OPIOID ANALGESICS & ANTAGONISTS

Prepared By

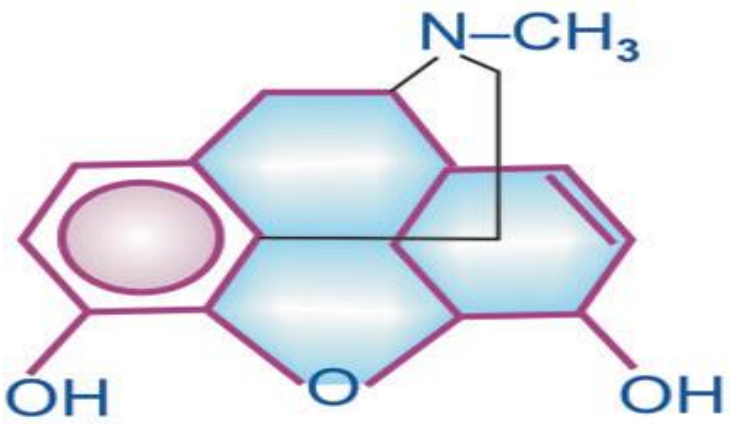
Doppalapudi Sandeep
M. Pharmacy,
Assistant Professor
Department of Physiology & Pharmacology
Chebrolu Hanumaiah Institute of Pharmaceutical Sciences, Chandramoulipuram, Chowdavaram, Guntur, Andhra Pradesh, India – 522019

- ***Algesia (pain):*** *It is an ill-defined, unpleasant* bodily sensation, usually evoked by an external or internal noxious stimulus.
- ***Analgesic:*** *A drug that selectively relieves pain* by acting in the CNS or on peripheral pain mechanisms, without significantly altering consciousness.
- Pain is a warning signal, primarily protective in nature, but causes discomfort and suffering; may even be unbearable and incapacitating.
- Excessive pain may produce other effects—sinking sensation, apprehension, sweating, nausea, palpitation, rise or fall in BP and tachypnoea.
- Analgesics relieve pain as a symptom, without affecting its cause.

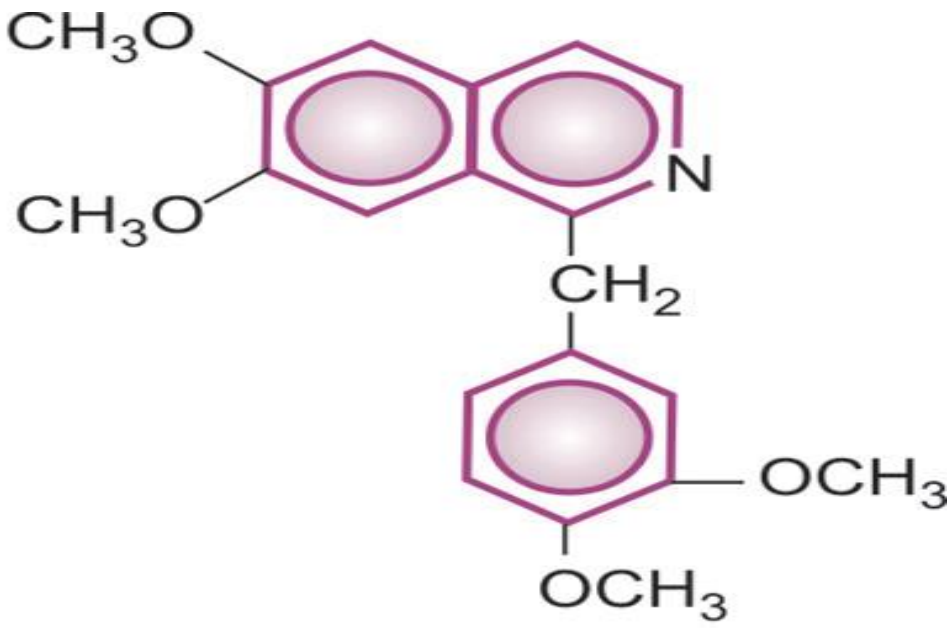
- Analgesics are divided into two groups, *viz.*
  - A. Opioid/narcotic/morphine-like analgesics.
  - B. Non-opioid/non-narcotic/aspirin-like/antipyretic or anti-inflammatory analgesics

CLASSIFICATION OF OPIOID ANALGESICS

- **Opium:** A dark brown, resinous material obtained from poppy (*Papaver somniferum) capsule.*
- It contains two types of alkaloids.
- ***Phenanthrene derivatives***
  - Morphine (10% in opium)
  - Codeine (0.5% in opium)
  - Thebaine (0.2% in opium), (Nonanalgesic)
- ***Benzoisoquinoline derivatives***
  - Papaverine (1%)
  - Noscapine (6%) Nonanalgesic



MORPHINE



PAPAVERINE

Compounds that are derived from opium /chemically related to morphine are called '*opiates', while all those having* morphine-like action, irrespective of chemical nature, are called '*opioids'.*

MORPHINE

- Morphine is the principal alkaloid in opium and is widely used till today.

PHARMACOLOGICAL ACTIONS

1. **CNS:** Morphine has site specific depressant and stimulant actions in the CNS by interacting primarily with the μ opioid receptor (for which it has the highest affinity), as a full agonist.

THE DEPRESSANT ACTIONS ARE:

- **(a) *Analgesia*** *Morphine is a strong analgesic.* Though dull, poorly localized visceral pain is relieved better than sharply defined somatic pain.
- Higher doses can relieve even severe pain.
- Nociceptive pain arising from stimulation of peripheral pain receptors is relieved better than neuretic pain (such as trigeminal neuralgia) produced by inflammation of or damage to neural structures.
- The associated reactions like apprehension, fear and autonomic effects are also reduced.
- Perception of pain and the emotional component (anxiety, fear, suffering, distress) induced by it are both altered so that pain is no longer as unpleasant or distressing, i.e. the patient tolerates pain better.

- Intrathecal injection of morphine has been shown to cause segmental analgesia without affecting other modalities.
- **Mechanism of actions:**
- Morphine acts in the substantia gelatinosa of dorsal horn to inhibit release of excitatory transmitters (e.g. substance P) from primary afferents carrying pain impulses.
- Release of glutamate from primary pain afferents in the spinal cord and its postsynaptic action on dorsal horn neurones is inhibited by morphine.
- It also sends inhibitory impulses through descending pathways to spinal cord.
- A ***peripheral action of opioids on small primary afferent*** **terminals** in skin or deeper structures, attenuating their sensitization following tissue injury has also been demonstrated.
- This may play a role in the analgesic action of morphine in conditions like burns and trauma.

(B) *Sedation:*

- *It is different from that* produced by hypnotics is seen.
- Drowsiness and indifference to surroundings as well as to own body occurs without motor incoordination, ataxia or apparent excitement.
- Higher doses progressively induce sleep and then coma.
- Morphine has no anticonvulsant action, rather, fits may be precipitated.

(C) *Cough centre:*

It is depressed by morphine, and is more sensitive than respiratory centre.

(D) *Temperature regulating centre:* *It is* depressed; hypothermia occurs in cold surroundings.

(E) ***Vasomotor centre:*** *It is depressed at higher* doses and contributes to the fall in BP.

(F) ***Mood and subjective effects:*** *These are* prominent.

- Morphine has a calming effect.
- Loss of apprehension
- Feeling of detachment,
- Lack of initiative
- Limbs feel heavy and body warm
- Mental clouding and inability to concentrate occurs.
- Patients in pain or anxiety, and especially addicts, perceive it as pleasurable floating sensation: refer it as ‘high’.
- Rapid I.V injection by addicts gives them a ‘kick’ or ‘rush’ which is intensely pleasurable.

(G) *Respiratory centre:*

- *Morphine depresses* respiratory centre in a dose dependent manner.
- Rate and tidal volume are both decreased.
- Death in morphine poisoning is due to respiratory failure.
- Neurogenic and later hypoxic drives to the respiratory centre are suppressed in succession.
- **Morphine stimulates:**

(A) CTZ:

- *Nausea and vomiting occur as side* effects, especially if stomach is full and the patient stands or moves about.
- Larger doses depress vomiting centre directly: emetics should not be tried in morphine poisoning.

(B) EYES:

- *Edinger Westphal nucleus of III nerve* is stimulated producing miosis.
- Decrease in intraocular tension.

(C) *Vagal centre:* *It is stimulated→ bradycardia.*

(D) *Certain cortical areas and hippocampal cells* *are stimulated.*

- *Muscular rigidity and* immobility occurs at high doses.
- Morphine lowers seizure threshold

2. Neuro-endocrine :

- **Hypothalamic activation** by afferent collaterals is dampened.
- Hypothalamic influence on pituitary is reduced.
- As a result FSH, LH, ACTH levels are lowered.
- Prolactin and GH levels are raised
- The sex hormone and cortisol levels are lowered.
- Heavy abusers often suffer loss of libido, impotence, menstrual irregularities and infertility.
- Morphine can release ADH and reduce urine volume.

3. CVS:

Morphine causes vasodilatation due to:

(a) histamine release.

(b) depression of vasomotor centre.

(c) direct action decreasing tone of blood vessels.

- Postural hypotension and fainting.
- Morphine has little direct effect on heart;
- Heart rate generally decreases due to stimulation of vagal centre.

4. ANS:

- **Morphine causes mild hyperglycaemia** due to central sympathetic stimulation.
- It has weak anti-cholinesterase action.

5. GIT:

- The enteric plexus neurones and g.i. mucosa are rich in opioid receptors.
- Constipation
- Decreased propulsive movements.
- Tone of duodenum and colon may be increased to the level of spasm.
- Spasm of pyloric, ileocaecal and anal sphincters.
- Decrease in all gastrointestinal secretions due to reduction in movement of water and electrolytes from mucosa to the lumen.
- Inattention to defecation reflex.
- Absorption of fluid is increased.

6. Other smooth muscles:

- ***Biliary tract:*** *Morphine causes spasm of* sphincter of Oddi → intrabiliary pressure is increased several fold → may cause biliary colic.
- ***Urinary bladder:*** *Tone of* sphincter muscle is increased → urinary urgency and difficulty in micturition.
- Contractions of ureter is also increased.
- ***Uterus:*** *M*ay slightly prolong labour.
- ***Bronchi:*** *Morphine releases histamine*, which can cause bronchoconstriction.

PHARMACOKINETICS

- The oral absorption of morphine is unreliable because of high and variable first pass metabolism.
- Oral bioavailability is 1/6th to 1/4th of parenterally administered drug.
- About 30% is bound to plasma proteins.
- Distribution is wide.
- Concentration in liver, spleen and kidney is higher than that in plasma.
- Only a small fraction enters brain rather slowly.
- Morphine freely crosses placenta and can affect the foetus more than the mother.
- It is primarily metabolized in liver by glucuronide conjugation.
- Morphine-6-glucuronide is an active metabolite (more potent than morphine on μ opioid receptors.
- Another metabolite, morphine-3-glucuronide has neuroexcitatory property.
- Plasma t½ of morphine averages 2–3 hours.
- Effect of a parenteral dose lasts 4–6 hours.
- Elimination is almost complete in 24 hours and morphine is noncumulative.
- However, small amounts persist in the body due to enterohepatic circulation.

ADVERSE EFFECTS

- Sedation
- Mental clouding,
- Lethargy
- Vomiting
- Constipation is common and distressing.
- Respiratory depression
- Blurring of vision.
- Urinary retention (especially in elderly male)
- BP may fall.
- ***Idiosyncrasy and allergy Allergic* reactions:**
- Urticaria
- Swelling of lips occur infrequently
- Thrombophlebitis
- ***Apnoea of the newborn:*** *This may occur* when morphine is given to the mother during labour.
- The blood-brain barrier of the foetus is undeveloped.

ADVERSE EFFECTS

- May lead to acute poisoning:
- Stupor or coma.
- Shallow and occasional breathing.
- Cyanosis
- Pinpoint pupil
- Fall in BP and shock
- Pulmonary edema occurs
- Convulsions treated by giving Naloxone 0.4–0.8 mg i.v. repeated every 2–3 min till respiration picks up.
- Tolerance and dependence occurs.

CONTRAINDIACTIONS:

- In asthmatics
- Infants and elderly
- Head injury
- Hypotensive and hypovolemic patients
- Unstable personalities

INTERACTIONS

- Phenothiazines, tricyclic antidepressants, MAO inhibitors, amphetamine and neostigmine potentiate morphine and other opioids, either by retarding its metabolism or by a pharmacodynamic interaction.
- Morphine retards absorption of many orally administered drugs by delaying gastric emptying.

Dose: *10–50 mg oral, 10–15 mg i.m. or s.c. or 2–6 mg i.v.; 2–3 mg* epidural or intrathecal; children 0.1–0.2 mg/kg. i.m. or s.c.

CLASSIFICATION OF OPIOIDS

1. ***Natural opium alkaloids:*** *Morphine, Codeine*
2. ***Semisynthetic opiates****: Diacetylmorphine* (Heroin), Pholcodeine, Ethylmorphine.
3. ***Synthetic opioids:*** *Pethidine (Meperidine),* Fentanyl, Methadone, Tramadol, Dextropropoxyphene.

CODEINE (methyl-morphine):

- Occurs naturally in opium, and is partly converted in the body to morphine.
- It is less potent than morphine (1/10th as analgesic), also less efficacious.
- It is a partial agonist at μ opioid receptor.
- Can relieve mild to moderate pain only.
- However, codeine is more selective cough.
- Subanalgesic doses (10–30 mg) suppress cough
- *Codeine has very low affinity for* opioid receptors.
- The analgesic action has been ascribed to morphine generated by its demethylation by CYP2D6.
- Codeine fails to produce analgesia in subjects with polymorphic CYP2D6 who cannot demethylate codeine.
- However, receptors involved in the anti-tussive action appear to be distinct, because they bind codeine as well as morphine.
- Codeine has good activity by the oral route (oral: parenteral ratio 1:2).
- A single oral dose acts for 4–6 hours.
- Constipation is a prominent side effect when it is used as analgesic.
- Codeine has been used to control diarrhoea.
- Other side effects are milder. The abuse liability is low.
- Though codeine phosphate is water soluble and can be injected, parenteral preparation is not available.

Heroin (Diamorphine, Diacetylmorphine):

- It is about 3 times more potent than morphine.
- More lipid soluble, therefore enters the brain more rapidly, but duration of action is similar.
- It is considered to be more euphorient (especially on i.v. injection) and highly addicting.
- Because of its high potency, it has been favoured in illicit drug trafficking.
- The sedative, emetic and hypotensive actions are said to be less prominent.
- However, it has no outstanding therapeutic advantage over morphine and has been banned in most countries except U.K.

Pholcodeine and Ethylmorphine:

- They have codeine like properties and have been used mainly as anti-tussive and claimed to be less constipating.

Pethidine (Meperidine)

- Pethidine was synthesized as an atropine substitute in 1939, and has some actions like it.
- Though chemically unrelated to morphine, it interacts with μ opioid receptors and its actions are blocked by naloxone.

Pethidine (Meperidine)

- Important differences in comparison to morphine are:

1. Dose to dose 1/10th in analgesic potency; however, analgesic efficacy approaches near to morphine and is greater than codeine.

2. After i.m. injection, the onset of action is more rapid but duration is shorter (2–3 hours).

3. It does not effectively suppress cough.

4. Spasmodic action on smooth muscles is less marked—miosis, constipation and urinary retention are less prominent.

5. It is equally sedative and euphoriant, has similar abuse potential.

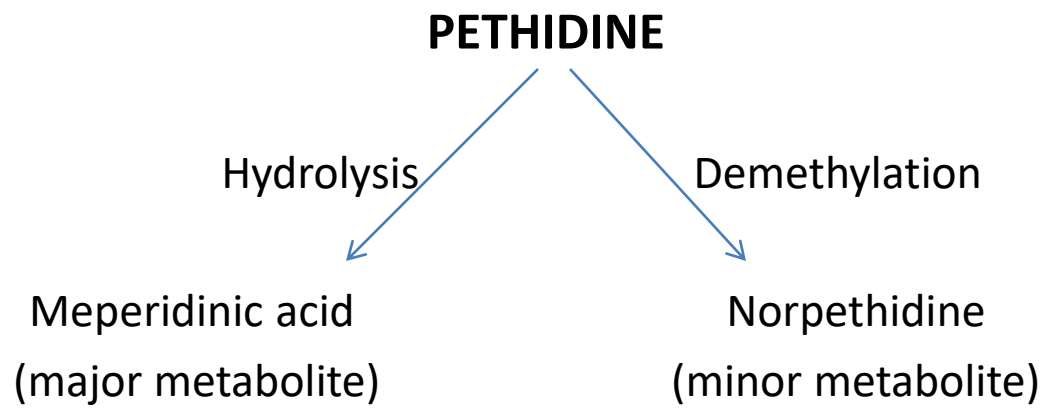
6. Tachycardia (due to antimuscarinic action) occurs instead of bradycardia.

7. It causes less histamine release and is safer in asthmatics.

8. It has local anaesthetic action: corneal anaesthesia is seen after systemic doses.

Pharmacokinetics:

- It is well absorbed, oral: parenteral activity ratio is higher (1/3 to 1/2).
- Pethidine is nearly completely metabolized in liver.
- The plasma t½ is 2–3 hours.
- Acidification of urine increases excretion of unchanged pethidine.



- Both are conjugated with glucuronic acid and excreted in urine.
- ***Side effects:***
- Some atropinic effects (dry mouth, blurred vision, tachycardia) may be noted in addition.
- Overdose of pethidine produces many excitatory effects—tremors, mydriasis, hyperreflexia, delirium, myoclonus and convulsions.
- This is due to accumulation of *norpethidine which has* excitant effects.
- Renal failure patients given repeated doses of pethidine are prone to experience similar effects.
- Nonselective MAO inhibitors interfere with hydrolysis but not with demethylation of pethidine. Here norpethidine is produced in excess and excitement occurs.
- Pethidine injected in patients receiving a selective serotonin reuptake inhibitor (SSRI) may produce the 'serotonin syndrome' *by enhancing 5-HT* release.
- Tolerance and physical dependence develop slowly with pethidine.
- Withdrawal syndrome develops more rapidly.

Uses:

- Pethidine is primarily used as an analgesic (substitute of morphine) and in preanaesthetic medication.
- Not primarily used for cough or diarrhoea.
- It has also been used to control shivering during recovery from anaesthesia.
- Potential adverse effects due to accumulation of norpethidine limit its utility in patients who require repeated dosing.
- It is the preferred opioid analgesic during labour.

Dose: *50–100 mg i.m., s.c. (may cause irritation, local fibrosis on* repeated injection). It is occasionally given orally or i.v.

Fentanyl :

- A pethidine congener, 80–100 times more potent than morphine, both in analgesia and respiratory depression.
- In analgesic doses it produces few cardiovascular effects.
- Cardiac contractility and heart rate are only marginally reduced.

Fentanyl :

- It has less propensity to release histamine.
- Because of high lipid solubility, it enters brain rapidly and produces peak analgesia in 5 min after i.v. injection.
- The duration of action is short: starts wearing off after 30–40 min due to redistribution, while elimination t½ is ~4 hr.
- In the injectable form it is almost exclusively used in anaesthesia.
- *Transdermal* fentanyl has become available for use in cancer/ terminal illness or other types of chronic pain for patients requiring opioid analgesia.
- Buccal use is possible, but not oral.
- DUROGESIC - transdermal patch delivering 12 µg/hr, 25 µg/hr, 50 µg/hr, 75 µg/hr or 100 µg per hour; the patch is changed every 3 days.

Methadone:

- A synthetic opioid, chemically dissimilar but pharmacologically very similar to morphine.
- It has analgesic, respiratory depressant, emetic, anti-tussive, constipating and biliary actions similar to morphine.
- The most important feature of methadone is high oral: parenteral activity ratio (1 : 2) and its firm binding to tissue proteins.
- In single doses it is only slightly more potent than morphine and has comparable duration of action (4–6 hours on i.m. injection).
- But it cumulates in tissues on repeated administration.
- Duration of action is progressively lengthened due to gradual release from these sites.

PHARMACOKINETICS:

- Plasma t½ on chronic use is 24–36 hours.
- Plasma protein binding is 90% and it is metabolized in liver, primarily by demethylation and cyclization.
- Metabolites are excreted in urine.
- Rifampin and phenytoin can cause withdrawal symptoms to appear in methadone dependent subjects by inducing its metabolism.

Methadone:

- Sedative and subjective effects are less intense.
- The abuse potential is rated lower than morphine.
- Tolerance develops more slowly.
- Methadone has been used primarily as substitution therapy for opioid dependence:
- 1 mg of oral methadone can be substituted for 4 mg of morphine, 2 mg of heroin and 20 mg of pethidine.
- Methadone can also be used as an analgesic for the same conditions as morphine.
- **Dose:** 2.5– 10 mg oral or i.m. but not s.c. Sometimes used antitussive.

TRAMADOL:

- This centrally acting analgesic is an atypical opioid which relieves pain by opioid as well as additional mechanisms.
- Its affinity for μ opioid receptor is low, while that for κ and δ is very low.
- Unlike other opioids, it inhibits reuptake of NA and 5-HT, increases 5-HT release, and thus activates monoaminergic spinal inhibition of pain.

TRAMADOL:

- Injected i.v. 100 mg tramadol is equianalgesic to 10 mg i.m. morphine.
- Oral bioavailability of tramadol is good (oral: parenteral dose ratio is 1.4).
- The t½ is 5–6 hours and effects last for 4–6 hrs.
- Tramadol causes less respiratory depression, sedation, constipation, urinary retention and rise in intrabiliary pressure than morphine. It is well tolerated.

SIDE EFFECTS:

- Dizziness, nausea, sleepiness, dry mouth, sweating and lowering of seizure threshold.
- Tramadol should not be given to patients taking SSRI therapy because of risk of 'serotonin syndrome'.

USES:

- Tramadol is indicated for mild-to-moderate short-lasting pain due to diagnostic procedures, injury, surgery, etc, as well as for chronic pain including cancer pain, but is not effective in severe pain.
- Abuse potential is low.
- ***Dose:*** *50–100 mg oral/i.m./slow i.v. infusion (children 1–2 mg/*kg) 4–6 hourly.

OPIOID RECEPTORS

- Morphine and other opioids exert their actions by interacting with specific receptors present on neurones in the CNS and in peripheral tissues.
- Radioligand binding studies divided the opioid receptors into three types:
  - μ, κ and δ
- Each has a specific pharmacological profile and pattern of anatomical distribution. Action depends upon affinity.
- Opioid ligands can interact with different opioid receptors as agonists, partial agonists or competitive antagonists.

ACTIONS OF DIFFERENT OPIOID RECEPTORS

M (mu)	κ (kappa)	δ (delta)
Analgesia	Analgesia	Analgesia
Respiratory depression	Respiratory depression	Respiratory depression
Sedation	Dysphoria, psychomimetic	Affective behaviour
Euphoria, Miosis	Miosis	Reinforcing actions
Muscular rigidity	Sedation	Reduced GI motility
Reduced GI motility	Reduced GI motility	Proconvulsant
Physical dependence	Physical dependence	

- It thus appears that μ and δ receptor responses are quite similar, but those exerted through κ receptor are distinct.
- In certain areas κ actions are antagonistic to μ actions.

NATURE OF INTERACTION OF OPIOID LIGANDS WITH RECEPTORS

Ligand	M (mu)	κ (kappa)	δ (delta)	Analgesic dose (mg)
Morphine	Agonist (S)	Agonist (W)	Agonist (W)	10
Nalorphine	Antagonist (S)	Agonist (M)	----------	----------
Pentazosine	Partial agonist; Partial Antagonist (W)	Agonist (M)	----------	30-60
Buprenorphine	Partial agonist;	Antagonist (M)	----------	0.3-0.4
Naloxone	Antagonist (S)	Antagonist (M)	Antagonist (W)	----------
Naltrexone	Antagonist (S)	Antagonist (S)	Antagonist (W)	----------
Met/leu enkephalin	Agonist (M)	----------	Agonist (S)	----------
β-endorphin	Agonist (S)	----------	Agonist (S)	----------

μ RECEPTOR

- It is the major receptor mediating actions of morphine and its congeners.
- Endogenous ligands for μ receptor—peptides called *Endomorphins 1 and 2, have* only recently been found in mammalian brain.
- They produce biological effects ascribed to μ receptor.
- Other opioid peptides *viz. β-endorphin,* enkephalins and dynorphins bind to μ receptor with lower affinity.
- High density of μ receptors has been detected in thalamus, nucleus tractus solitarious and nucleus ambiguus.
- Two subtypes of μ receptor have been proposed:
- μ1: Has higher affinity for morphine, mediates supraspinal analgesia and is selectively blocked by naloxonazine.
- μ2: Has lower affinity for morphine, mediates spinal analgesia, respiratory depression and constipating action.

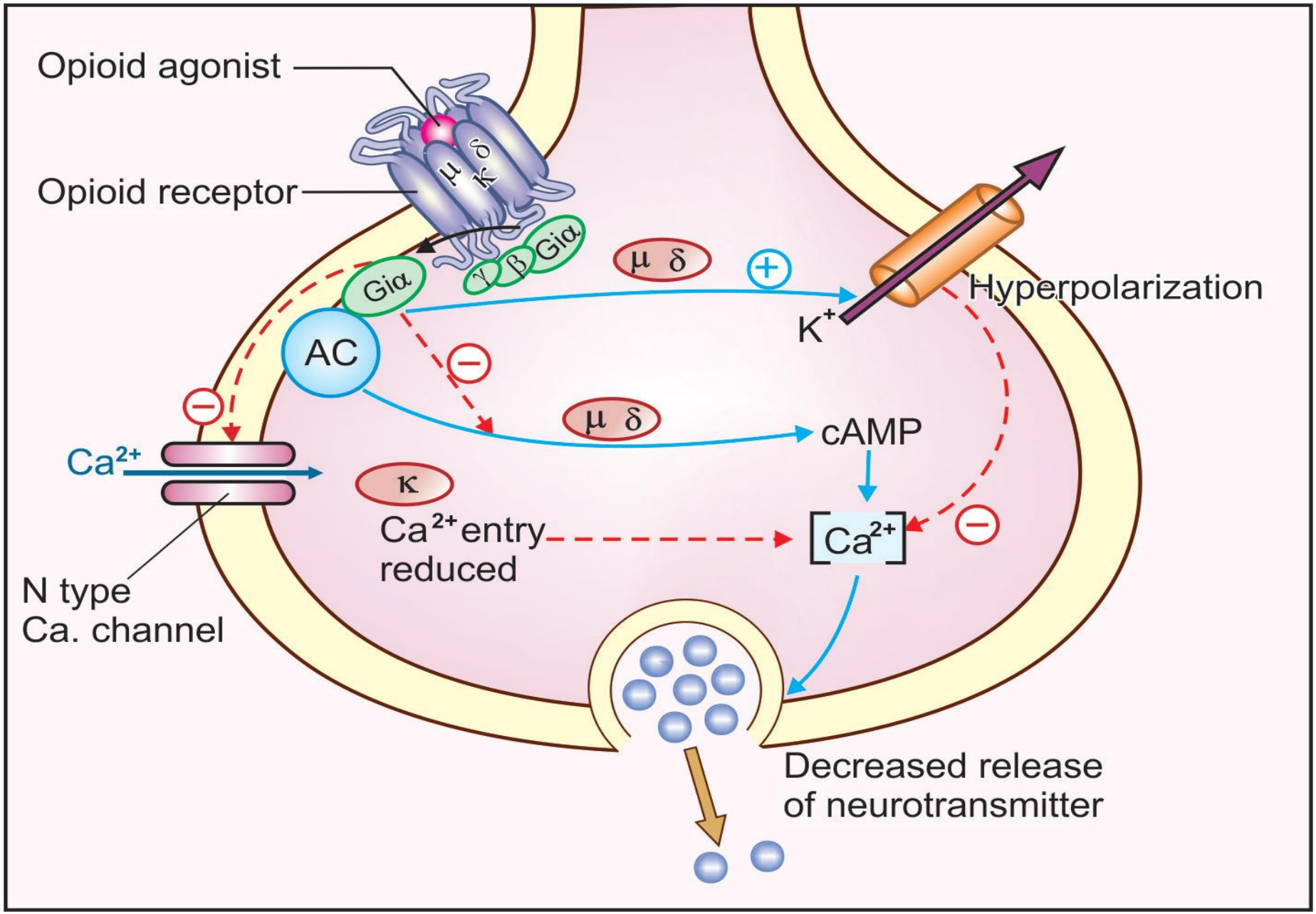
κ RECEPTOR

- This receptor is defined by its high affinity for ketocyclazocine and dynorphin A;
- The latter is considered to be its endogenous ligand.
- *Norbinal-torphimine is a selective κ* antagonist.
- Two subtypes of κ receptor – κ1 and κ3 are functionally important.
- Analgesia caused by κ agonists is primarily spinal (through κ1 receptor).
- However, κ3 receptors mediate lower ceiling supraspinal analgesia.

δ RECEPTOR

- This receptor has high affinity for leu/met enkephalins which are its endogenous ligands.
- The δ mediated analgesia is again mainly spinal.
- δ receptors are present in dorsal horn of spinal cord.
- The limbic areas are rich in δ receptors.
- The pro-convulsant action is more prominent in δ agonists.
- Myenteric plexus neurones express high density of δ receptors, which mediate reduced g.i. motility.
- *Naltrindole is a selective* δ antagonist.

OPIOID RECEPTOR TRANSDUCER MECHANISMS



OPIOID ANTAGONISTS

Classification: 3 types

- **1. *Agonist-antagonists (κ analgesics)***

  Eg: Nalorphine, Pentazocine, Butorphanol

- **2. Partial/weak μ agonist + κ antagonist**

  Eg: Buprenorphine

- **3. *Pure antagonists***

  Eg: Naloxone, Naltrexone, Nalmefene

- Clinically, the agonist-antagonist (agonist at one opioid receptor, antagonist at another) and partial/weak agonist (low intrinsic activity) opioids are analgesics of limited efficacy equivalent to low doses of morphine.
- They cause low ceiling respiratory depression and have lower abuse potential.

NALORPHINE – It is N-allyl-normorphine.

- It was the first opioid antagonist introduced in 1951 which could reverse morphine action.
- Later it was found to have agonistic action on κ receptor as well, producing lower ceiling analgesia.
- It is not used clinically because of dysphoric and psychotomimetic effects.

PENTAZOCINE

- It is the first agonist-antagonist to be used as an analgesic.
- It has weak μ antagonistic and more marked κ agonistic actions.
- The profile of action is similar to morphine.
- Analgesia caused by pentazocine is primarily spinal (κ1) and has a different character than that caused by morphine.
- Parenterally 30 mg pentazocine = 10 mg morphine.
- Sedation and respiratory depression is 1/3 to 1/2 of morphine at lower doses.
- Tachycardia and rise in BP are produced at higher doses.
- Biliary spasm and constipation are less severe.
- Vomiting is less frequent. Other side effects are sweating and lightheadedness.

PENTAZOCINE

- Subjective effects are pleasurable (morphine like) at lower doses.
- At higher doses, psychomimetic effects appear.
- Tolerance, psychological and physical dependence to pentazocine develops on repeated use.
- 'Drug seeking' occurs.
- Abuse liability is rated lower than morphine.
- Injected in morphine dependent subjects, it precipitates withdrawal.

PHARMACOKINETICS:

- Pentazocine is effective orally, though considerable first pass metabolism occurs.
- Oral: parenteral ratio is 1 : 3.
- It is oxidized and glucuronide conjugated in liver and excreted in urine.
- Plasma t½ is 3–4 hours, duration of action of a single dose is 4–6 hours.

DOSE:

- *Oral dose: 50–100 mg, efficacy like codeine.*
- *Parnteral dose: 30–60 mg i.m., s.c.,*

USES:

- Postoperative and moderately severe pain in burns, trauma, fracture, cancer, etc.

BUPRENORPHINE: It is a synthetic thebaine congener.

- Highly lipid-soluble μ analgesic that is 25 times more potent than morphine.
- The onset of action is slower and duration longer.
- After a single dose, analgesia lasts for 6–8 hours.
- With repeated doses, duration of action is up to 24 hrs (tissue accumulation).

ADVERSE EFFECTS:

- Sedation, vomiting, miosis, cardiovascular effects and constipation (less).
- Postural hypotension is prominent.
- Respiratory depression (and analgesia) exhibit ceiling effect.
- Lower degree of tolerance, physical and psychological dependence (chronic).
- Drug seeking is present. Abuse liability is rated lower than morphine.
- Naloxone (high dose) can prevent buprenorphine effects.

PHARMACOKINETICS:

- Buprenorphine has good efficacy by sublingual route.
- It is highly plasma protein bound and remains in tissues for several days.
- t½ is 40 hours. It is mostly excreted unchanged in bile and finds its way out of the body in faeces.
- **Dose:** 0.3–0.6 mg i.m., s.c. or slow i.v., also sublingual 0.2–0.4mg 6–8 hourly.

BUPRENORPHINE uses:.

- It is indicated for long-lasting painful conditions. e.g. cancer pain.
- It has also been recommended for premedication, postoperative pain, in myocardial infarction and in the treatment of morphine dependence.

NALTREXONE

- It is chemically related to naloxone and is another pure opioid antagonist, that is devoid of subjective and other agonistic effects, but very high doses have caused unpleasant feelings in some individuals.
- It is more potent than naloxone.
- Naltrexone differs from naloxone in being orally active and having a long duration of action (1–2 days).
- It is suitable for 'opioid blockade' therapy of postaddicts: 50 mg/day is given orally so that if the subject takes his/her usual shot of the opioid, no subjective effects are produced and the craving subsides.
- Alcohol craving is also reduced by naltrexone.
- Nausea is a common side effect; another is headache.
- High doses can cause hepatotoxicity.
- **DOSE: 50 mg.**

NALOXONE

- It is N-alylnor-oxymorphone and a competitive antagonist on all types of opioid receptors.
- However, it blocks μ receptors at much lower doses.
- It is devoid of any kind of agonistic activity even at high doses.
- No subjective or autonomic effects are produced in individuals who have not received an opioid.
- No physical/psychological dependence or abstinence syndrome was observed.
- Injected intravenously (0.4–0.8 mg), it antagonizes all actions of morphine.
- At 4–10 mg dose it also antagonizes the agonistic actions of nalorphine, pentazocine, etc.
- Actions of buprenorphine are prevented but not effectively reversed by naloxone.
- Naloxone 0.4 mg i.v. precipitates morphine withdrawal in dependent subjects: the syndrome lasts for 2–3 hours; 5 mg or more is required to precipitate nalorphine and pentazocine withdrawal.
- Naloxone also blocks the actions of endogenous opioid peptides.
- Naloxone does not produce hyperalgesia or other effects in normal individuals.

NALOXONE: It blocks *placebo, acupuncture and stress-induced analgesia.*

- It partly antagonizes respiratory depression produced by N_2O and diazepam.

PHARMACOKINETICS:

- Naloxone is inactive orally because of high first pass metabolism in liver.
- Injected i.v. it acts in 2–3 min. Metabolism is mainly by glucuronidation.
- Plasma t½ is 1 hour in adults and 3 hours in newborns.
- Adverse effects of naloxone are uncommon; may include rise in BP and pulmonary edema.

DOSE: 0.4 mg in 1 ml (adult) and 0.04 mg in 2 ml (infant).

USES: Naloxone is the drug of choice for morphine poisoning

- **Dose**: 0.4–0.8 mg i.v. every 2– 3 min: max 10 mg.
- For reversing neonatal asphyxia due to opioid use during labour.
- To treat overdose with other opioids and agonist-antagonists (except buprenorphine).
- Diagnosis of opioid dependence.
- It also partially reverses alcohol intoxication.
- To reverse respiratory depression due to intraoperative use of opioids: 0.1–0.2 mg i.v.