Pain Killers and their Mechanisms of Action

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Abstract

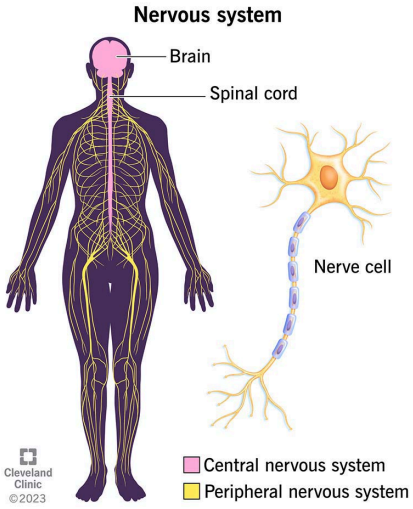
Pain can be defined as ‘An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage.’ For the 1 in 125 million people diagnosed with CIPA (Congenital Insensitivity to pain with anhidrosis), the lack of sensitivity to pain and temperature results in 20% of CIPA patients dying before they pass the age of 3. This reveals the crucial role of pain, with its aversive nature able to protect us from danger, and in doing so, granting us the gift of survival.

Introduction

The induction of pain through the reception of a stimuli, comes from the vast network of nerves which work together to form the nervous system. This paper introduces the intricacies of our CNS and PNS before moving onto explore the varying ways humans can inhibit the perception of pain. By explaining the biochemical interactions between Analgesics and our nervous system, this paper can provide greater public understanding over the pain killing medications we receive in clinics and hospitals around the world today.

The Nervous System

The detection and response to pain is carried out by our nervous system; this consists of the CNS (Central Nervous System) and the PNS (Peripheral Nervous System). The CNS comprises of the brain and spinal cord, while the PNS is made of nerves running through our entire body.



It is important to understand the nervous system in addition to the stimulation and natural response of the human body toward pain before delving into the functions of painkillers. This is fundamentally due to most types of painkillers affecting our nervous systems rather than physically reducing the pain we feel.

The Anatomy of Pain

When a painful stimulus causes potential tissue damage, pain receptors in the skin (Nociceptors) are activated. These stimulate electrical nerve impulses, which travel up the PNS, through the spinal cord, and into the brain. Between neurons in the CNS, electrical nerve impulses are converted into chemical neurotransmitters which diffuse across the synaptic cleft. These are then transferred back into electrical impulses where they travel rapidly towards the brain.

Within the brain, the thalamus receives these nerve impulses and serves as an organizing hub, sending electrical signals to differing parts of the brain. This includes areas such as the somatosensory cortex (region responsible for physical touch), the frontal cortex (region accountable for thought processes), and the limbic system (region liable for emotion). This results in a sensation felt within your body at the site of tissue damage, and a response through either a muscle contraction or an emotional response to the pain.

Painkillers

In some situations, the sensation of pain is undesirable; this led to the production of ‘painkillers.’ Also known as Analgesics, painkillers are medications that allow patients to alleviate their feelings of pain. Whether it's chronic pains, sustained injuries, or just a simple headache, there are many different types of existing painkillers that work in slightly different ways. There are 4 main types of Analgesics:

- Non-Opioid Analgesics
- Opioid Analgesics
- Compound Analgesics
- Adjuvant Analgesics

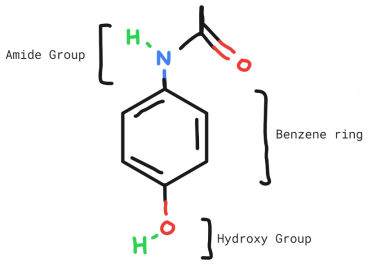
They mainly function by disrupting the transmission of electrical nerve impulses and tricking the body into feeling less pain. Summarizing these 4 types of Analgesics would reveal paracetamol and aspirin as Non-Opioid Analgesics, which function by inhibiting the activities of the COX enzymes. Common Opioid Analgesics would include fentanyl and morphine, which bind to opioid receptors in the CNS to block nerve impulses. Compound Analgesics are medications consisting of both Opioid and Non-Opioid analgesics, while anti-depressants and steroids are adjuvant analgesics that reduce transmission of pain signals.

Non-Opioid Analgesics

Examples: Paracetamol, Aspirin, Ibuprofen

Used for: Fever, Headaches, Toothaches, Period Pains

Non-Opioid Analgesics consists of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and paracetamol. Both paracetamol and NSAIDs work by affecting the hormone-like substance Prostaglandins; high concentrations of prostaglandins are found near the site of inflammation, so reducing its production can stop the pain and swelling. NSAIDs inhibit the production of cyclooxygenase enzymes (COX), which are needed in the synthesis of prostaglandins; this results in a reduction in the levels of prostaglandin and the alleviation of pain and inflammation.



Paracetamol's molecular structure consists of a benzene ring, a hydroxyl group (functional group with formula –OH), and an amide group (functional group where a Nitrogen atom forms a single bond with the beta carbon atom, while also forming a bond with a hydrogen atom).

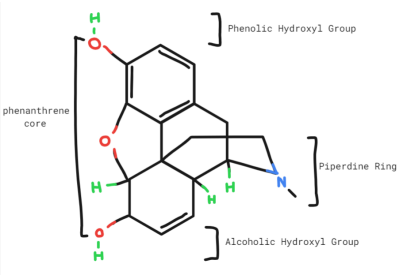
Unlike NSAIDs, paracetamol doesn't directly inhibit COX enzymes by binding into its active site. Instead, the Hydroxyl and Amide groups undergo chemical reactions to interact with the oxidative state of COX enzymes to reduce their activities.

Opioid Analgesics

Examples: Fentanyl, Morphine, Tramadol

Used for: Cancer, End of Life Care, Anesthesia, Severe Trauma

Opioid Analgesics differs from NSAIDs and paracetamol through its direct interaction and impact on the nervous system. The Opioids are ingested and bind to opioid receptors found within the PNS and CNS. Here, the opioids can block pain messages, transported as nerve impulses, from being sent through the body to the spinal cord and the brain, and in doing so can effectively relieve pain.



Morphine's molecular structure is made up of three fused benzene rings, which form a phenanthrene core. Attached to these are a piperidine ring and another benzene ring; these contain the phenolic hydroxyl group and the alcoholic hydroxyl group.

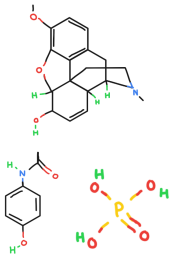
When Morphine interacts with Opioid receptors, their benzene rings and phenanthrene core latch onto amino acids (such as phenylalanine and tyrosine) found in the binding site of the opioid receptors. In addition, the functional groups of phenolic and alcoholic hydroxyl groups found on the surface of Morphine form hydrogen bonds with polar residues (types of amino acids) in the receptors binding area. This all leads to opioid receptors being restricted, and the therapeutic effects of Opioid Analgesics such as Morphine.

Compound Analgesics

Examples: Co-codamol, Co-codaprin, Co-dydramol

Used for: Fractures, Postoperative Pain, Arthritis, Migraine Relief

Compound Analgesics are combinations of at least 1 analgesic with another medicine. They commonly consist of either NSAIDs or Opioids; if the medication contains multiple analgesics, they will be different types to allow multiple ways to alleviate the pain.



Co-codamol's molecular structure consists of 2 analgesics and phosphoric acid. Codeine found within co-codamol is an opioid analgesic which is very similar to morphine. Acetaminophen (also known as paracetamol), is found alongside the codeine. The phosphoric acid serves as an excipient, by acting as both a pH adjuster and a buffer agent to maintain a specific pH range.
The codeine within the co-codamol acts similarly to morphine by latching onto amino acids found within the binding site of the opioid receptors. On top of this, the acetaminophen contains Hydroxyl and Amide groups, which undergo chemical reactions to interact with the oxidative

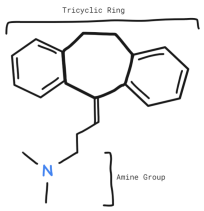
state of COX enzymes to reduce their activities. With Co-codamol containing multiple analgesics, it has the ability to impact numerous pain pathways, leading to greater pain relief.

Adjuvant Analgesics

Examples: Amitriptyline, Duloxetine, Cyclobenzaprine

Used for: Anti-depressants, Anti-convulsant, Muscle Relaxants, Antihistamines

Adjuvant Analgesics are used alongside other analgesics in order to reduce the effects of pain. They can assist in cases where opioids and NSAIDs are not strong enough, by increasing the number of neurotransmitters. Although this process isn't fully understood, increasing the concentration of neurotransmitters can affect emotions by altering the electrical pain signals sent to the brain.

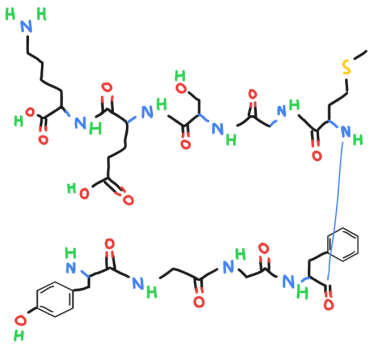


Amitriptyline's molecular structure consists of a tricyclic ring (3 fused benzene rings); attached to the center benzene ring is an anime group. To form the amine group, hydrogen atoms have been replaced, allowing the nitrogen atom to form a lone pair.

Amitriptyline relieves pain and stress by binding onto specific neurotransmitter transporters. This reduces the uptake of neurotransmitters such as serotonin and norepinephrine in the presynaptic neurons. This allows more neurotransmitters to diffuse across the synaptic cleft, increasing the concentration of neurotransmitters, and reducing pain.

Endorphins

Although humans can take pain killers, our body naturally releases hormones known as Endorphins when it feels pain or stress. Endorphins are formed in the pituitary gland in the brain, and travel towards opioid receptors. Here they function in the same way as opioid analgesics by binding onto the opioid receptors to block the transmission of pain messages. Our body contains 3 types of opioid receptors: mu, delta, and kappa; all of which contribute to alleviating pain in slightly different ways. The difference between our body's natural painkillers and opioid analgesics lies with the secretion of dopamine from the brain. The endorphins binding onto opioid receptors stimulate the secretion of dopamine; this hormone gives you feelings of pleasure and gratification.



Beta-endorphins are the most frequently observed amongst the 20 different types of endorphins. They are all proteins, with beta-endorphins specifically being a polypeptide chain made up of 31 amino acids. Each of the 31 amino acids contain a specific active site, which is complimentary to the opioid receptors. By binding onto these receptors, they block pain messages and reduce the feeling on pain.

The Future for Analgesics

Although painkillers are practical ways to alleviate pain, they still contain risks and can become less and less effective (tolerance). Side-effects include damage to internal organs, heart problems, nausea, deafness and can even be very addictive; this is due to their unwanted interactions with various systems within our bodies. For the future, we can use 'personalized medicine' to observe the genetic profile of an individual. Using this genetic information, we can tailor make specific drugs to interact in specific ways for different people, and minimize the unwanted side-effects which would further damage the human body.

Further Reading

- https://www.cancerresearchuk.org/about-cancer/coping/physically/cancer-and-pain-control/treating-pain/painkillers/types-of-painkillers/opioids
- https://rsv.org.au/moving-away-from-opioids/#:~:text=Given the high priority of,VX-548 for postoperative pain
- https://www.ncbi.nlm.nih.gov/books/NBK560692/
- https://patient.info/treatment-medication/painkillers#can-i-buy-painkillers

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