emotional experience associated with actual or potential tissue damage.

1. Acute pain:-

free nerve endings receptors, respond to somatic tissue stress. **A-δ fiber.**

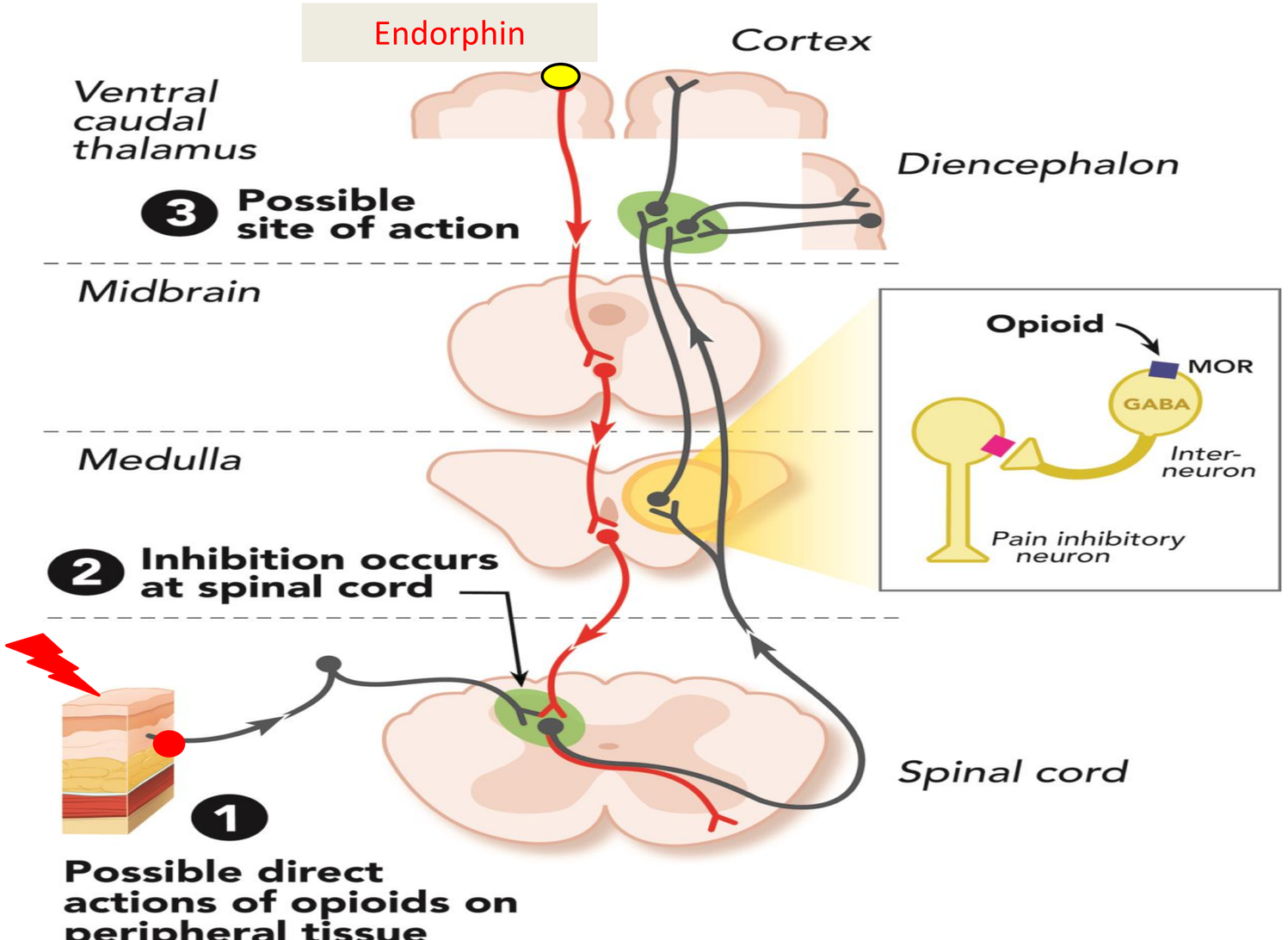
2. Nociceptive pain:

Poly-modal pain receptors, respond to somatic & visceral tissue **damage.** c-*fiber.*

(release of mediators : PG, Bradykinin, 5HT, sub P… .)

3. Neuropathic pain:-

Stimuli abnormally processed by the N.S. **e.g. amputation-phantom, diabetic neuropathy.**


Endorphin
Cortex
Ventral caudal thalamus
Diencephalon
3 Possible site of action
Midbrain
Medulla
Opioid
MOR
GABA
Inter-neuron
Pain inhibitory neuron
2 Inhibition occurs at spinal cord
Hot pin
Spinal cord
1
Possible direct actions of opioids on peripheral tissue

pain modulators

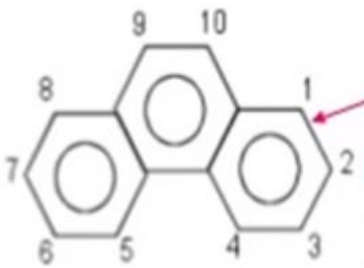
- **Endogenous peptides** (pain modulators) are **enkephalins & endorphins**, act on Opioid receptors: Mu (μ), Kappa (κ) , Sigma (σ) . The (mu) μ-receptor most responsible for analgesic.

- These peptides have other physiological functions : regulation of temp. , behaviour, gastrointestinal motility, appetite, thirst etc.

Opioids - Opium

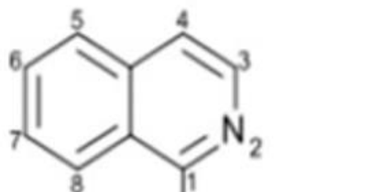
- A dark brown, resinous material obtained from poppy (*Papaver somniferum*) Capsules.

OPIUM



PHENANTHRENE

- Morphine 9-14%
- Codeine 0.5-2%
- Thebaine 0.2-1%



BENZYLISOQUINOLINE

- Papaverine 0.8-1%
- Noscapine 3-10%
- Narcine 0.2-0.4%

Narcotic – Analgesic	---
Spasmogenic	Spasmolytic
Addiction	No addiction

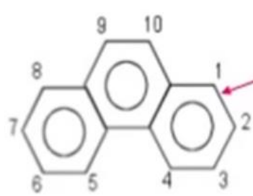
Opioid Classification

Natural

Opioids - Opium

- A dark brown, resinous material obtained from poppy (*Papaver somniferum*) Capsules.

OPIUM



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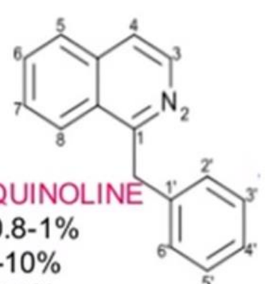
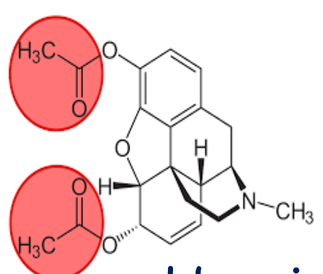


BENZYLISOQUINOLINE
- Papaverine 0.8-1%
- Noscapine 3-10%
- Narcine 0.2-0.4%

Semisynthetic

- Heroin
- Hydromorphone



Heroin

Synthetic

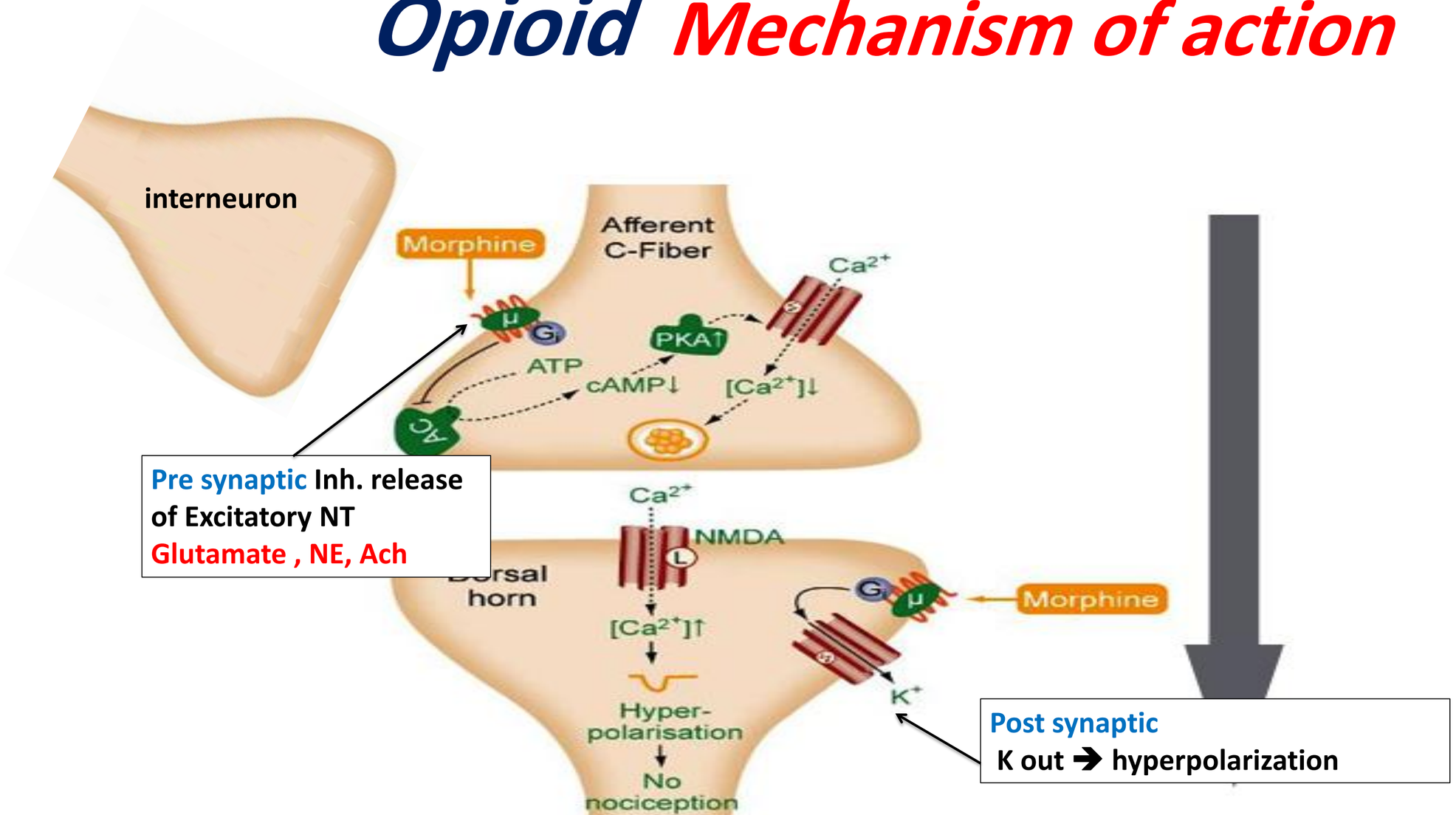
Agonist

- Meperidine
- methadon
- tramadol
- fentanyl

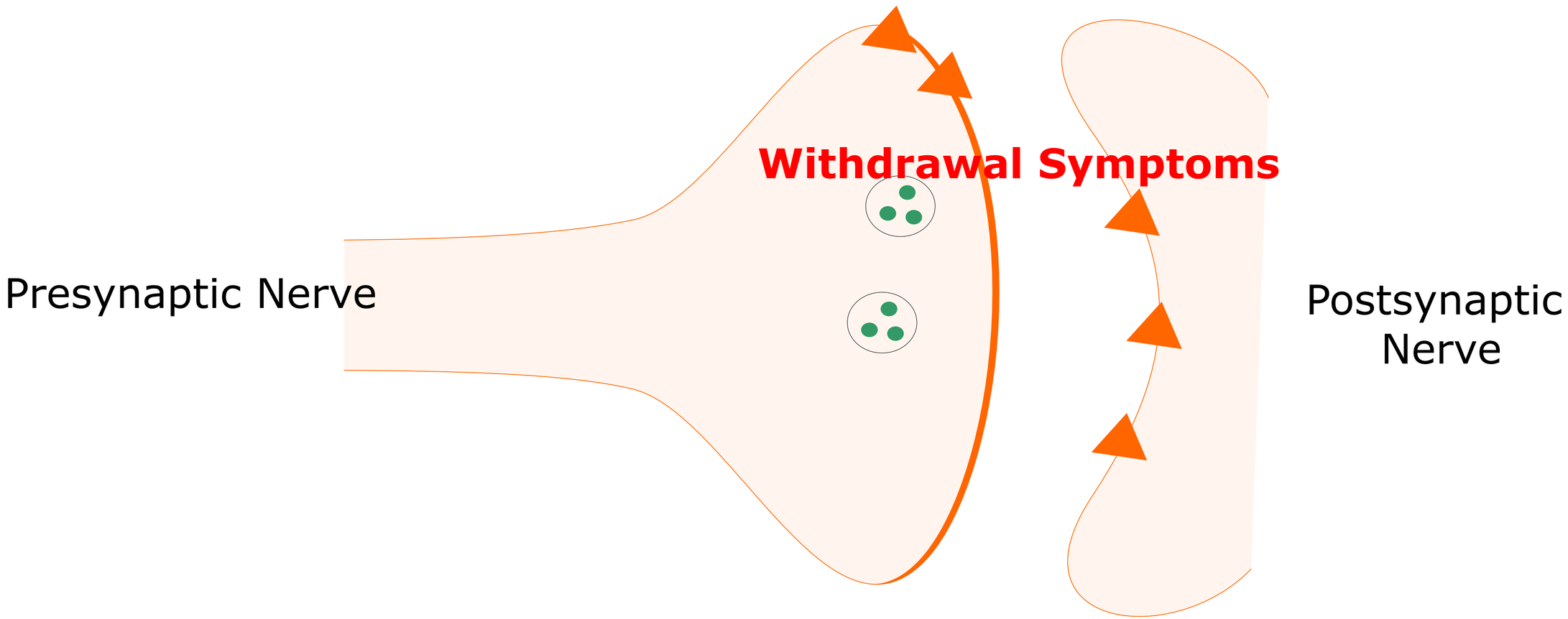
Mixed Agonist

- Nalbufine
- pentazocine
- Butorphanol

Opioid Mechanism of action



Opioid Physical Dependence



- Exogenous Opioid causes –ve feedback on the release of the endogenous opioid.

- Upon **subsequent administration** the effect of a particular (first) dose will be reduced (i.e. tolerance develops, a larger dose to produce the same effect). In this condition biological adaptation (dependence on exogenous substance).

- Upon **withdrawal** of the exogenous opioid, ➔ **unmasking excitatory NT** ➔ withdrawal symptoms

Opioid Withdrawal Symptoms

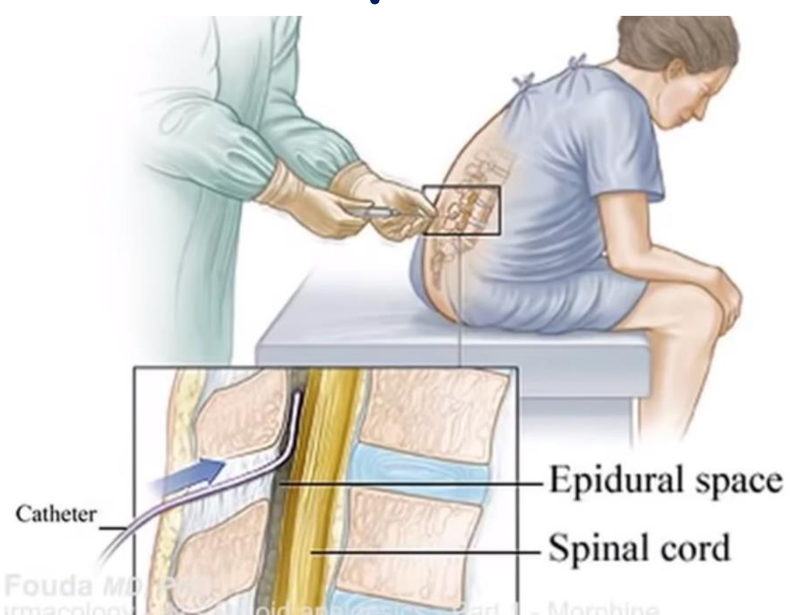
Treatment of Withdrawal Syndrome

- **Methadone** (oral, long acting, less addictive)
- **Diazepam** **(for insomnia, agitation)** **substituted gradually methadone**
- **Clonidine ..!!!**

Morphine

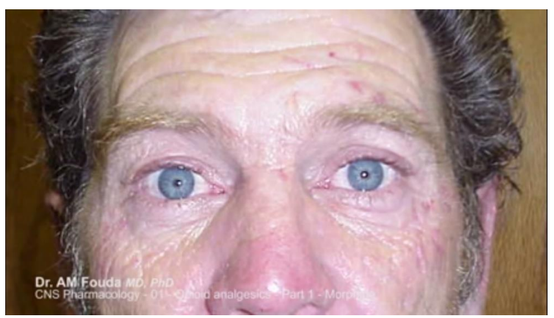
- **Pharmacokinetic**
  - low bioavailability F=25 due to 1st pass metabolism
  - metabolized by glucoronidation in liver
  - **S.C (best absorbed), tablet or ER tab , I.V (give 1/2 amp) or epidural injection**
  - Duration of analgesia is 4-6 hr.

NB: If maintained dose 15mg oral twice a day in break through pain give 1/6 of total Dose



Morphine Central effect

1. **Analgesia** ↓ sensory at level of spinal cord & by descending p.w (supra-spinal)
   by inhibit NE in CNS → **↓ emotional pain**
   by ↓ inflammatory mediators locally (recent).



2. **Euphoria (good mood)** Dis-inhibition of the dopamine-containing neurons of the ventral tegmental area.
3. **miosis (pin point)** stimulation of receptor centrally in occulomotor cranial nerve (III)
4. **Nausea & vomiting** due to stimulation of CTZ
5. **Vagal stimulation** → Bradycardia
6. **Cough center inhibition**
7. **Respiratory center inhibition** in high dose (apnoea in addict)
8. ↑ **Intracranial pressure** due to cerebral vasodilation (↑ volume and press on brain tissue).

Morphine Peripheral effect

1. **CVS** : Hypotension due vagal stimulation and histamine release & bradycardia
2. **Smooth muscle:** activation of opioids receptor in
   * sm. m of intestine → spasm & constipation **precaution in colic or use Atropine with it**
   * bronchi → bronchoconstriction (also due to Histamine release) **C.I in asthma**
   * urinary bladder contraction of dome and sphincter → feeling of urgency and difficulty of urination. **so precaution in enlarged prostate**
   * gall bladder contraction of gall bladder & Oddi sphincter. **C.I in biliary colic**
   * Uterus interfere with contraction of uterine during labor and spasm of cervix → prolonged labor duration. **Avoided in labor**

Therapeutic uses of Morphine

- Analgesia for moderate to sever pain (cancer)
- acute MI or pulmonary edema due to LVF
  1- Stimulates vagal centre (M) leading to ↓ heart rate
  2- Releases histamine → vasodilatation
  3- Tranquillising action, thus ↓ mental distress
  4- Decreases central sensitivity to afferent stimuli from the congested lung leading to decreased respiratory distress
- adjuvant anesthesia in major surgery

side effects of morphine

- tolerance & addiction (→ in high dose cause respiratory inhibition).
- ↑ intracranial pressure
- bronchoconstriction
- bradycardia
- feeling of urgency with difficult micturition
- prolong labor
- constipation (ptn. on morphine give laxative).

Morphine toxicity

- Chronic toxicity = **addict** = miosis , emaciation , itching .

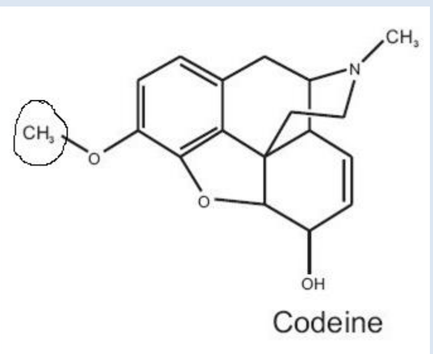
  withdrawal syndrome tachycardia, nervousness, insomnia , agitation

  (After 48 hr. of withdrawal may kill for morphine)

- Acute toxicity **high dose of morphine →** Resp distress syndrome coma.

  ttt by **ventilator**, **naloxone** (must assessing ptn /hr until normal respiration)

NB: not give **naloxone** for addict ptn >> acute withdrawal syndrome > suicidal.

Narcotic agent	Kinetics	Principal features
Codeine (**methyl**-morphine)  Codeine	t1/2 3hr Duration: 4hr Absorbed Orally F= 60% Demethylated to morphine in liver (genetic variation) **Potency :** Must give 100mg to equi-effective morphine **BUT** get Resp. depression	* mild-to-moderate pain, combined with non-opioid analgesics (e.g. aspirin) to produce greater analgesic action; & * cough suppressant (10 mg **not give for children < 6hr**); **Adverse-effects**: sedation and constipation.

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Narcotic agent	Kinetics	Principal features
Pethidine (meperidine) عالم الماني اكتشفه فجأة عند صنع مركب شبيه بالاتروبين	t1/2 2hr Duration 2-3 F=50% Oral , inj	Synthetic Opioid with **atropine like** effect. Therefore for biliary colic & for labour & intestinal , renal colic. metabolite to **Nor-meperidine** (neurotoxic) stimulate 5HT Rc→ 5HT syndrome.

Narcotic agent	Kinetics	Principal features
Fentanyl Derivative of Meperidine	$t_{1/2}$ 3 hr duration 0.3hr Sever 1st pass met [no oral] Skin patch Or epidural	Eighty times more potent than morphine; & more efficacious, used in surgery. - **Fentanyl + Droperidol** = Neuroleptic Analgesia **Safe** in renal Failure

Narcotic agent	Kinetics	Principal features
Methadone	t1/2 8hr duration **24hr** **good absorbed** Orally	equieffective of morphine Long duration of action, used to cover opioid withdrawal **because less addictive** & for chronic pain in palliative care.

Narcotic agent	Principal features
Tramadol	act on μ receptor. ↓ reuptake of NE & 5HT → Neuropsychiatric complex (seizure) Block 5HT2c Receptor !!!! Used as analgesic in orthopaedic surgery 10% of potency of Morphine Cause addiction

Narcotic agent	Principal features
Loperamide	act on μ receptor **peripherally only** **Used in diarrhoea**

Mixed Agonist-Antagonist

- **Pentazocine ; Nalbuphine ; Butorphanol ;Naluphine**

- Mode of action : Agonist (κ) – Antagonist (μ)
- κ receptor →spinal analgesia
- less respiratory depression .. since not act on μ receptor
- less euphoria → less addiction… since not act on μ receptor
- Not used for addict … acute withdrawal syndromes
- peripherally vasoconstriction so not used in MI

Opioid Blocker

Naloxone & Naltrexone

- **Naloxone** (I.V .. duration 1 hr)

  1- **Treatment of :**

  - **acute** opioids poisoning (0.4mg IV)
  - Neonatal asphyxia if mother given opioid

    (IM to mother before labour or IV to neonate). **NB:** If mother addict no naloxone

  2- **Dx** of Morphine addict (SC >> withdrawal symptoms).

- **Naltrexone** (as Naloxone but Orally .. duration 48hr) used in: maintaining opioid free state in treated addict.