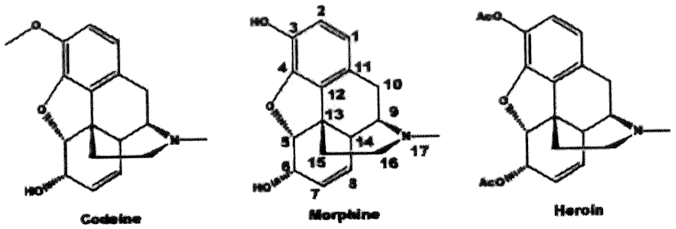
structures



- **Esterification of the phenolic functions, such as in the formation of diacetylmorphine, results in a compound with increased lipid solubility and increased potency and toxicity.**

MECHANISM OF TOXICITY

- **The mechanism of opiate toxicity is an extension of its pharmacology and is directly related to interaction with stereo-specific and saturable binding sites or receptors in the CNS and other tissues.**
- **These receptors are classified according to the empirical observations noted for the variety of opioid effects.**
- **The opioid receptors are biologically active sites of several endogenous ligands, including the two pentapeptides, methionine-enkephalin and leucine-enkephalin.**

- **Several larger polypeptides that bind to opioid receptors,**
- **such as ß-endorphin, are the most potent of the endogenous opioid-like substances.**
- **In addition, three receptor classes have been identified:**

In non-Western medicine, opium refers to the dried capsule from which the latex has been extracted.

Collectively, the term endorphin refers to the three families of endogenous opioid peptides: the enkephalins, the dynorphins, and the

- *ß-endorphins.*

- **1. Compounds that selectively bind to the mu – receptor(μ) exhibit morphine-like analgesia, euphoria, respiratory depression, miosis, partial gastrointestinal (GI) inhibition, and sedative effects.**

- **2. Narcotic antagonists such as :**
- **pentazocine, nalorphine, and levorphanol appear to bind to the kappa- receptor(k) , although analgesia, sedation, delusion, hallucinations (psychotomimesis), GI inhibition, and miotic effects still persist.**

- 3. Pentazocine and nalorphine are also described as having affinity for the delta- receptors (δ) although this binding is primarily associated with dysphoria and mood changes (inhibition of dopamine release).

- The sigma receptor (σ), purported to have affinity for pentazocine, was once understood to represent an opioid receptor.

TOXICOKINETICS

- Morphine is rapidly absorbed from an oral dose and from i.m. and s.c. injections.
- Peak plasma levels occur at 15 to 60 min and 15 min, respectively.
- Morphine is metabolized extensively, with only 2 to 12% excreted as the parent molecule, while 60 to 80% is excreted in the urine as the conjugated glucuronide.
- Heroin is rapidly biotransformed, first to monoacetylmorphine and then to morphine.

- Both heroin and mono- acetylmorphine disappear rapidly from the blood ($t_{1/2}$ = 3 min, 5 to 10 min, respectively).
- Thus, morphine levels rise slowly, persist longer, and decline slowly.
- Codeine is extensively metabolized, primarily to the 6-glucuronide conjugate.
- About10 to 15% of a dose is demethylated to form morphine and norcodeine conjugates.
- Therefore, codeine, norcodeine, and morphine in free and conjugated form appear in the urine after codeine ingestion.

SIGNS AND SYMPTOMS OF CLINICAL TOXICITY

- Effect on mood, movement, and behavior correlate with interaction with receptors in the globus pallidus
- mental confusion and euphoria (or dysphoria) alter neuronal activity in the limbic system.
- Hypothalamic effects are responsible for hypothermia.
- Miosis (pin point pupils) is thought to occur from-receptor stimulation of the oculomotor nerve.

- The clinical presentation of the opioid toxidrome (triad) is characterized by
- 1-CNS depression (coma), 2-miosis, and
- 3-respiratory depression.

Miosis is generally an encouraging sign, since it suggests that the patient is still responsive.

Respiratory depression is a result of depressed brain stem and medullary respiratory centers responsible for maintenance of normal rhythm.

- Mu-receptor agonists depress respiration in a dose dependent manner and can lead to respiratory arrest within minutes.

- Fifty percent of acute opioid overdose is accompanied by a frothy, non-cardiogenic, pulmonary edema, responsible for the majority of fatalities.

- The condition involves:
- loss of consciousness and hypoventilation, probably resulting from hypoxic, stress-induced, pulmonary capillary fluid leakage.

- Peripheral effects include bradycardia, hypotension, and decreased GI motility.
- Urine output also diminishes as a consequence of increased antidiuretic hormone (ADH) secretion.

CLINICAL MANAGEMENT OF ACUTE OVERDOSE

- Maintenance of vital functions, including respiratory and cardiovascular integrity ,is of paramount importance in the clinical management of acute opioid toxicity.
- Gastric lavage and induction of emesis are effective if treatment is instituted soon after ingestion.
- It is possible to reverse the respiratory depression with opioid antagonists.