Analgesic and antipyretics

By

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Pain

• Pain is an unpleasant sensory and emotional experience of tissue damage.

• Pain gives a warning signal of repairing activities or to be repaired and that is why it is protective in function.

• When the pain has a sharp well defined onset of action with a short duration of action, it is called acute pain.

• Acute pain can be 2 types : Nociceptive and inflammatory. The acute pain disappears as soon as the cause disappears. The acute pain responds to analgesics and NSAIDs.
Acute pain

- The acute pain examples are post operative pain, post traumatic pain (fracture, soft tissue injury-cut or burns).
- Acute pain is produced by potential noxious (i.e. tissue damaging) stimuli when it affects the body tissue such as heat, squeezing a skin fold or over-rotating a joint.
- Such a pain is called physiological nociceptive pain.
- Pain protects tissue from being further damaged.
- The withdrawal reflexes do the supportive function.
- Pathophysiological nociceptive pain occurs when the tissue is inflamed or injured.
- It is known as inflammatory pain.
Other terms for pain

• Hyperalgesia is the extreme pain felt because of noxious stimulation.
• Allodynia is the pain of low intensity, normally below pain threshold.
• The peripheral sensory nerve endings in the skin are called Nociceptors.
• Nociceptors are present in skin, bone, connective tissue, muscles and viscera (deep organs) and respond to only noxious stimuli.
• Pain felt at a distant point from that of the cause of the pain is called a referred pain.
• The nociceptive and inflammatory pain respond to NSAIDs and Opioids.
Chronic Neuropathic Pain

- A chronic pain arises from inflammatory or neuropathic factors.
- Neuropathic pain: Pain due to direct consequence of a lesion or a disease affecting the somato-sensory system resulting in long lasting pain. (nerve damage or injury).
- They do not give any signal of repairing or for any useful purpose.
- Chronic pain persist for longer times, months to years even decades.
- Peripheral neuropathic pain is often described as burning, tingling sensation, stabbing or pin and needles.
Analgesics and antipyretics

- The drugs used for relieve of pain without loss of consciousness are called analgesics. The drugs used in reducing elevated body temperature to normal temperature are called antipyretics.
- Antipyretics are used in fever.
- The NSAIDs are used in inflammatory pains.
- The opioids are used in nociceptive pains.
Antipyretics

• The antipyretic analgesics reduce elevated body temperature in fever and reduce pain. The drugs of this group are acetaminophen (Paracetamol), Acetanilide, Phenacetin, Antipyrine, Aminopyrine.

• The antipyretic analgesics do not inhibit COX-1 and COX-2 enzymes.
Antipyretic analgesic

Acetaminophen / paracetamol

Antipyrine

Aminopyrine
Opioids analgesics

• Opioids are the best known centrally acting analgesics used for blunt pains.

• Opiates are the compounds structurally related to morphine.

• Opioids are any compounds that have morphine like actions. The natural opium alkaloids, the synthetic derivatives of morphine and the endogenous or synthetic peptides having morphine like actions, all are categorised as opioids.
Opioids

- **Opioids** are classified into eight categories.
- **4,5-Epoxymorphinan derivatives**: Morphine, Codeine, Heroin, Hydromorphone, Hydrocodone, Oxycodone and Oxymorphone.
- **Morphinan derivatives**: Levorphanol, Dextromethorphan
- **Benzomorphan (Benzazocine) derivatives**: Pentazocin
- **4-Phenylpiperidin derivatives**: Meperidine, diphenoxylate and Loperamide
- **4-Anilidopiperidine derivatives**: Fentanyl, Sufentanil, Alfentanil, Remifentanil
- **Diphenylheptane derivatives**: Acetylmethadol, Propoxyphene, Butorphanol, Methadone.
- **Miscellaneous**: Tramadol.
- **Mixed agonist antagonists**: Nalbuphine, Buprenorphine, Butorphanol.
4,5-Epoxy morphinan derivatives: Morphine, Codeine, Heroin, Hydromorphone, Hydrocodone, Oxycodone and Oxymorphone.

- **Morphine** is the alkaloid of opium and the prototype μ receptor agonist. It is used for severe pain and when NSAID and mild opioids agonist are inactive in alleviating pain. It has a CNS depression action. It is effective against the dull and poorly localised pain. It has sedative and euphoric action.

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\begin{align*}
\text{Morphine} = N \quad &\quad \text{(Structure)}
\end{align*}
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- **Morphine**
4,5-Epoxymorphinan derivatives

- **Codeine** is the alkaloid of opium and is the 3-methylmorphine. It has similar actions to morphine but less potent analgesic than morphine.
4,5-Epoxymorphinan derivatives

- **Heroin** is 3, 6-diacectylmorphine. Because of acetylating of the two hydroxyl groups, the heroin easily crosses the blood brain barrier and produce euphoric action, which may result to addicting the patient. Heroin is metabolised in the brain to 3-acetylelmorphine and 6-acetyl morphine. 3-acetylelmorphine is quite inactive but the 6-acetylelmorphine is 2 to 3-times more active than morphine. It is not used clinically.

- **Hydromorphone** is a synthetic analog of morphine. Hydromorphone is prepared by oxidation of 6-hydroxyl group to ketone and reducing 7th & 8th positions of morphine. It is more potent than morphine. Alcohol potentiates the action of hydromorphone.

- **Hydrocodone** is 3-methylhydromorphone. It is equally potent to morphine. Hydrocodone is combined with anticholinergic agents to reduce abuse of the drug. It is used in combination with paracetamol or aspirin for the treatment of pain. Other agents from this group are oxymorphone and oxycodone.
4,5-Epoxy morphinan derivatives

- Heroine
- Hydromorphone
- Hydrocodone
- Oxycodone
- Oxymorphone
Morphinan derivatives

- **Levorphanol** is a levorotatory isomer of methorphan. It is a Morphinan derivative. The morphinan is devoid of ring-E in its structure. Levorphanol is more flexible to bind with all opioid receptors.

**Dextromethorphan** is the dextrorrotatory isomer of Levorphanol. It is available in various dosage forms in over the counter cough and cold formulations. It has been used to relieve phantom pain, acute nociceptive and neuropathic pain. It is an NMDA antagonist.
Benzomorphan (Benzazocine) derivatives

• **Benzomorphan** is the derived product of morphine where both the Ring-C and Ring-E of morphine are removed. Benzomorphan derivatives are also known as benzazocines.

• **Pentazocin** is the only Benzomorphan that has been used clinically.

• It has mixed agonist/antagonist activity.
4-Phenylpiperidines are simplified form of Benzomorphan, where the ring-B is also removed from the morphine structure.

Meperidine (Pethidine) is less potent as analgesic. It has much higher penetration in the brain than morphine and quick onset of action and high abuse potential.

Diphenoxylate is very weak as analgesic. It has been used in combination with atropine as anti-diarrheal.

Loperamide is also a 4-phenylpiperidine derivative. It decreases the peristaltic movement and used as anti-diarrheal.
4-Phenylpiperidine derivatives

- Meperidine (pethidine)
- Diphenoxylate
- Loperamide
4-Anilidopiperidine derivatives

- 4-Anilidopiperidines are 4-anilinopiperidine derivatives. Fentanyl is more potent than Meperidine. It is used as an analgesic and also used as anaesthetic adjunct.

- Other members of this group are Sufentanil, Alfentanil and Remifentanil are also used as anaesthetic adjuncts.
4-Anilidopiperidine

- Fentanyl
- Sufentanil
- Alfentanil
- Remifentanil
Diphenylheptane derivatives

- **Diphenylheptane** derivatives are too used as opioids agonists. Methadone is used as analgesic as well as for the recovery treatment of addiction.

- **Propoxyphene** is a modified form of methadone. It is less potent as analgesic but have same adverse effects of morphine.

[Chemical structures of Butorphanol, Propoxyphene, and Acetylmethadol]
Miscellaneous compounds

• Miscellaneous drugs include Tramadol is a weak μ-agonist and less potent analgesic.
• It has been used as an adjunct of anaesthetics.
Mixed agonist/antagonist

- Nalbuphine, Butorphanol and Buprenorphine are the mixed opioid receptor agonist/antagonist.
Transmission of nociception

• Pain sensation moves to the brain for perception in four stages namely the transduction, transmission, modulation and perception.
• 1st stage: Transduction is the process of converting the injury or insult into electrical impulse or action potential.
• This happens in the Nociceptors of myelinated afferent neuron (Aδ) fibres and non-myelinated afferent nerve (C-fibres).
• The chemical mediators, such as prostaglandin and serotonin stimulate directly or sensitise to receive the pain signal.
• Similarly the potassium (K⁺), adenosine triphosphate (ATP) and hydrogen (H⁺), ions from cells in the site of injury directly stimulate the Nociceptors.
Transmission of nociception

• Stimulation of the Nociceptors open the voltage gated Sodium and Calcium channel to influx into the cytoplasm, which lead to develop action potential.

• 2nd stage: The transmission of the action potential through the primary, secondary and tertiary afferent nerves to the somatosensory cortex is the second stage.

• The action potential moves faster in the myelinated afferent neuron (Aδ) fibres by the saltatory action.

• They carry acute and sharp pain sensations.

• The afferent C fibres are non-myelinated that carry dull pain sensation at a slower rate.
Transmission of nociception

• **3rd stage:** The third stage is the modulation, which means blocking or altering the action potential of pain while travelling through the spinal column.

• The cortex in need sends inhibitory signal down through the midbrain to the interneuron at the synapse of the secondary and primary neurons, where the interneuron sends inhibitory signals to reduce secretion of excitatory glutamate from the presynaptic primary neuron, thereby reducing transmission of action potential.

• **4th stage:** Finally in the perception stage, the cortices receive the signal, integrate and convert it into a perceptive pain.
Mechanism of action of opioids

• By the signals of the sensory cortex the interneurons at the synaptic site of primary and secondary neurons release endogenous opioids, the encephalins, which are inhibitory to release glutamate at the synapse.

• Therefore pain transmission is modulated.

• The opioid drugs like morphine and congeners bind to the same receptors of the endogenous encephalin and modulate the transmission of pain.

• The opioids also signal to block calcium (\(\text{Ca}^{++}\)) channel and opening of Potassium (\(\text{K}^{+}\)) channel. Potassium channel opening causes high influx of potassium ion to produce hyperpolarisation and nerve block.