Narcotics and Non-Narcotics Analgesics

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Analgesics

An **analgesic**, or **painkiller**, is any member of the group of drugs used to achieve analgesia — relief from pain.

Major classes of Analgesic Drugs include:

- Opioids
- NSAIDs
- Acetaminophen/ PCM
- Flupirtine
- Ziconotide

Narcotics Analgesic/Opioids

Narcotic analgesics are drugs that relieve pain, by binding to opioid receptors, which are present in the central and peripheral nervous system, can cause numbness and induce a state of unconsciousness.

Classified into:

Natural Compounds: Morphine, Codeine, Papaverine

Semi-Synthetic: Diacetylmorphine (Heroin), benzylmorphine and ethylmorphine

Synthetic Derivatives: Fentanyl, Pethidine, Methadone, Tramadol and Propoxyphene

Loperamide, an opiate that does not enter the brain and therefore lacks analgesic activity.

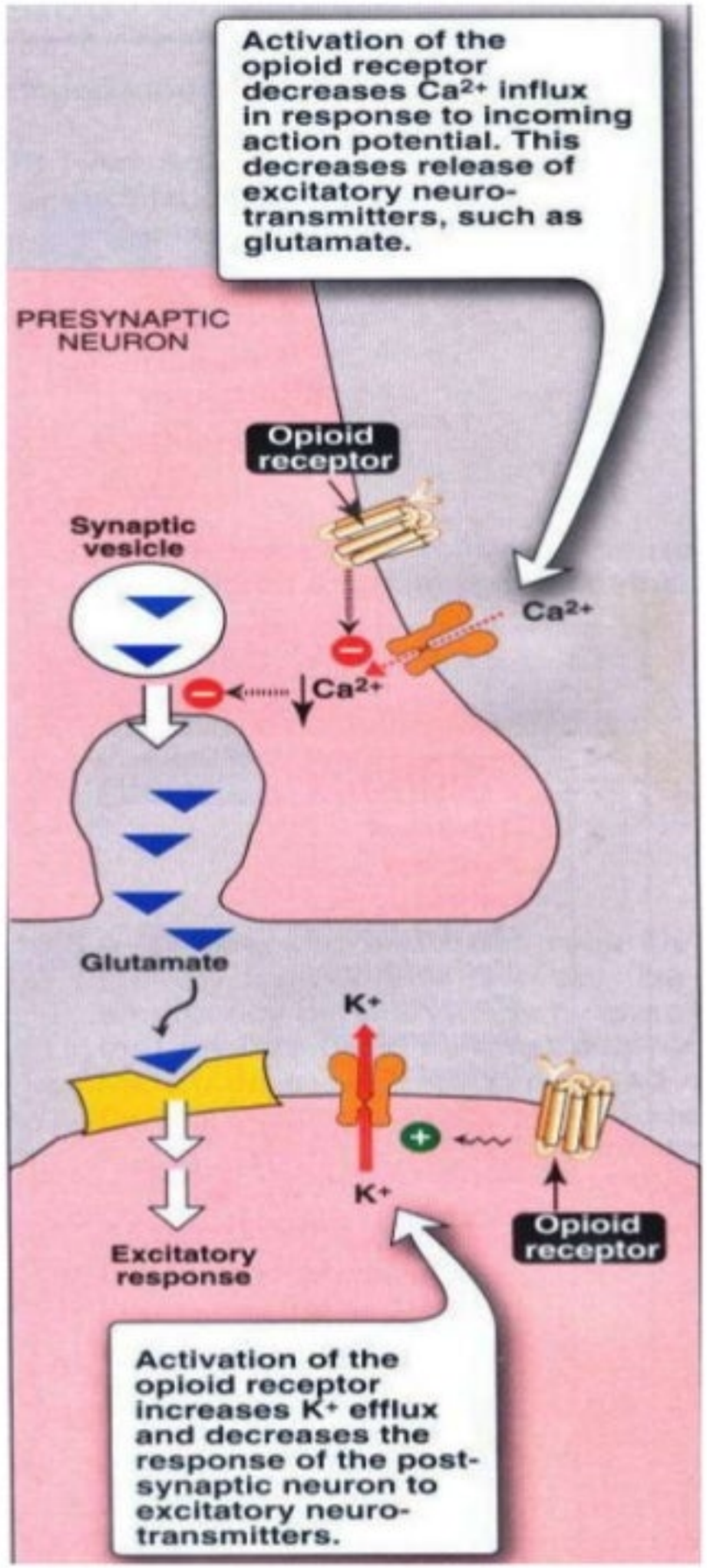
Mechanism of Action

All opioid receptors are G-protein coupled receptors and inhibit adenylate cyclase.

They are also involved in

- Postsynaptic hyperpolarization (increasing K+ efflux)
- Reducing presynaptic Ca^{++} influx

thus inhibits neuronal activity.



Opioid Receptors

All opioid receptors are linked through G-proteins to inhibition of adenylate cyclase. They also facilitate opening of potassium channels (causing hyperpolarisation) and inhibit opening of calcium channels (inhibiting transmitter release).

They are of 4 types:

- μ receptor
- σ receptor
- δ receptor
- K receptor

μ-Receptors are thought to be responsible for most of the analgesic effects of opioids, and for some major unwanted effects. Most of the analgesic opioids are μ-receptor agonists.

Mu-Receptor: Two Types

Mu-1

- Located outside spinal cord
- Responsible for Central interpretation of Pain

Mu-2

- Located throughout CNS
- Responsible for respiratory depression, spinal analgesia, Physical dependence, and Euphoria

- κ-Receptors contribute to analgesia at the spinal level and may elicit sedation and dysphoria, but produce relatively few unwanted effects and do not contribute to dependence.

- δ-Receptors are probably more important in the periphery and may also contribute to analgesia.

- σ-Receptors are not true opioid receptors and it is unclear that what delta actually responsible for but may regulate mu receptor activity.

Agonist and Antagonist

Opiates vary not only in their receptor specificity but also in their efficacy at the different types of receptor. Thus some agents act as agonists on one type of receptor, and antagonists or partial agonists at another, producing a very complicated pharmacological picture.

Pure Agonists

This group includes most of the typical morphine-like drugs. They all have high affinity for μ receptors and generally lower affinity for δ and κ sites. Some drugs of this type, notably codeine, methadone are sometimes referred to as weak agonists because their maximal effects, both analgesic and unwanted, are less than those of morphine, and they do not cause dependence. Whether they are truly partial agonists is not established.

Pure agonist drugs include Morphine, Heroin, Methadone, Fentanyl, Codeine.

Morphine

Morphine is the major analgesic drug contained in crude opium and is the prototype strong agonist.

Morphine may be given by injection (intravenous or intramuscular) or by mouth, often as slow-release tablets. It is metabolized to morphine-6-glucuronide, which is more potent as an analgesic.

Actions of Morphine:

- Analgesia
- Euphoria and sedation
- Respiratory depression and suppression of cough
- Nausea and vomiting
- Reduced gastrointestinal motility, causing constipation
- Histamine release, causing bronchoconstriction.

Disadvantage:

- Drug of addiction due to euphoric effect
- Over dose causes poisoning i.e. Coma and Respiratory Depression.
- Cause dryness of mouth, mental clouding, vomiting, headache, fatigue, constipation etc.

Methadone

Methadone is a synthetic, orally effective opioid that is approximately equal in potency to morphine but induces less euphoria and has somewhat longer duration of action.

Methadone is readily absorbed following oral administration. The drug is biotransformed in the liver and is excreted in the urine, mainly as inactive metabolites.

Adverse effects: Methadone can produce physical dependence like that of morphine.

Fentanyl

Fentanyl and **sufentanil** are highly potent phenylpiperidine derivatives, with actions similar to those of morphine but with a more rapid onset and shorter duration of action, particularly sufentanil. Their main use is in anesthesia, and they may be given intrathecally. They are also used in patient-controlled infusion systems, where a short duration of action is advantageous, and in severe chronic pain, when they are administered via patches applied to the skin.

Partial Agonist and Mixed Agonist-Antagonists

These drugs, nalorphine and pentazocine, combine a degree of agonist and antagonist activity on different receptors. Nalorphine, for example, is an agonist when tested on guinea pig ileum, but it also inhibits competitively the effect of morphine on this tissue. Pentazocine and cyclazocine, on the other hand, are antagonists at μ-receptors but partial agonists on δ and κ-receptors. Most of the drugs in this group tend to cause dysphoria rather than euphoria, probably by acting on the κ-receptor.

Others include Buprenorphine, Nalbuphine, Pentazocine.

Nalorphine

Nalorphine is closely related in structure to morphine and has a more complicated action. In low doses, it is a competitive antagonist and blocks most actions of morphine in whole animals or isolated tissues. Higher doses, however, are analgesic and mimic the effects of morphine. These effects probably reflect an antagonist action on μ-receptors, coupled with a partial agonist action on δ and κ-receptors, the latter causing dysphoria, which makes it unsuitable for use as an analgesic.

- **Pentazocine** is a mixed agonist-antagonist with analgesic properties similar to those of morphine. However, it causes marked dysphoria, with nightmares and hallucinations, rather than euphoria, and is now rarely used.

- **Buprenorphine** is a partial agonist on μ receptors. It is less liable to cause dysphoria than pentazocine but more liable to cause respiratory depression.

Antagonist

These drugs produce very little effect when given on their own but block the effects of opiates.

The most important examples are:

- Naloxone
- Naltrexone

Naloxone

Naloxone was the first pure opioid antagonist, with affinity for all three opioid receptors.

The main clinical uses of naloxone are to treat respiratory depression caused by opiate over dosage. It is usually given intravenously, and its effects are produced immediately. It is rapidly metabolized by the liver, and its effect lasts only 2-4 hours, which is considerably shorter than that of most morphine-like drugs. Therefore it may have to be given repeatedly.

Naloxone has no important unwanted effects of its own but precipitates withdrawal symptoms in addicts. It can be used to detect opiate addiction.

Naltrexone

Naltrexone is very similar to naloxone but with the advantage of a much longer duration of action (half-life about 10 hours). It may be of value in addicts who have been 'detoxified', because it nullifies the effect of a dose of opiate should the patient's resolve fail. Its use in other conditions, such as alcoholism and septic shock, is being investigated, although the role of opioid peptides in these conditions is controversial.

Specific antagonists at μ, δ and κ-receptors are available for experimental use but not yet for clinical purposes.

Drugs	Uses	Adverse Effects
Morphine	Widely used for acute and chronic pain	Sedation Respiratory depression Tolerance and dependence Euphoria
Methadone	Chronic pain Maintenance of addicts	As morphine but little euphoric effect Accumulation may occur because of long half-life
Pethidine	Acute pain	As morphine, anticholinergic effects Risk of excitement and convulsions
Pentazocine	Mainly acute pain	Irritation at injection site. May precipitate morphine withdrawal syndrome

Fentanyl	Acute pain Anesthesia	As morphine
Codeine	Mild pain	Mainly constipation No dependence liability
Dextropropoxyphene	Mild pain	Respiratory depression May cause convulsions No longer recommended
Tramadol	Acute (mainly postoperative) and chronic pain	Dizziness May cause convulsions

Non Narcotic Analgesics

NSAIDs
Acetaminophen/PCM
Flupirtine
Ziconotide

Acetaminophen

- Popular, safer alternate to Aspirin (as anti-pyretic and analgesic)
- Domestic analgesic
- Used in both adults and children
- Over the counter drug (OTC)
- Rapidly absorbed, mostly metabolized by conjugation and excreted by kidney
- Very less adverse effect in there therapeutic dose

Mechanism of Action

Paracetamol has no significant action on COX-1 and COX-2, which left its mode of action a mystery but did explain its lack of anti-inflammatory action and also, more importantly, its freedom from gastrointestinal side effects typical of NSAIDs.

Now, recent research has shown the presence of a new, previously unknown cyclooxygenase enzyme COX-3, found in the brain and spinal cord, which is selectively inhibited by paracetamol, and is distinct from the two already known cyclooxygenase enzymes COX-1 and COX-2.

It is now believed that this selective inhibition of the enzyme COX-3 in the brain and spinal cord explains the effectiveness of paracetamol in relieving pain and reducing fever without having unwanted gastrointestinal side effects.

The action of paracetamol at a molecular level is unclear but there is considerable evidence that the analgesic effect of paracetamol is central and is due to activation of descending serotonergic pathways, but its primary site of action may still be inhibition of PG synthesis.

Uses

- Useful in mild to moderate pain like headache, pyrexia, myalgia etc
- In case of patients allergic to Aspirin
- Patient with hemophilia.
- Patient with PUD (peptic ulcer disease)
- Patients who are taking other uricosuric drugs (salicylate competes with the uric acid in tubular secretion)

Flupirtine

Flupirtine is a centrally acting, non-opioid analgesic that is available in a number of European countries for the treatment of a variety of pain states.

Flupirtine acts indirectly as NMDA receptor antagonist by activation of K^+ channels. Activation of this channel leads to hyperpolarization of neuronal membrane and the neuron becomes less excitable; thus, there is stabilization of resting neuronal membrane. Experimental evidence suggests that flupirtine might suppress channel opening by acting as an oxidizing agent at the redox site of the NMDA receptor. This action inhibits the transmission of nociceptive impulses during neuronal excitation.

Ziconotide

Ziconotide (Prialt) is a non-narcotic pain reliever that is used to treat severe chronic pain in people who cannot use or do not respond to standard pain-relieving medications.

Mechanism: Ziconotide acts as a selective N-type voltage-gated calcium channel blocker. This action inhibits the release of nociceptive neurochemicals like glutamate and substance P in the brain and spinal cord, resulting in pain relief.

In humans, spinal infusion of Prialt produces significant pain relief in patients with intractable pain associated with cancer, AIDS and in some neuropathic pain conditions.

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