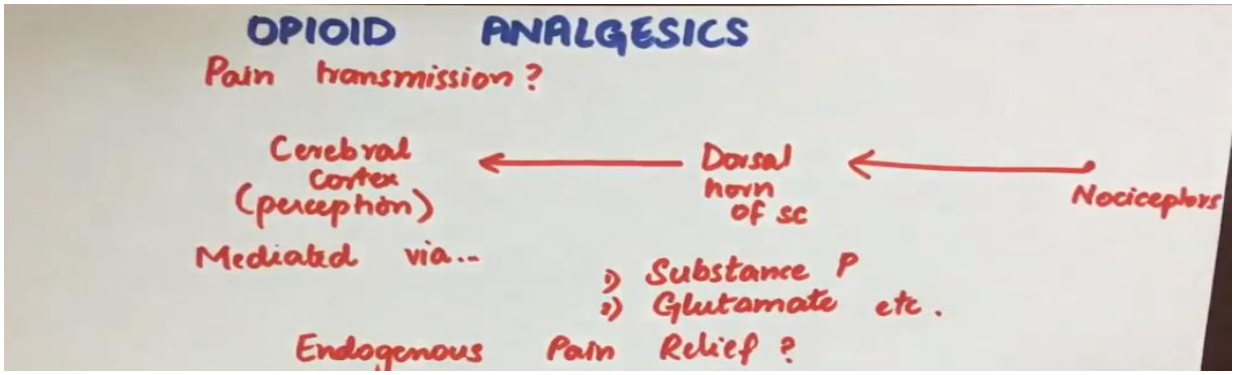
Opioid agents

Pain or algesia is an unpleasant subjective sensation. It cannot be easily defined. Pain is a warning signal and indicates that there is an impairment of structural and functional integrity of the body

Pain may be acute or chronic. Acute pain may result from wounds, irritants, burns or from ischaemia. The cause is usually well defined.

In chronic pain the origin may not be well defined. Example: Pain due to arthritis, cancers and neuropathic pain



Analgesic

Analgesic is a drug which relieves pain without loss of consciousness. Analgesics only afford symptomatic relief from pain without affecting the cause

Analgesics are of 2 classes.

- Opioid or morphine type of analgesics
- Non-opioid or aspirin type of analgesics

'Opioid' is the term used for drugs with morphine-like actions. They were earlier called narcotic analgesics.

CLASSIFICATION OF OPIOIDS

1. *Natural opium alkaloids:* Morphine, Codeine

2. *Semisynthetic opiates*: Diacetylmorphine (Heroin), Pholcodeine.
Many others like—Hydromorphone, Oxymorphone,
Hydrocodone, Oxycodone, are not used in India.

3. *Synthetic opioids:* Pethidine (Meperidine), Fentanyl, Methadone,
Dextropropoxyphene, Tramadol.

Morphine

Morphine is the most important alkaloid of opium. Many new opioids with actions similar to morphine have been synthesized. But none of them are superior to morphine as an analgesic.

Morphine and other opioids produce their effects by acting on specific opioid receptors. These receptors are abundant in the CNS and other tissues.

The opioid receptors are *mu* (μ), *kappa* (k) and *delta* (δ).

It is found that there are 3 families of endogenous opioid peptides released in the body is response to pain *viz* the *enkephalins*, the *endorphins* and the *dynorphins*.

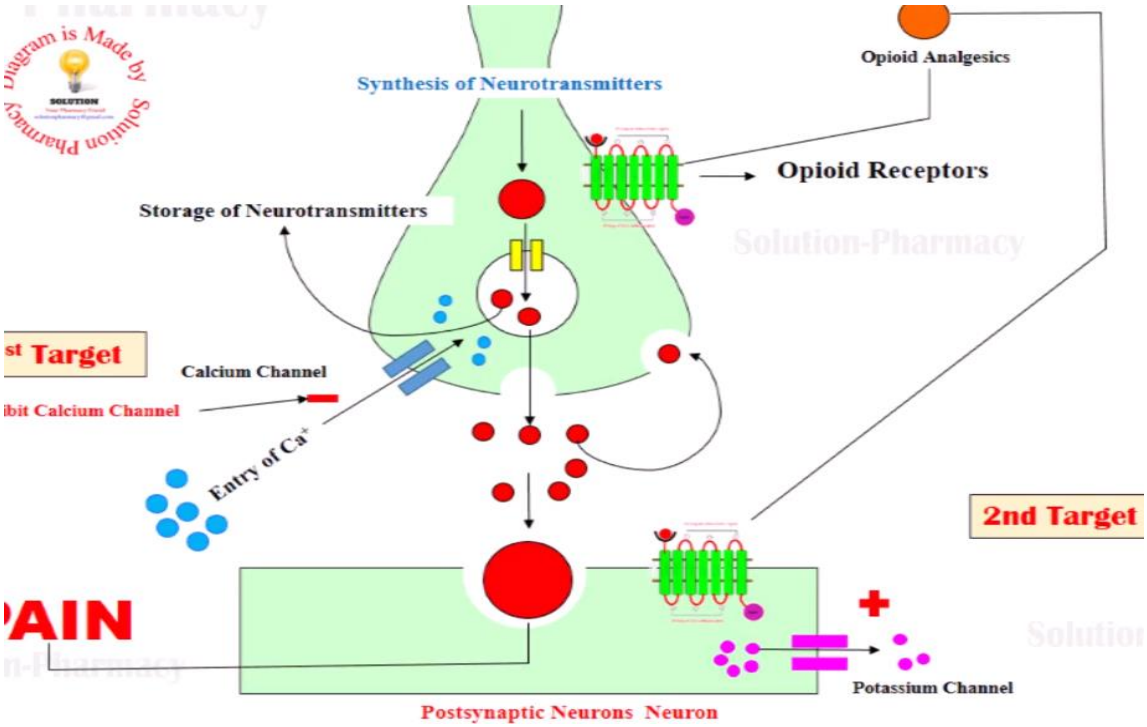
This indicates that we have a natural system in the body that releases various opioid peptides in response to pain.

These opioid peptides act on opioid receptors and relieve pain. Most pharmacological effects of opioids including analgesia, sedation, euphoria, respiratory depression, miosis and constipation are mediated through μ receptors.

All opioid receptors are G-protein-coupled receptors. Stimulation of these receptors inhibits adenylyl cyclase resulting in decreased intracellular cAMP formation.

They also facilitate the opening of K+ channels leading to hyperpolarisation and inhibit the entry of calcium into the cell. In addition to this they inhibit the opening of calcium channels. All these result in a decrease in the intracellular calcium which, in turn, decrease the release of neurotransmitters.

Various neurotransmitters including dopamine, glutamate, GABA, NA, 5HT and substance P are involved in transmission of pain impulses.



Pharmacological Actions

Central Nervous System

1. *Analgesia* Morphine is a potent analgesic and relieves pain without loss of consciousness. Dull aching visceral pain is relieved better than sharp pricking pain But in higher doses it relieves even the severe pain .Morphine alters both the perception and reaction to pain. It raises the pain threshold and thus increases the capacity to tolerate pain. Further, it alters the emotional reaction to pain. Euphoria and sedation also contribute to its analgesic effects

Respiration Morphine produces significant respiratory depression. It directly depresses the respiratory centre in the brainstem. This action is dose dependent

Nausea and emesis Morphine directly stimulates the CTZ in the medulla causing

nausea and vomiting. In higher doses it depresses the vomiting centre and hence there is no vomiting in poisoning

Pupils Morphine produces miosis resulting in a characteristic pinpoint pupil in high doses
Vagus Morphine stimulates vagal centre causing bradycardia.

GIT

Opioids decrease the motility of the gut. *Stomach* Gastric motility is decreased resulting in increased gastric emptying time.

Pharmacokinetics

Given orally, absorption of morphine is slow and incomplete. Morphine undergoes extensive first pass metabolism. Bioavailability is 20 to 40%. Some opioids are also given as rectal suppositories while highly lipid soluble opioids are available as transdermal preparation.

Other Opioids

Heroin or diamorphine or diacetyl morphine is converted to morphine in the body. It has higher lipid solubility because of which euphoric effects are faster and greater resulting in higher abuse potential.

Levorphanol is similar to morphine but it is longer acting.

Codeine is a naturally occurring opium alkaloid. Codeine depresses the cough centre in subanalgesic doses. It is effective orally and is well-absorbed.

It is less potent (one-sixth) than morphine as an analgesic (60 mg codeine = 10 mg morphine).
It produces less respiratory depression and is less constipating. Codeine has less addiction liability and tolerance is uncommon.

Hence codeine is used as an antitussive. It is well-absorbed when given orally compared to morphine. Duration of action is 4-6 hours. 10 to 30 mg is the antitussive dose.

About 10% of codeine is converted to morphine. Constipation is the most common side effect.