# How opioids work. The risks and benefits associated with this group of drugs.

## Introduction (history of opioids)

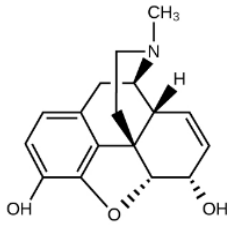
The first recorded instance of opium being used dates to over 8,000 years ago, as observed on hardened Sumerian clay-tablets (Bandyopadhyay, 2019). Derived from the opium poppy plant, the opioid class of drugs has been used for a multitude of purposes. On the medicinal front, they have been analgesic (relieving pain), antitussives (suppressing coughing), and antidiarrheals (KuKanich and Wiese, 2017). This clinical side of their usage only started once morphine was extracted from *Papaver Somniferum* (Opium poppy) in 1806, and further escalated after 1853, when hypodermic needles were discovered (Dhaliwal and Gupta, 2023a).

However, opioids have also been prevalent as recreational drugs, evoking a sense of euphoria and thus causing widespread havoc throughout various dynasties throughout history. Notable examples of this include the Opium wars between China and the British Empire, or more contemporarily the devastating effects of synthetic opioids like fentanyl on the United States of America due to their addictive properties.

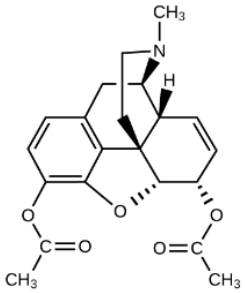
# The structure of opioids

All opioids are organic compounds. While they all share a common backbone, they differ in overall structure. From figure 1, we can see the structure of morphine, which is the quintessential opioid. It consists of 3 fused benzene rings, with two hydroxyl groups and an N-methyl group at the top. When protonated, this nitrogen atom becomes electrostatically charged and is the binding site with its receptor.

As we can see from diamorphine (heroin), amending these hydroxyl groups drastically changes the functionality of the molecule (Trescot et al., 2008). In this case, heroin is formed when both hydroxyl groups are O-acetylated (forming esters of ethanoic acid), forming a much more addictive substance (Wacowich-Sgarbi and Department, 2018). If only one of these hydroxyl groups is e.g. O-methylated, the milder analgesic codeine is produced.



morphine



heroin

*Fig 1*

*A diagram showing the chemical structure of morphine.*

*Sourced from: Wacowich-Sgarbi and Department (2018.)*

# What mechanisms do opioids use:

As briefly mentioned earlier, there are two branches of opioids: Synthetic and non-synthetic opioids. While the latter are naturally occurring, the former can be synthesised in a laboratory illicitly, or legally for medicinal applications such as palliative care (e.g. fentanyl patches). Nevertheless, both share the same mechanisms of action; they stimulate opioid receptors in the brain that inhibit pain signalling between the brain and the body ("Opioids | Johns Hopkins Medicine," n.d.). There are three main types of these opioid receptors - μ opioid receptors, κ opioid receptors, and δ opioid receptors (MOR, KOR, and DOR respectively) (Dhaliwal and Gupta, 2023). All of these are G-protein-coupled receptors (GPCRs), which mediate responses to many external stimuli, including light, smell and hormones (Weis and Kobilka, 2018).

As a matter of fact, industry professionals estimate that between 1/3 and ½ of medicinal drugs on the market are GPCR agonists ("GPCR | Learn Science at Scitable," n.d.), which demonstrates the salience of understanding them.

Broadly speaking, the MOR agonists are responsible for euphoria and handling stress, while KOR agonists cause dysphoria and stress, and DOR agonists are anxiolytic (Rita J Valentino and Volkow, 2018). (Fig 2 below demonstrates their functions within the body.). Because the MOR is responsible for analgesia, it is the primary focus of research and of this essay.

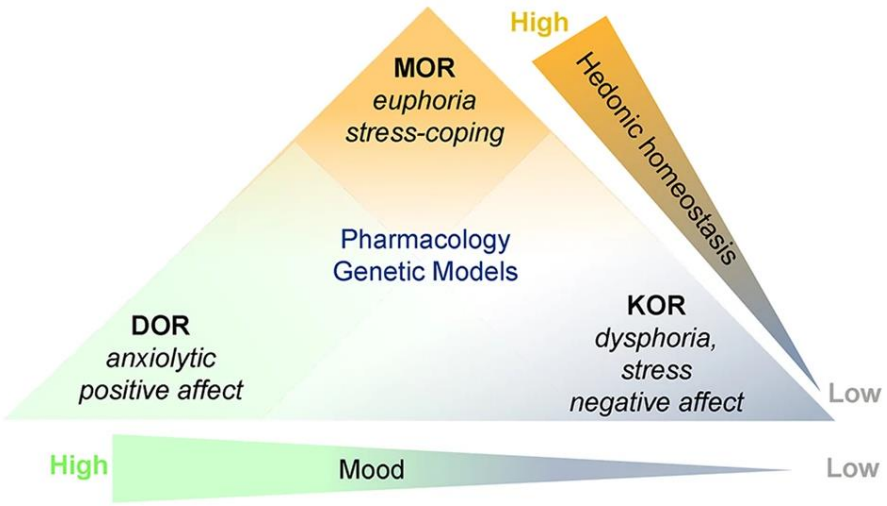



*Fig 2*

*A diagram showing what each of the 3 opioid receptors do*

*Sourced from: Rita J. Valentino and Volkow (2018)*

# The signalling pathway of Opioid receptors

As humans, our desire to effect change can be approach based, or avoidance based. Several millennia ago, this would have consisted of e.g. hunting to catch food or running to escape predation, respectively. As a consequence of the necessity for motivation, the body's endogenous opioid system evolved. The MORs are the most frequently expressed receptors in this system and are situated in the central nervous system (CNS). They are found in higher concentrations in the cerebral cortex, spinal cord and peripheral nervous system ("Mu Receptors – Opioid Peptides," 2019). MORs evolved as a mechanism to regulate pain, reward and addiction, which are three salient entities for survival.

To understand how the MOR receptor functions, we must first understand how a generic inhibitory G-protein coupled receptor works. There are four main G-protein subunits. This essay will focus on the $G_{\alpha i}$ type GPCRs, as this is the type of MORs.

While other excitatory GPCR pathways exist, they aren't relevant to the binding of opioid-based substances, which produce inhibitory effects.

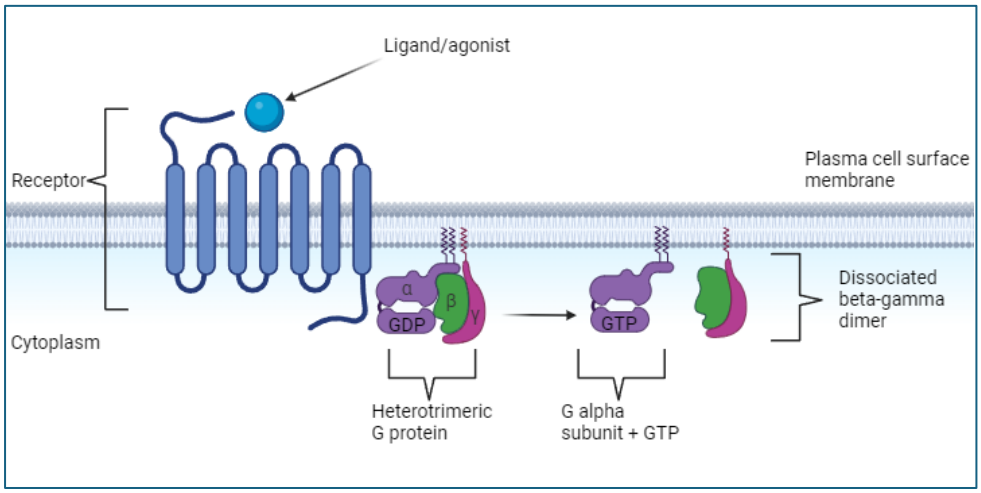



*Fig 3*

*A self-made illustration demonstrating the mechanism of G-protein coupled receptors*

*Created in BioRender.com*

As Fig 3 shows, GPCRs are situated on the plasma membrane of cells, and are called seven-transmembrane receptors due to them existing across the membrane. During the first step of the mechanism, an agonistic ligand binds to the GPCR, and causes a conformational change. This causes the nearby heterotrimeric G protein (comprised of 3 subunits – α, β, γ), which is situated on the inside of the phospholipid bilayer, to bind

to either guanosine diphosphate (GDP) or guanosine triphosphate (GTP), both of which are nucleotides. When the receptor is inactivated, the $G_a$ subunit is naturally bonded to GDP. However, when the agonist activates the receptor, GTP replaces the GDP and the G protein dissociates into a GTP-bound $G_a$ molecule, and a beta-gamma dimer. Now that the G protein is no longer bound to the receptor (more specifically $G_a$), it can oscillate horizontally along the cell membrane and interact with other molecules to effect downstream signalling ("GPCR | Learn Science at Scitable," n.d.).

In the case of Mu-opioid receptors, this initial extracellular opioid binding causes three main downstream effects.

The first of these effects, is the inhibition of the enzyme adenylyl cyclase by both the $G_a$ subunit and β-γ dimer. This enzyme is crucial in that it is the only enzyme to synthesize cyclic AMP (cAMP), which is second messenger that mediates responses such as olfaction, cell differentiation and metabolism (Yan and Tang, 2002). When cAMP levels decrease, the activity of protein kinase A (PKA) decreases, which results in reduced phosphorylation of e.g. metabolic enzymes and neurotransmitter receptors + ion channels that modulate neuron firing (Sun et al., 2020). This results in decreased neuronal activity which, physiologically, can cause analgesic effects, drowsiness, and decreased neuroplasticity (the impairment of memory/learning capabilities). These symptoms occur because pain is a neurological signal, which travels along nerves, eventually into the CNS where it is processed, particularly in the thalamus and the cortex. By reducing the efficacy of neurotransmitter receptors, these inter-neuronal signals are slower, which reduces the degree of pain experienced.

The second of these effects, is the opening of GIRK (G protein-gated inwardly rectifying potassium) channels by the $G_{\beta\gamma}$ subunits (β-γ dimer). When the $G_{\beta\gamma}$ structure separates from the $G_a$ subunit, it binds to the GIRK channels, and opens them (Kano et al., 2019).

Since under normal circumstances the concentration of $K^+$ ions inside the cell is higher than outside the cell, there is an efflux of $K^+$ ions (McDonald and Lambert, 2016). This is because voltage across the membrane (membrane potential) is greater than the equilibrium potential of the $K^+$ ion (Kano et al., 2019). Because equilibrium potential refers to the membrane potential at which the electrical force of ions balances

diffusion, a greater membrane potential results in a force that drives $K^+$ ions out of the cell. The following diagram (Fig 4) highlights the steps of this process.

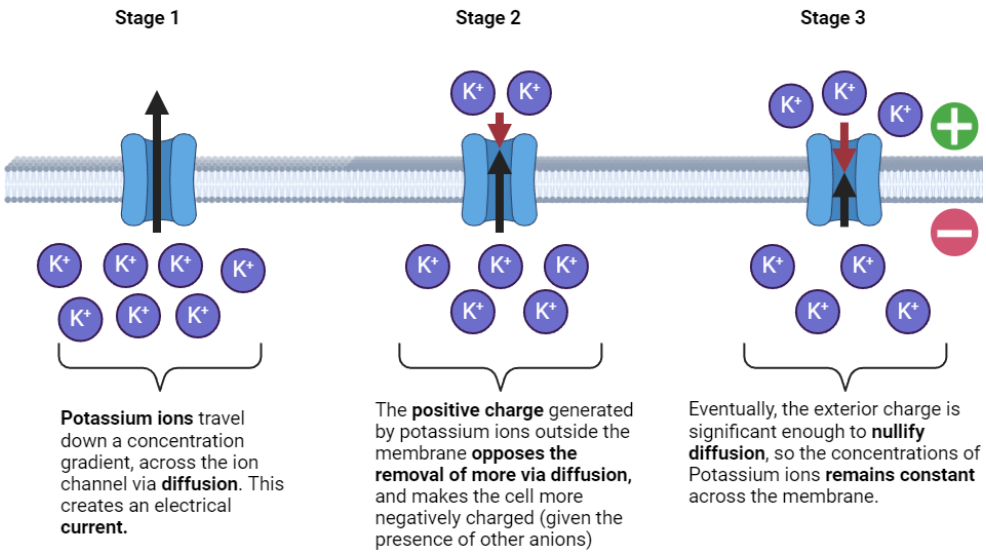



*Fig 4*

*A self-made illustration detailing the process of membrane hyperpolarisation*

*Created in BioRender.com*

As referenced in Fig 4, this removal of Potassium ions (cations) results in membrane hyperpolarization, where the exterior surface of the cell develops a greater positive charge to the interior. This makes it improbable for neurons to fire, as cations are not able to leave the cell due to electrostatic repulsion.

Ultimately, this process results in lowered transmission of e.g. pain signals, and thus analgesic effects.

The final of these effects is the hindrance of presynaptic calcium channels. This closing of the calcium channels is caused by the beta-gamma subunit of the G protein, which directly binds to the channels much like with the GIRK channels, but to produce the opposite effect (Currie, 2010). This causes reduced absorption of calcium ions into the neurons (Cohen and Vanhoutte, 1995). Because $Ca^{2+}$ ions have been shown to trigger synaptic vesicle exocytosis, a decrease in $Ca^{2+}$ concentration hinders the release of neurotransmitters into the synaptic cleft. As a result, neurons are less able to communicate via neurotransmitters such as GABA (gamma-aminobutyric acid), glutamate, and acetylcholine (Südhof, 2012).

Furthermore, by reducing the flow of calcium ions, the effects of an action potential disappear. Because action potential describes the changes in voltage across the membrane, a lowered $Ca^{2+}$ concentration would make synaptic vesicle exocytosis even less probable, thus inhibiting the propagation of the electrical signal (Kuszak, 2019). When combined with the hyperpolarisation of neurons, there is lowered neuronal firing and propagation of nerve impulses. This, inhibition of signal transfer causes analgesic effects.

Finally, at the end of this process, the enzyme GTPase causes the hydrolyzation of GTP back into GDP, which deactivates the G protein and the overall inhibitory mechanism.

## Why are opioids useful in medicine?

As discussed in the introduction, opioids have and continue to be prominent in the field of medicine, with mainstream drugs containing opioids such as codeine, morphine, oxycodone and many others (“Heroin and Opioid Awareness | Opioid Facts,” 2022).

These drugs are essential to medicine, as they are the only ones which induce analgesia to the required degree post severe trauma or surgery. While non-opioid alternatives such as paracetamol do exist, their degree of effect is insufficient during these severe circumstances.

While this analgesic effect is primarily caused by the mechanisms outline in the previous section, opioids also manipulate brain chemistry, in particular, the neurotransmitters dopamine and GABA.

## Dopamine and GABA

Dopamine is the most well-known neurotransmitter and is primarily responsible for feelings of pleasure and satisfaction. When exogenous opioids such as morphine are injected into the body, they cause a surge in dopamine levels, which, according to Yale medicine, can be up to ’10 times more than a natural reward’ (“How an Addicted Brain Works > News > Yale Medicine,” 2022).

Specifically, this process starts in the ventral tegmental area (VTA), which is the reward centre of the brain (Cai and Tong, 2022). The most dominant neuron within this region is the dopaminergic neuron, or in other words the neuron that synthesizes dopamine (Chinta and Andersen, 2005). Punctuating these neurons are GABAergic interneurons, which produce Gamma-aminobutyric acid (GABA – inhibitory neurotransmitter). When opioids bind to the MORs on these GABAergic interneurons, they stop producing as much GABA, which in turn reduces the suppression of dopamine production. This causes an increase in dopamine particularly in the nucleus accumbens, which leads to the euphoric sensation that is commonly known as a ‘high’.  This ‘high’ can be a good thing, as it suppresses pain and makes a patient feel better.

## Why are opioids dangerous?

While opioids do have varied medicinal applications, they are most well known for their recreational usages. In 2021, just under 110,000 lives were lost due to drug overdose within the USA. Within this, the U.S Department of Justice reports that '66% of overdose deaths were attributable to opioids' ("Heroin and Opioid Awareness | Opioid Facts," 2022). Moreover, in the UK in 2022, Gov.Uk reports that 73% of drug misuse deaths were caused by opioids in England, with 60%, 82% and 60% in Wales, Scotland and Northern Ireland respectively ("Expansion of life-saving opioid overdose treatment - GOV.UK," 2024).

When administered illegitimately, opioids are delivered quickly to the brain, via nasal inhalation of powder or injection straight into the bloodstream. As Dr Olga Runcie stated in our interview conducted on August 16th, 2024, they 'hijack the transmission of excitatory and inhibitory neurotransmitters', such as glutamate, dopamine and GABA, to produce sedative effects. While in small doses, this can be productive, uncontrolled exploitation of these substances can result in respiratory arrest and ultimately death.

However, while these effects are deadly, the most devastating consequence of opioid consumption is addiction and withdrawal, which ultimately has more serious ramifications. Moreover, as more opioids are consumed, Dr Runcie notes that the 'dose must escalate to achieve similar effects'. This vicious circle of dependency is the other contributing factor to the danger of these substances as the 'body is now accustomed to function with these substances.'

Addiction and dependency arise primarily as a result of the activation of the brain's reward system, alongside a physiological development of tolerance. These two circuits are interlinked, and cause withdrawal by positive reinforcement alongside negative reinforcement (Gibney and Petrić Howe, 2024). In other words, an addict feels good when they consume opioids so they continue doing so, and they feel bad when they don't so they must continue as a result.

## The Mesolimbic pathway (dopamine reward system)

Human behaviour is driven by necessity. The ‘’reward system’’ is a mechanism developed to assess the value of a reward relative to the cost of an action. To process this, dopaminergic neurons in the VTA interact with those in the nucleus accumbens, and release dopamine when a difficult task is completed (Halber, 2018). Therefore, synapses that mediate positive memories are strengthened, and those that don’t are weakened. This is why we tend to remember elation more than dejection. Dr Runcie noted that this release of dopamine is strongly guarded for special occasions, in order to drive motivation.

When a strong opioid like fentanyl (having a high affinity to the receptor) is introduced to the body, it causes a large secretion of dopamine for the reasons discussed earlier. This is remembered positively and creates a false necessity that one needs to continue consuming the substance as though it were food. It also breaks this protective mechanism to generate transient euphoria.

After this initial consumption, addiction results in sustained exposure to opioids. To adapt, the body changes the expressions of receptors and their responses to certain proteins such that it becomes accustomed to function regularly in the presence of opioids. According to Dr Runcie, in this tolerant state a sudden lack of opioids can result in the body becoming acutely sensitive to e.g. adrenaline, whose response is inhibited by opioids. In this hyperactive state, people can experience anxiety, dysphoria and even diarrhoea as opioids can disturb the gastrointestinal system. Moreover, with this desensitised reward system, the body loses its natural way of regulating emotions, so people can become unstable, and violent. Furthermore, with more opioids in the system, the liver and kidneys become strained. This is because they are responsible for metabolising these substances, and incessant strain may lead to permanent damage.

## The development of opioid tolerance

Earlier, I have discussed the dopamine reward system, and the processes of negative and positive reinforcement to fuel motivation.

However, the question of why the body becomes accustomed to high levels of opioids remains unanswered thus far.

The answer to this question lies with the GPCRs, and more specifically the opioid receptors.

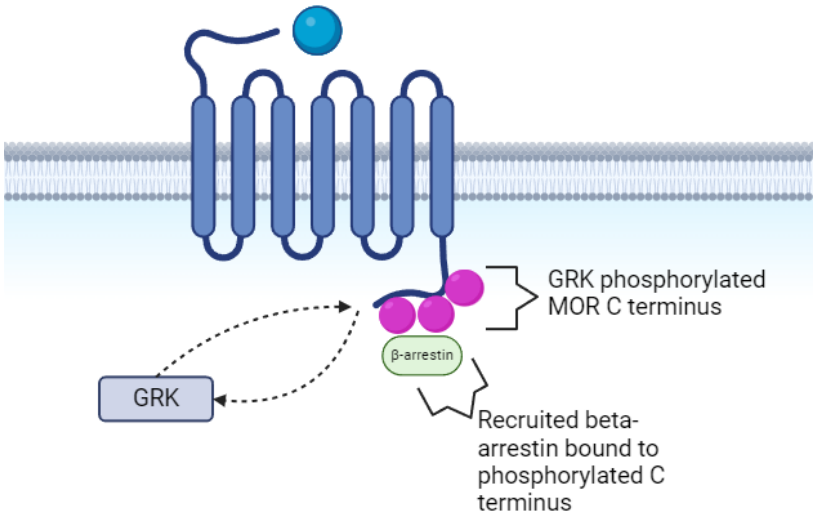



*Fig 5*

*A self-made illustration demonstrating the mechanism of GPCR desensitization by G protein kinases and β-arrestins*

*Created in BioRender.com*

## μ opioid receptor desensitization

The first step in this process is the desensitization of the μ opioid receptor.

This desensitization is modulated by two proteins; A protein called β-arrestin, and GRKs (G protein coupled receptor kinases).

### *G protein coupled receptor kinases*

As Fig 5 above shows, when the MOR is frequently activated by the opioid ligand, enzymes known as GRKs (G protein coupled receptor kinases) attach a phosphate ($PO_3$) group to the molecule, in a process known as phosphorylation (Arttamangkul et al.,

2018). This causes a conformational change that hinders the receptor's ability to interact with G proteins and subdues its ability to signal.

### *The β-arrestin signalling pathway*

Once this process is complete, the protein β-arrestin binds to the phosphorylated regions of the receptor. Due to steric hindrance, or the principle that a bulkier molecule is less reactive, the MOR is less able to recruit G proteins for signalling. On top of this steric hindrance, the beta-arrestin molecules outcompete G proteins, as all available binding sites are occupied (Gurevich and Gurevich, 2019). This is the secondary mechanism that desensitizes the receptor fully, and is shown in Fig 5 above.

## μ opioid receptor Internalization

Once the β-arrestin has bound to the MOR, a process known as endocytosis occurs. Recent literature indicates that this internalization isn't as greatly stimulated by agonists such as morphine, but occurs more with fentanyl, methadone, and even more with synthetic opioid peptides such as DAMGO, which is used for preclinical research (Talbot, 2007).

The process of endocytosis results in the receptor being engulfed by the membrane, and absorbed into the cytoplasm within a vesicle. Eventually, the receptor is reformed back at the cell surface. Nevertheless, the process of endocytosis results in lowered levels of MOR receptors on the plasma membrane, because the rate of recycling is lower than the rate of endocytosis. This can be described as downregulation, and generates tolerance as opioid substances have a lowered probability of interacting with a receptor.

This process of developing tolerance can help to explain why opioids are frequently so deadly to people who take them illicitly. This is because, after this process of desensitisation has occurred there are less MORs on the surfaces of cells.

However, if a user stops taking opioids, for instance due to lack of access, efforts to quit etc, the opposite of this process occurs in a mechanism known as re-sensitisation.

During receptor re-sensitisation, the presence of MORs on cell surfaces increases due to the lack of opioids in the system causing them to be internalised. If, after abstaining from opioid consumption for a prolonged duration of time, a user decides to take their priorly regular dose of opioids, the body's response is much greater because there are more MORs in their system. This inordinate response can engender respiratory depression, and subsequent death if ventilation is insufficient to sustain cellular life via respiration. Importantly, a reversal agent known as naloxone is available, but it is still not widely available in many communities. Efforts to increase the provision of naloxone will be pertinent in terminating unnecessary death via overdose.

## Conclusion (Are they good or bad overall)

To conclude, we have discussed the structure, mechanisms, benefits and drawbacks of consuming opioid-based substances. Generally, for medicinal practitioners, opioids have been and will continue to be invaluable for application in patient care and more specifically pain relief and reduction. When applied correctly, they have little downsides, as they are part of the body's endogenous system. However, if abused, there is a significant risk. In the US, misinformation alongside pharmaceutical pressure has led to doctors prescribing oxycodone for too long, which has contributed to the current addiction crisis we see today, where each year there are more and more opioid-related deaths. This is why I believe we should look to researching opioid-free forms of analgesia as these will free society from the depravity associated with opioid-related criminality.

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