OPIOID ANALGESICS (NARCOTIC ANALGESICS)

- **Analgesia: Relief of pain without loss of conciousness.**
- **Opiates: From Poppy plant (morphine, codeine etc.)**
- **Opioid drugs: natural opiates + synthetic morphine-like drugs.**

OPIOID ANALGESICS

- **Opioid Analgesics:**
- **Morphine (PROTOTYPE AGENT)**
- **Heroin**
- **Codeine**
- **Hydromorphone**
- **Oxymorphone**
- **Oxycodone**
- **Dextromethorphan**
- **Meperidine (pethidine)**
- **Alphaprodine**
- **Fentanyl**
- **Sufentanil**

- Diphenoxylate
- Loperamide
- Methadone
- Propoxyphene

- Mixed Agonists and Antagonists
- Pentazocine
- Nalbuphine
- Butorphanol
- Buprenorphine

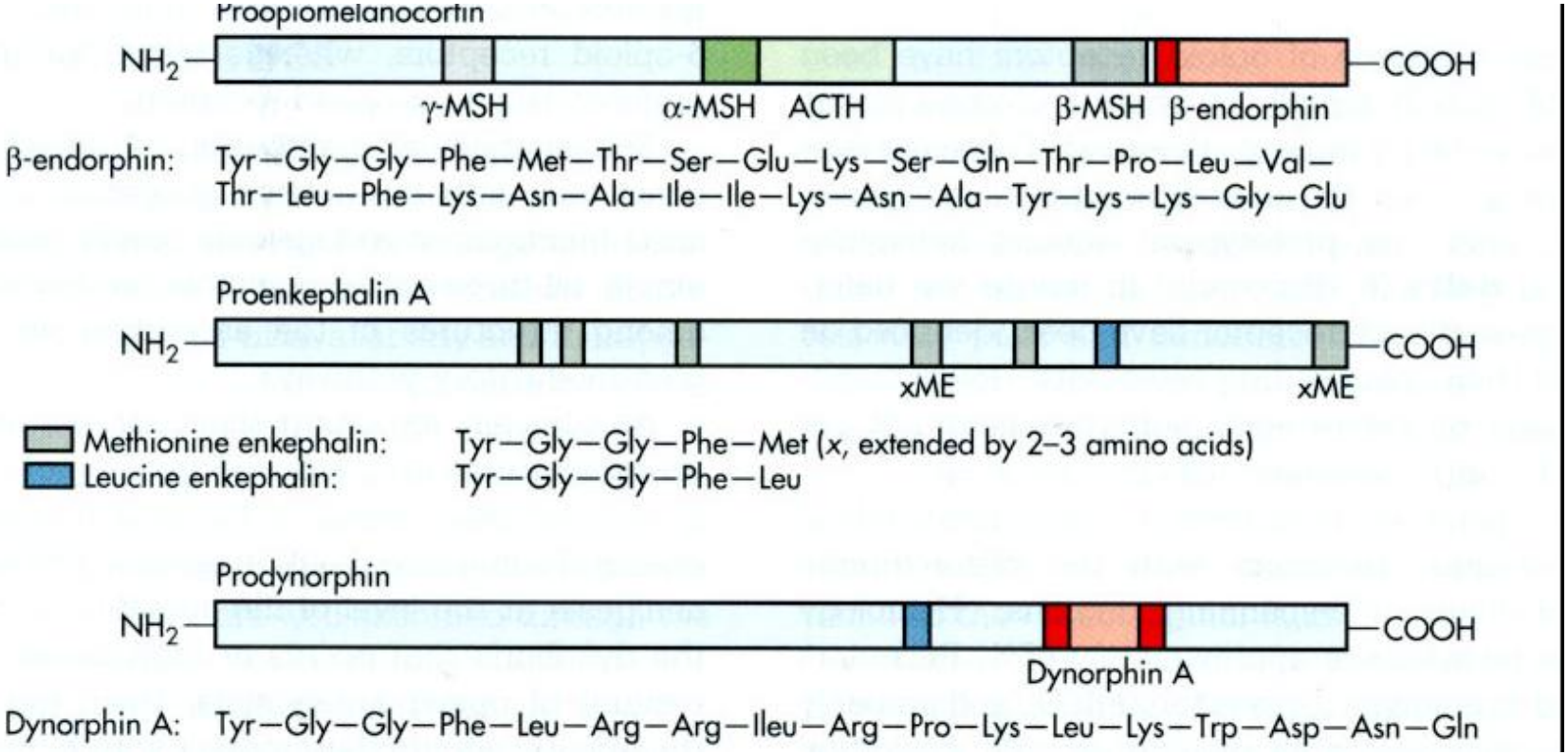
- Opioid Antagonists
- Naloxone
- Naltrexone
- Nalmephine

I. Introduction

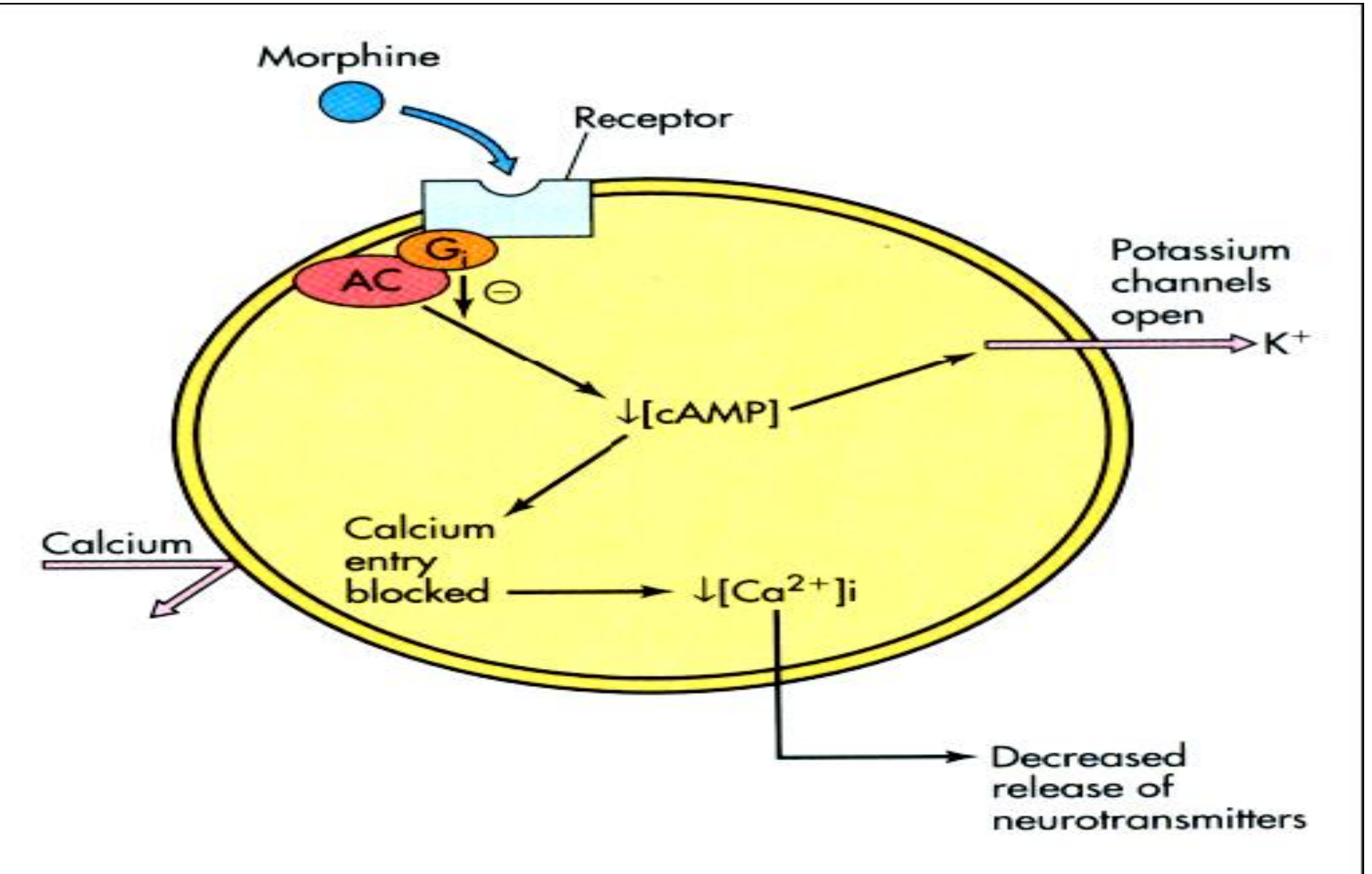
- A. The opioid agonists and antagonists act at specific receptor sites to produce their pharmacological effects.
- B. Opioid Receptors: μ (μ1, μ 2)
  κ (κ1, κ2, κ3)
  δ
- C. Endogenous Agonists:(stimulate opioid receptors)
  - [Met]enkephalin: Tyr-Gly-Gly-Phe-Met
  - [Leu]enkephalin: Tyr-Gly-Gly-Phe-Leu
  - Beta Endorphin: a 31 amino acid peptide with [Met]enkephalin at N-terminal sequence
  - Dynorphin: a 17 amino acid peptide with [Leu]enkephalin at N-terminal sequence

- D. Three genes have been identified which code for opioid peptides
  - Beta endorphin and ACTH
  - Enkephalins
  - Dynorphins
- These neuropeptides are released by stress and appear to modulate the release of other neurotransmitters.

Opioid Genes



Mechanisms of Action



Mechanisms of Action

Morphine impairs the normal sensory awareness and response to tissue injury through:

- Blockade of calcium channels which leads to decreased release of substance P and glutamate from the 1st neuron of the sensory pathway (in substantia gelatinosa and medulla).
- Decreased c-AMP which leads to opening of K-channels and hyperpolarisation of the 2nd neuron of the sensory pathway.

- Effects due to μ-receptor stimulation:

  Supraspinal analgesia, euphoria, respiratory depression, miosis, decreased GIT motility, physical dependence.

- Effects due to κ-receptor stimulation:

  Spinal analgesia, dysphoria, respiratory depression (less), miosis (less).

Morphine

- Effective orally, but is much less effective than when given parenterally due to first-pass metabolism in the liver.

- Metabolism involves glucuronide formation, the product of which is excreted in the urine.

- **1. Central Nervous System Effects**

  • Morphine has mixed depressant and stimulatory actions on the CNS.

  - depressant effects predominate in man.

  - excitatory effects predominate in cats and horses.

a) Analgesia:

- - drowsiness is common
- - continuous dull pain relieved more effectively than sharp intermittent pain
- - most patients indicate that they can still feel the pain, but that it no longer bothers them
- - morphine is an agonist at μ and κ opioid receptors.

b) Euphoria

- the euphoric effects appear to depend upon: the individual; why the drug was administered; and how the drug was administered.

c) Emesis

- morphine directly stimulates the chemoreceptor trigger zone, but later depresses the vomiting center in the brain stem. This center is outside the blood/brain barrier.

d) antianxiety

- opiates appear to relieve anxiety; patients and addicts often appear to be in a state of dreamy indifference.

e) Cough reflex is inhibited.

- dextromethorphan will suppress cough but will not produce analgesia.

f) Respiration is depressed

- due to a direct effect on the brain stem respiratory center.
- death from narcotic overdose is nearly always due to respiratory arrest.
- the mechanism of respiratory depression involves:
  - a reduction in the responsiveness of the brain stem respiratory centers to an increase in pCO_2.
  - depression of brain stem centers that regulate respiratory rhythm.

-Cause bronchoconstriction (due to histamine release)

g) Other effects

- Morphine causes the release of histamine and abolishes hunger.

  - causes the body to feel warm and the face and nose to itch.

- Pupils are constricted (pinpoint pupil).

  - due to stimulation of the nuclei of the third cranial nerves.

  - tolerance does not develop to this effect.

2. Cardiovascular Effects

- Postural orthostatic hypotension.

  - due primarily to decreased V.M.C. activity leadind to peripheral vasodilation, which may be due in part to histamine release.

- In congestive heart failure, morphine decreases the left ventricular workload and myocardial oxygen demand.

3. Endocrine Effects

- Increases prolactin secretion
- Increases vasopressin (ADH) secretion (oliguria).
- Decreases pituitary gonadotropin (LH & FSH) secretion.
- Decreases stress induced ACTH secretion.

4. Gastrointestinal Tract Effects

- Constipation (tolerance does not develop to this effect).
- Several of these agents can be used in the treatment of diarrhea.

They decrease GIT motility and peristalsis

- **B. Adverse Reactions**
- Generally direct extensions of their pharmacological actions.
- 1. respiratory depression, apnea
- 2. nausea and vomiting
- 3. dizziness, orthostatic hypotension, edema
- 4. mental clouding, drowsiness
- 5. constipation, ileus
- 6. biliary spasm (colic)
- 7. dry mouth
- 8. urine retention, urinary hesitancy
- 9. hypersensitivity reactions (contact dermatitis, urticaria)

- **C. Precautions**
- 1. respiratory depression, particularly in the newborn
- 3. orthostatic hypotension
- 4. histamine release (asthma, shock)
- 5. drug interactions (other CNS depressants)
- 6. tolerance and cross tolerance to other opioids:

  - analgesia, euphoria, nausea and vomiting, respiratory depression
- 7. dependence (psychological & physiological)

- Therapeutic uses:

  - Analgesia: myocardial infarction, terminal cancer, surgery, obstetrical procedures

  - Dyspnoea due to pulmonary oedema

  - Severe diarrhoea.

II. Other Opioid (Narcotic) Analgesics

- **A. Heroin (diacetyl morphine)**
- 1. μ- agonist
- 2. Heroin is more lipid soluble than morphine and about 2½ times more potent
- 3. It enters the CNS more readily
- 4. It is a schedule I drug and is not used clinically, but it is a drug of abuse.

- **B. Codeine**
- 1. From opium or synthesized by methylation of morphine
- 2. Has a much better oral /parenteral absorption ratio than morphine.
- 3. Effective for mild to moderate pain, cough, diarrhoea.
- 4. Metabolized in part to morphine by O-demethylation.
- 5. μ- receptor agonist.
- 6. Appears to have a more potent histamine-releasing action than does morphine.
- 7. Dependence liability of codeine is somewhat less than that of morphine, but it is still classified as a Schedule II drug.
- 8. 1/12 as potent as morphine

- **C. Dextromethorphan (Romilar)**
- 1. Excellent oral antitussive
- 2. No analgesic effect
- 3. No GI effects
- 4. No respiratory depression

- **D. Meperidine (Pethidine)**
- 1. Produces analgesia, sedation, euphoria and respiratory depression.
- 2. Less potent than morphine, 80-100 mg meperidine equals 10 mg morphine.
- 3. Shorter duration of action than morphine (2-4 hrs).
- 4. Meperidine has greater excitatory activity than does morphine and toxicity may lead to convulsions.
- 5. Meperidine appears to have weak atropine-like activity (mydriasis).
- 6. Does not constrict the pupils to the same extent as morphine.
- 7. Does not cause as much constipation as morphine.

  8. Purely synthetic μ- agonist
- 9. Not an effective antitussive agent.

- 10. Adverse reactions to Meperidine
  - respiratory depression
  - tremors
  - delirium and possible convulsions
  - dry mouth

- **E. Alphaprodine (Nisentil)**
- 1. Related chemically and pharmacologically to meperidine.
- 2. More rapid onset and shorter duration of action than meperidine.
- 3. Good oral effectiveness.
- 4. Produces less nausea, vomiting and constipation than morphine.

- **F. Fentanyl (Sublimaze)**
- 1. μ- agonist, related chemically to meperidine.
- 2. Approximately 80 times more potent than morphine analgesia and respiratory depression.
- 3. Duration of action very short (t1/2 20 min).
- 4. Used for neuroleptanalgesia: Fentanyl & Droperidol (Innovar).

G. Sufentanil (Sufenta)

- 1. A synthetic opioid related to fentanyl.
- 2. About 7 times more potent than fentanyl.
- 3. Has a slightly more rapid onset of action than fentanyl.

- **H. Methadone (Dolophine)**
- 1. Pharmacology and analgesic potency similar to morphine; μ- receptor agonist.
- 2. Very effective following oral administration.
- 3. Longer duration of action than morphine due to plasma protein binding (t1/2 approximately 25 hrs).
- 4. Used in methadone maintenance programs for drug addicts and for opiate withdrawal. Opiate withdrawal is more prolonged but is less intense than it is following morphine or heroin.

- **I. Propoxyphene (Darvon)**
- 1. A methadone analog.
- 2. Used orally to relieve mild to moderate pain.
- 3. A typical opioid, it does not possess anti-inflammatory or antipyretic actions, but has little or no antitussive activity.
- 4. Has a low addiction potential
- 6. The most common adverse side effects are:
    - dizziness, drowsiness, and nausea and vomiting.
- 7. Withdrawal symptoms have occurred in both adults and in neonates following use of the drug by the mother during pregnancy.
- 8. CNS depression is additive with other CNS depressants.

III. Mixed Narcotic Agonists/Antagonists

These drugs all produce analgesia, but have a lower potential for abuse and do not produce as much respiratory depression.

A. Pentazocine (Talwin)

1. κ- agonist (analgesia) and μ-antagonist (less respiratory depression).
2. Orally, it has about the same analgesic potency as codeine.
3. In contrast to morphine, cardiac workload tends to increase due to an increase in pulmonary arterial and cerebrovascular pressure. Blood pressure and heart rate both also tend to increase.
4. Adverse reactions to Pentazocine
   - Nausea, vomiting, dizziness.
   - Psychotomimetic effects, such as dysphoria, nightmares and visual hallucinations.
   - Constipation is less marked than with morphine.

- can precipitate withdrawal in addicts

- **B. Nalbuphine (Nubain)**

- 1. Resembles pentazocine pharmacologically.
- 2. Like morphine, nalbuphine reduces myocardial oxygen demand. May be of value following acute myocardial infarction due to both its analgesic properties and reduced myocardial oxygen demand.
- 3. Most frequent side effect is sedation.

- **C. Butorphanol (Stadol)**

  1. Resembles pentazocine pharmacologically.

  2. 3.5 to 7 times more potent than morphine.

  3. Produces respiratory depression, but psychotomimetics are rare.

- **D. Buprenorphine (Temgesic)**
- 1. A partial agonist at μ-receptor.

  2. 200 times more potent than morphine.
- 3. Duration of action only slightly longer than morphine, but respiratory depression and miosis persist well after analgesia has disappeared.
- 4. Low potential abuse, but can precipitate withdrawal in addicts.
- 5. Approximately 96% of the circulating drug is bound to plasma proteins.

IV. Opiate Antagonists

Opiate antagonists have no agonist properties. They are utilized to reverse opiate induced respiratory depression and to prevent drug abuse.

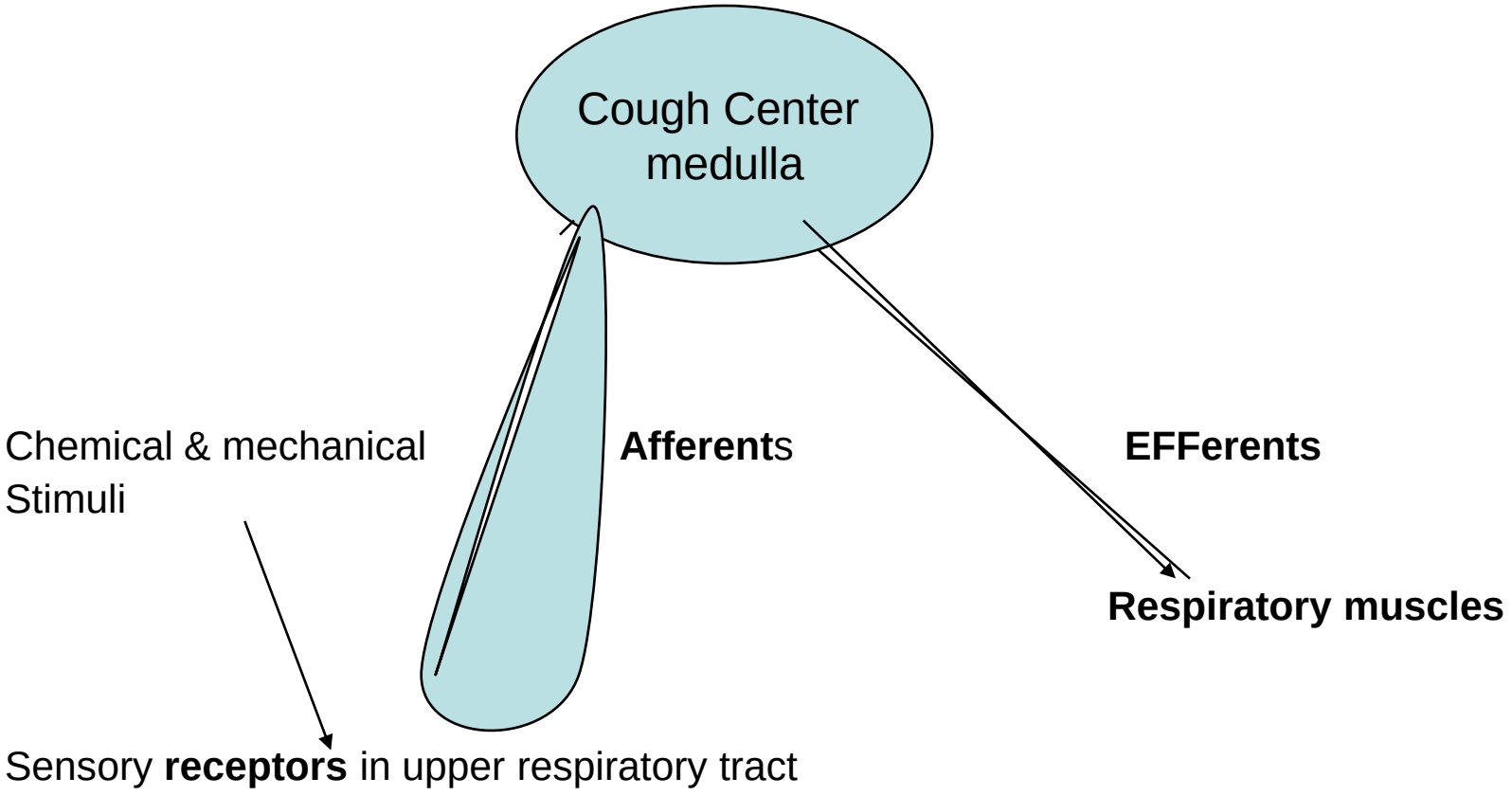
- **A. Naloxone (Narcan)**
  1. Pure opiate antagonist at all opioid receptors
  2. Given parenterally -Short duration of action (1-4 h)
  3. Can precipitate withdrawal in addicts.
- **B. Naltrexone**
  1. Oral pure opioid antagonist
  2. Long duration of action
  3. Contraindicated in liver disease
  4. Used in late stages of opioid addiction treatment (also in treatment of alcoholism).

- Nalmefene:

  Long-acting parenteral opioid antagonist.

Antitussives

- Antitussives: against cough
- Coughing is a protective reflex



- Antitussives depress cough center, therefore depress the cough reflex.
- Antitussives include:

1. Opioids:

Codeine, dextromethorphan, hydrocodone, hydromorphone.

They are opioid agonists against dry cough.

They are of low abuse potential.

Side effects include: drowsiness and constipatiopn.

- Non-opioids: e.g. butamirate citrate which depress the cough center.
- Peripherally acting antitussives: These prevent irritation of sensory receptors in the upper respiratory tract. Local anesthetics also depress the cough center. They include:

  a) demulcents: liquorice, honey

  b) local anesthetics: benzonatate

N.B.: Antitussives should not be used in productive cough.

Protussives

- **Protussives are for wet cough.**
- **A) Steam inhalations (alone or with compound benzoin or menthol or eucalyptus oil).**

  These are demulcents and they reduce viscosity of sputum.

  B) Expectorants: e.g. Guaifensin

  These are demulcents and they reduce viscosity of sputum.

  C) Mucolytics e.g. Ambroxol

  - systemic mucolytics

  - break disulphide bonds of fibres of sputum (reduce viscosity of sputum).

  - have no effect on gastric barriers.