MORPHINE

Dr. Rima Bondarenko

HISTORY

- *Morphine was isolated from raw opium in 1805 by a German pharmacologist Friedrich Wilhelm Adam Serturner (1783-1841).*

- *Morphine is a potent suppressor of pain and is a very useful drug in painful conditions, especially in severe chest pain arising due to heart attacks. It also induces sleep in no time*

HISTORY

- *Barely eighteen years after morphine was discovered, it was used for homicide. In 1823, a twenty-seven year old French doctor, Edme Castaing, mixed morphine in the wine given to his friend Auguste Ballet, to kill him.*

HISTORY

- *In fact the name morphine comes from the Greek 'god of dreams Morpheus. Incidentally Morpheus was the son of Hypnos, the Greek 'god of sleep', and our word hypnosis'is derived from it. Hypnos was also the brother of Thanatos, the god of death'.*

- *Morphine not only brings sleep and dreams but may cause death when taken in large doses.*

DEFINITION

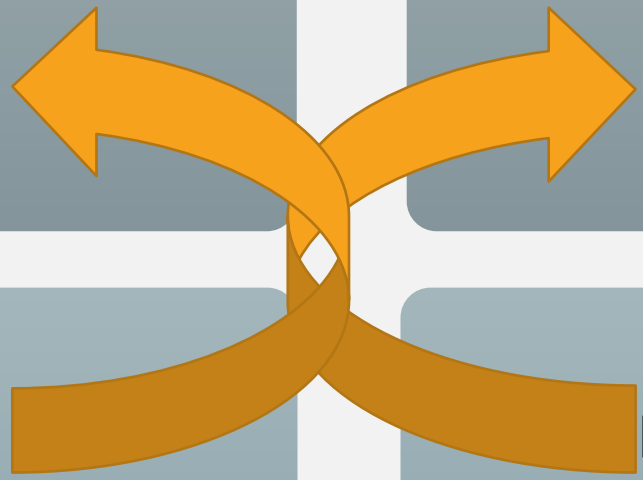
- *Morphine is a natural opium alkaloid.*
- *It is a dried extract obtained from the capsules of the poppy plant known as papaver somniferum.*
- *It requires approximately 10 kg of raw opium to produce 1 kg of morphine*

CLASSIFICATION

According to ring structure .1

Morphine -
Thebaine -
Codeine-

Papaverine -
Noscapine -



Phenanthrene derivatives

Benzo-isoquinoline derivatives

CLASSIFICATION

According to .2 synthesis

A. Natural opium alkaloids

Morphine -

Codeine -

B. Semi synthetic opium alkaloids

- Heroine
- Pholcodeine

C. Synthetic opiods

Pethidine -

Methadine -

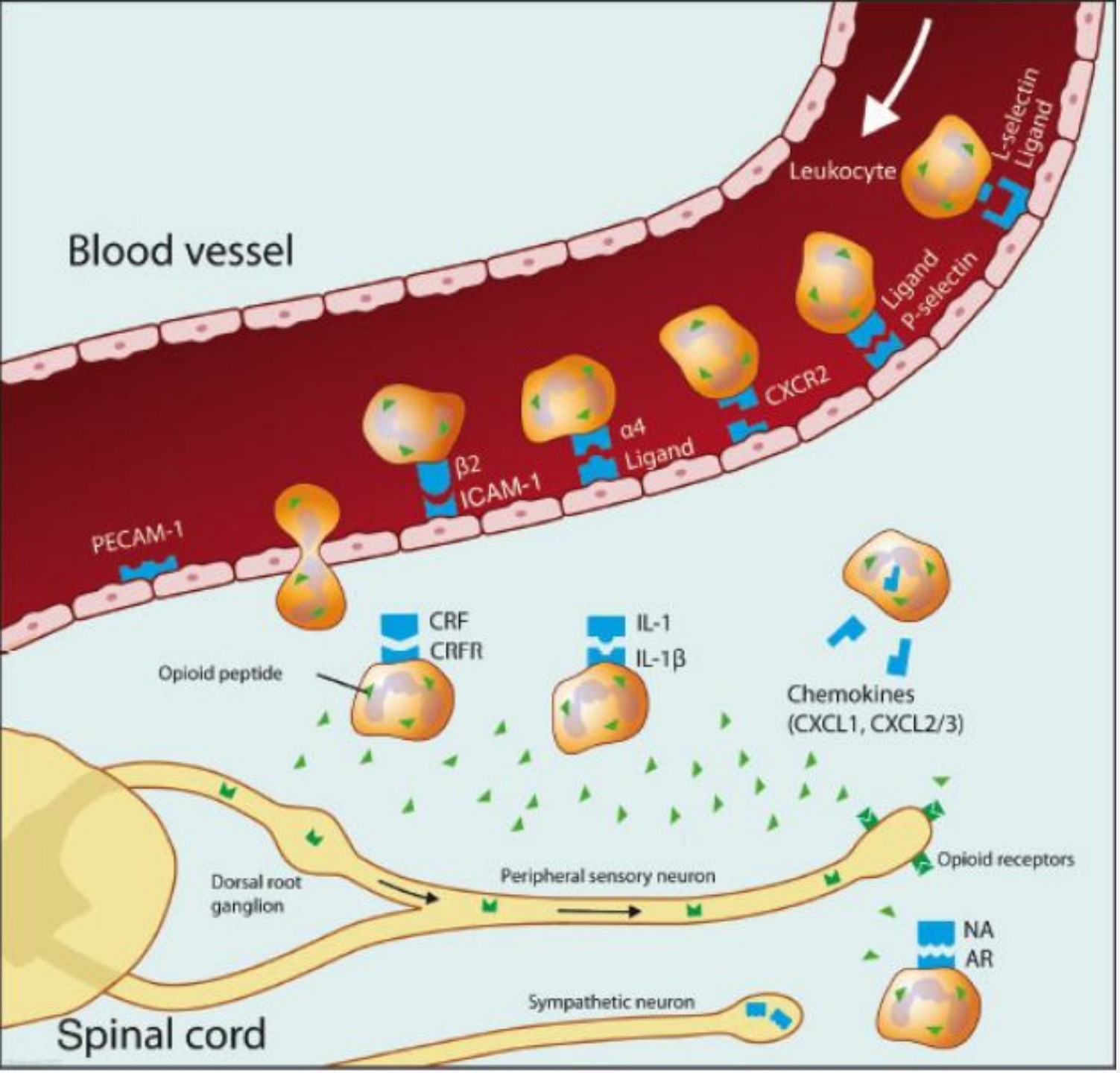
MECHANISM OF ACTION

- *Opioids exert their major effects by interacting with opioid receptors in the CNS*
- *Opioids activate 7- transmembrane GPCRs located presynaptically and postsynaptically along pain transmission pathways*
- *High densities of opioid receptors known as mu, delta and kappa are found in the dorsal horn of the spinal cord and higher CNS centers*
- *Most currently used opioid analgesics act mainly at mu- opioid receptors*
- *Morphine acts at kappa receptors in lamina I and II of the substantia Granulose of the spinal cord and decreases the release of substance p, which is modulates pain perception in the spinal cord*

MECHANISM OF ACTION

- *Opioids have an onset of action that depends on the route of administration*
- *Opioids causes hyper polarization of nerve cells, inhibition of nerve firing and presynaptic inhibition of transmitter release*
- *Cellular effects of these drugs involve enhancement of neuronal potassium efflux (hyperpolarizes neurons and makes them less likely to respond to a pain stimulus) and inhibition of calcium influx (decreases neuro- transmitter release from neurons located along the pain transmission pathway)*
- *Brainstem opioid receptors mediate respiratory depression produced by opioid analgesics Constipation results from activation of opioid receptors in the CNS and in the GIT*

MECHANISM OF ACTION



SCHEMATIC DIAGRAM ILLUSTRATING THE ROLE OF OPIOIDS IN ANALGESIA OF PERIPHERAL

PHARMACOKINETICS

- *Absorption of morphine from GI T is slow and incomplete*
- *Quick effect is produced on subcutaneous injection*
- *It is partly bound to plasma proteins*
- *It is metabolized by conjugation with glucuronic acid*
- *It is almost completely excreted in urine within 24 hours*
- *Bioavailability is 20 to 40 per cent*
- *Given sc, onset of action is in 15- 20 min, peak effect in 1 hrs*
- *Duration of action is 3-5*

PHARMACOLOGICAL ACTIONS

- **1. *Analgesia***
- *- Morphine causes analgesia*
- *- Morphine relieves severe deep seated pain like visceral pain and pain of trauma*
- *Mechanisms*
- *- Opioids relieve pain both by raising the pain threshold at the spinal cord level and more importantly by altering the brains perception of pain*
- *- It alters the emotional reaction to pain*
- *- The analgesic action morphine is primarily due to its effect on endogenous opioid receptors in midbrain and brain stem areas*
- *- Inhibitory impulses from these areas to the dorsalhorn constitute the gating system*
- *- The morphine also acts directly on the dorsal horn where it inhibits the release of substance P .*

PHARMACOLOGICAL ACTIONS

- **2. CNS**
- *- Morphine produces euphoria in presence of pain*
- *- But in the absence of pain, it produces dysphoria& restlessness*
- *- With an increased dose, it produces sleep*
- *- Tolerance is noted to both euphoria (mu receptor) and dysphoria (kappa receptors)*
- **3. Sedation**
- *- Morphine induces sedation in analgesic doses and is useful when pain is accompanied by insomnia*

PHARMACOLOGICAL ACTIONS

- **4. Anti-tussive property**
- *- Morphine has anti-tussive property*
- *- Morphine depress the medularly cough centre, an effect not blocked by naloxone*
- *- It is not used clinically and related drugs like codeine, with less respiratory depressant and addictive liability are used*
- **5. Nausea & vomiting**
- *- Nausea and vomiting are common features with analgesic doses and induced by stimulation of the chemoreceptor tiger zone (CTZ)*
- *- Tolerance develops to vomiting on prolonged use*
- *- Higherdoses of morphine inhibit the vomiting centre*

PHARMACOLOGICAL ACTIONS

- **6. Papillary constriction**
- *- Morphine produces constriction of pupil (miosis)*
- *- Miosis is induced by mu and kappa mediated stimulation of the oculomotor nucleus*
- *- The effect is blocked by atropine*
- *- Morphine addicts have constricted pupll*
- *- Tolerance to papillary constriction is not seen in addicts and pinpoint pupils are indicative of morphine abuse and diagnostic in morphine poisoning (other respiratory depressants induce papillary dilatation)*

PHARMACOLOGICAL ACTIONS

- **7. Respiration**
- *- The action of morphine on the respiration is dose dependent*
- *- Analgesic doses of morphine induce depression of the respiratory centre resulting in increase in plasma carbon dioxide concentrations*
- *- Respiratory center depression is mediated by mu receptors and is the cause of death in morphine poisoning*
- *- At higher doses it produces respiratory depression*
- *- Respiratory depression is the most common cause of death in acute overdose*
- **8. Heat regulation**
- *- Opioids shift the equilibrium point of heat-regulating centre so that body temperature falls slightly*

PHARMACOLOGICAL ACTIONS

- **9. Gastro-intestinal tract**
- *- Morphine decreases peristaltic propulsive movements*
- *- It produces spasm of intestinal smooth muscles and sphincters*
- *- Gastric emptying is delayed*
- *- It also increases absorption of water, So the feces get dried All these effects leads t o constipation*
- **10. Billary tract**
- *- Morphine increase billiary tract pressure due to contraction of the gallbladder and constrictor of the biliary sphincter*
- *- This produces increase in intrabiliary pressure*
- *- Atropine antagonizes this effect*

PHARMACOLOGICAL ACTIONS

- **11. Cardiovascular system**
- *- Normal dose of morphine produces no effect on heart rate, blood pressure or circulation*
- *- But hypo tension and bradycardia may be produced at toxic dose*
- *- Hypotension is due to dilation of peripheral veins and arterioles, histamine release and reduced sympathetic activity and in large doses due to depression of medularly vasomotor center*
- *- Bradycardia is due to stimulation of the vagal nucleus*
- *- Because of respiratory depression and carbon dioxide retention, cerebral vessels dilate and increase the cerebrospinal fluid pressure*
- *- Morphine is usually contraindicated in individuals with severe brain injury*

PHARMACOLOGICAL ACTIONS

- **12. Histamine release**
- - Morphine releases histamine from mast cells, causing urticaria, sweating and vasodilatation
- - Morphine can cause the bronco-constriction, asthmatics should not receive the drug
- **13. Hormonal actions**
- - Morphine inhibits release of GRH and corticotrophic releasing hormone and it decreases the concentration of luteinizing hormone, FSH & ACTH
- - It increases prolactin and growth hormone release by diminishing .
- - It increases antidiuretic hormone and leads to urinary retention

PHARMACOLOGICAL ACTIONS

- ***14. Uterus***
- *- No significant effect. May prolong labor in high doses*
- ***15. On excretion***
- *- Tone and amplitude of contractions of the urters is increased tone of external sphincter and volume of the bladder are increased*
- *- Opioids inhibit urinary voiding reflex*
- *- All these result in urinary retention especially in orderly male with prostate hypertrophy*
- ***16. Excitory effect***
- *- In high doses it produce convulsions. They may increases the excitability of the spinal cord*

ADVERSE REACTIONS

- *Acute morphine poisoning characterized by respiratory depression, pin point pupil cyanosis, reduced body temperature, hypotension, shock and coma R naloxone 0.4-0.8mg iv*
- *- GIT Symptoms - Nausea, vomiting and constipation*
- *- Central effects like dysphoria and mental clouding*
- *- Intolerance like tremor, delirium and skin rashes*
- *- Depression of fetal respiration*

ADVERSE REACTIONS

- **Drug interactions**
- *- The depressant actions of morphine are enhanced by phenothiazines, monoamine oxidase inhibitors and tricycle antidepressants*
- *Tolerance and dependence*
- *- Repeated use of drug produces tolerance to the respiratory depressant, analgesic, euphoric and sedative effects of morphine*
- *- Physical and psychological dependence readily occur with morphine*
- *- Withdrawal produce a series of autonomic, motor and psychological responses that incapacitate the individual and cause serious unbearable symptoms*
- *Treatment of withdrawal syndrome is oral methadone*

CONTRAINDICTIONS

- *- Infants and elder people*
- *- Respiratory conditions such as bronchial asthma*
- *- Head injury*
- *- Acute abdominal pain*
- *- Hypothyroidism*

DOSAGE

Preparation	Dose
Tincture opium	to 2 ml 0.3 by mouth
Morphine sulphate	mg by 8-20 mouth or by injection
Morphine hydrochloride	mg by 8-20 mouth or by injection

USES

- *1. It is an analgesic for the relief of severe pain*
- *2. Used as pre-anesthetic medication*
- *3. For producing sleep and sedation*
- *4. Used as anti-tussive*
- *5. For the treatment of diarrhea*
- *6. In the treatment of acute left ventricular failure*


Thank
you