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Opioids and their Receptors

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ABSTRACT

Opioids, derived from *Papaver somniferum*, have played a significant role in human history since 3400 BC, spanning recreational and medicinal uses. Opioid receptors in the central and peripheral nervous systems mediate their effects, primarily through inhibitory GABAergic interneurons. These are G-protein coupled receptors, with three primary types: μ, κ, and δ, each influencing various physiological and psychological functions. Opioids are classified based on their action on these receptors as full agonists, partial agonists, mixed agonist-antagonists, or antagonists. The endogenous opioid system, comprising opioid receptors and their endogenous ligands, regulates numerous physiological processes, including nociception, emotional behaviour, learning, memory, and reward pathways. Addiction to opioids, driven by the mesolimbic dopaminergic system, results in significant neurological changes, leading to tolerance, dependency, and severe withdrawal symptoms. Opioid use can cause short-term effects like analgesia and stress reduction, but long-term use leads to tolerance, dependency, and various physiological disorders. The opioid epidemic in the United States shows the urgent need for a deeper understanding of opioid mechanisms to develop effective treatment and prevention strategies, to address this ongoing crisis with comprehensive knowledge and intervention.

Introduction

The general term opioid is used to describe any substance, semisynthetic or synthetic derived specifically from *Papaver somniferum*, commonly known as the opium poppy. When harvested, the often green, fig-shaped seed pod produces a milky fluid. This liquid is opium, the natural opioid derived from the poppy plant. The fluid is often sun-dried to a resin-like consistency for further natural purification (Drug Enforcement Administration, 2021).

The earliest referenced opium farming and cultivation is in 3400 BC. Opium was collected by Sumerians living in lower Mesopotamia and recreationally used as well as used as an analgesic. Its usage spread through the Silk Roads and Indian Ocean Trade routes, where it spread Eastwards to China and westwards to the European nations. Britain utilized this drug as a way to increase trade with China by smuggling opium into China and rapidly increasing the addiction rate of the Chinese people, leading to the famous Opium Wars (Drug Enforcement Administration, 2021).

Considering this extensive history spanning from the beginning of human civilization, it can be understood that opioids are an integral part of human history, akin to the production of gunpowder and the discovery of electricity. But just as how revolutionary the aforementioned “things” are, its dangers are also comparable, and the same applies to opioids. Having a thorough understanding of how opioids work and affect us is critical for us to harness their infinite potential.

Opioid Receptors

To trigger the effects that they commonly provide, opioids attach to special receptors within the central and peripheral nervous system called opioid receptors. These receptors are normally responsible for the management of pain, but the triggering of these receptors by opioids can give a person a high as well as the analgesic effects.

Structure

Opioid receptors sit on inhibitory GABAergic interneurons within the central and peripheral nervous system. GABAergic interneurons are present throughout the body and are responsible for releasing GABA, the primary inhibition neurotransmitter of the brain. GABA is released at axon-axonic synapses and is responsible for the inhibition of neurotransmitter release in the postsynaptic axon. When opioid receptors are activated, the release of GABA is inhibited, and the postsynaptic neuron proceeds to freely release their respective neurotransmitters. In areas related to pain management, such as the thalamus, brainstem and spinal cord, the release of serotonin and norepinephrine is inhibited (Bear et al., 2020). Activation of these areas provides the customary analgesic effects of opioids. In areas such as the ventral tegmental area, the nucleus accumbens, the limbic system, and the prefrontal cortex, the release of dopamine is affected, giving the characteristic euphoric effects of opioid use. The activation of these areas also facilitates the process of addiction development (Baik, 2020).

Opioid receptors are G-protein coupled receptors (GPCRs), one of the most common cell signalling methods. GPCRs are transmembrane proteins that snake through the membrane in 7 transmembrane segments. The extracellular portion of the receptor, called the N-terminus, is where the ligand attaches and the intracellular portion, called the C-terminal end, is attached to the G-protein itself. There are a variety of G-proteins used by GPCRs, but the G_i protein and the G_0 proteins are the ones associated with opioid receptors. G-proteins comprise 3 subunits: the α, β, and γ subunits. The α unit is attached to GTPase, the enzyme to converts GTP, a compound similar to ATP, to GDP for energy, while the β and γ subunits are connected. When in a resting state, the G-protein is whole and connected, attached to the membrane by the α and γ subunits. The α subunit is attached to GDP during this time. When a ligand, such as an opioid, attaches to the receptor, the GDP is replaced with GTP, causing the separation of the α subunit and the β and γ subunits, called the $\beta\gamma$ complex. Within an opioid receptor, the α subunit attaches to adenylyl cyclase, inhibiting its function. The $\beta\gamma$ complex attaches to ion channels, where they close the Ca^{2+} channels and open K^+ ion channels, leading to repolarization of the action potential within the neuron and thus stopping GABA release (Navadiya, 2021).

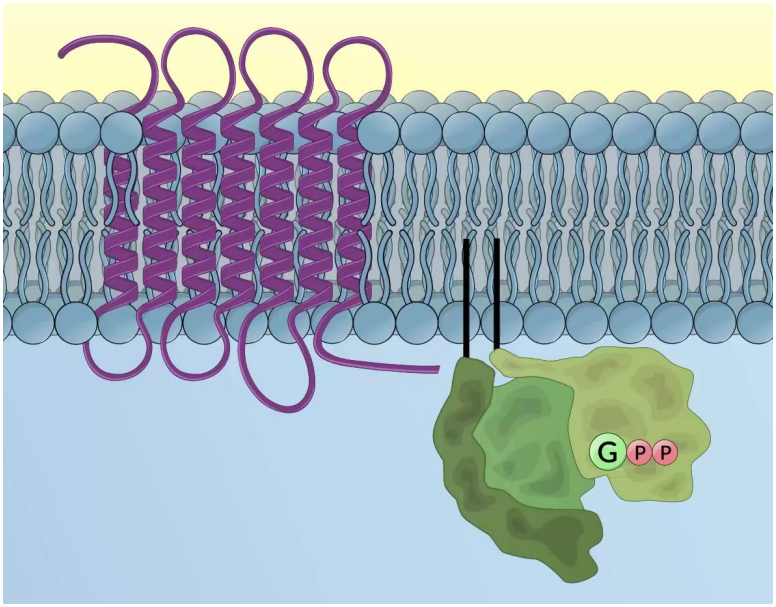

Figure 1. Diagram of a GPCR.

Types of Receptors

Research into these receptors is ongoing and there is much discussion regarding the various types of opioid receptors. However, it is generally accepted that there are at least 3 types of opioid receptors: μ, κ, and δ. μ-opioid receptors (MOR) are the most well-studied and best-understood of the three and it is known that there are 3 types of MOR. The activation of μ-1 receptors provides analgesia and also plays a role in developing dependence. μ-2 also plays a similar role but is also responsible for producing the signs of being high, such as euphoria, dependence, respiratory depression, miosis (pupil constriction), and decreased digestive tract motility. Vasodilation when using opioids is due to the activation of μ-3 receptors (Dhaliwal & Gupta, 2020). Nearly all research regarding opioid receptors has been done on MOR, so our understanding of κ-opioid receptors (KOR), and δ-opioid receptors (DOR) is limited.

KORs primarily attach to dynorphins produced within the body. They are widely distributed throughout the nervous system, and their activations have been shown to produce similar analgesic effects to MOR activation, with the added bonus that it does not have the addictive properties of MOR-activating compounds such as morphine. Current research is being done into the utilization of KOR agonists as a possible alternative to MOR agonists which are most commonly used in the medical setting. The main setback regarding this is due to the side effects of KOR activation, such as diuresis, salivation, nausea and dysphoria. There is minimal research done on DORs, but DOR activation is known to be induced by enkephalins and affects gastric mobility and respiration (Wang et al., 2010).

Opioids

Opioid is a general term used for a variety of different narcotic drugs. All opioids share the same basic structure molecularly, with only slight changes to differentiate between the various types but their efficacy and addiction potential greatly vary.

One of the most common ways that opioids are classified is by their basis of action, or how they act when attached to an opioid receptor. There are 4 categories that these drugs can fall under: full agonists, partial

agonists, mixed agonist-antagonists, and full antagonists (Opioids, 2012). Full agonists attach to opioid receptors and can fully inhibit the release of GABA. These include morphine, methadone, fentanyl, meperidine, codeine, hydrocodone, oxycodone, and heroin. This class of opioids are one of the strongest analgesics used in medicine, which explains their continuous presence within the field despite the addictive properties of nearly all of them. Partial agonists only partially inhibit the release of GABA. Some examples include buprenorphine, butorphanol, pentazocine, and tramadol. Of the ones mentioned, buprenorphine, butorphanol, and pentazocine are mixed agonist-antagonists, meaning they act as agonists of one type of opioid receptor and antagonist on another e.g. buprenorphine is a partial agonist at the MOR and antagonist at the KOR. Antagonists include naloxone and naltrexone and attach to receptors without triggering a response. This capability, along with the fact that antagonists would compete for receptors by replacing already attached opioid molecules, is why naloxone is a common treatment for those experiencing an opioid overdose, although its efficacy depends (study-medical, 2021).

Their chemical structures can also be utilized for differentiation. 4,5 epoxymorphinans all have a phenanthrene structure and are considered the commonly known opioids. Some opioids that are part of this group include morphine, oxycodone, codeine, hydrocodone, and buprenorphine (Drewes et al., 2012). Phenylpiperidines describe fentanyl, alfentanil, sufentanil, and remifentanil. These derivatives are commonly used as anaesthetics and analgesics within medical facilities, and fentanyl is a highly regulated substance, due to its high addiction potential (Urman et al., 2017). Diphenylheptanes include methadone and other similarly structured compounds e.g. propoxyphene and methadol. Pentazocine is one of the outliers of these criteria and is most often used as a last-resort pain medication in combination with naloxone (Trescot et al., 2008). Tramadol is another outlier, considered an atypical opioid for its monoamine reuptake inhibition. Thus, tramadol is a viable option, along with the currently used methadone, to treat opioid withdrawal (DEA Office of Diversion Control, 2014).

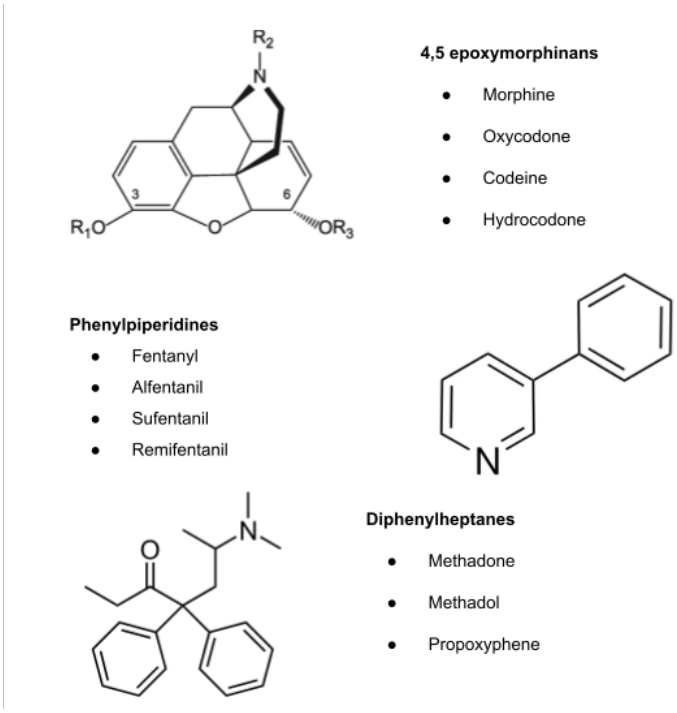

Figure 2. Diagram detailing the subtypes of opioids based on chemical structure. The base structure of each subtype is provided along with examples of substances that belong to each criterion.

Legally, opioids and other drugs are organised by the DEA into schedules. Schedule I are drugs with high addictive potential that serve no medical purpose, and include heroin among other non-opioid drugs such as ecstasy and LSD. Schedule II are drugs which also hold high addictive potential but have a medical use, and include oxycodone, fentanyl, methadone, and morphine among others. Schedule III includes drugs such as hydrocodone and codeine, that have medical uses and a moderate potential for addiction. Finally, Schedule IV have those with low drug addiction potential, and includes tramadol and pentazocine-naloxone combinations (United States Drug Enforcement Administration , 2018).

The Endogenous Opioid System

The endogenous opioid system (EOS) consists of opioid receptors and their endogenous peptide ligands are extensively distributed throughout the central nervous system and peripheral tissues. This widespread distribution assists the EOS in controlling multiple physiological processes, including nociception, emotional behaviour, learning, memory, and reward pathways.

There are three families of endogenous peptides, all derived from one of three precursors: proopiomelanocortin, proenkephalin, and prodynorphin. These compounds create several endogenous peptides, such as β-endorphin, met-enkephalin, leu-enkephalin, dynorphins, and neo-endorphins. Each opioid receptor has a distinct affinity for these endogenous ligands. For example, β-endorphin has a higher affinity for MOR compared to KOR or DOR, while met- and leu-enkephalin show a 20-fold higher affinity for DOR compared to MOR. Dynorphins primarily bind to KOR. All these peptides share a crucial N-terminal sequence required for the activation of opioid receptors. Additionally, endomorphin-1 and -2 have been proposed as selective ligands for MOR, although their genes and precursor proteins have not yet been identified (Trigo et al., 2010).

Opioid receptors and their endogenous ligands play a vital role in brain reward processes and influence the behavioural and neurochemical effects of various drugs of abuse. Components of the EOS are highly expressed in brain regions associated with reward and motivation, including the ventral tegmental area (VTA), nucleus accumbens (NAcc), prefrontal cortex (PFC), hypothalamus, and extended amygdala. These regions are integral to the modulation of reward circuits and contribute to the addictive properties of many substances, including opioids (Alcaro et al., 2007).

Methodology of Addiction

An addiction is a chronic, compulsive urge to partake in an action or use a substance, despite its clear negative effects. Whether addicted to a substance, such as alcohol or drugs, or behaviour, such as sex or self-harm, addiction always has a biological basis that encourages the abuse of these substances or actions, including when suffering from opioid addiction. Understanding how our body enables this addictive behaviour is critical not only for the treatment of those with substance abuse disorder but also to prevent the development of these addictive compulsions in the first place.

Within our brain, there are a variety of different pathways that control various aspects of our functioning. One of the most critical ones is dopaminergic pathways (DA), which are pathways controlled by the usage of dopamine. The DA is composed of a variety of cerebral regions, including the VTA, the PFC, and the substantia nigra and the dorsal striatum. The major reward centre of our brain and the system that relates to addiction is the mesolimbic dopaminergic system (ML-DA). The region in the ML-DA releases or interacts with dopamine to manage positive and negative reinforcement, incentive, aversion, and decision-making, giving it the name of the reward system (Restak, 2000).

The process begins in the midbrain. This area consists of dopaminergic neurons and is the production site for dopamine within the brain. The dopaminergic neurons are clustered within various groups: A8 cells in

the retrorubral field or the A9 cells in the substantia nigra (SN). The cells that are part of the ML-DA are the A10 cells of the VTA. These dopaminergic cells of the VTA extend to a variety of brain regions in the forebrain. The primary structure affected by the Ml-DA is the NAcc, a region within the basal forebrain that is responsible for controlling motivation and drive. This area of the brain is what contributes to inspiration when faced with a reward, feelings of incentive and extrinsic drive. The NAcc is divided into 2 portions, the core and the shell. While the core primarily connects to motor systems the shell of the NAcc is closely connected to the subcortical limbic system, contributing to emotionally motivated drives (Baik, 2020).

Opioids that bind to receptors within the ML-DA increase the production of dopamine within the VTA. This greater quantity of dopamine is sent to the NAcc, where that sense of reward is produced, and due to the NAcc's close connection to the limbic system, feelings of euphoria are produced. When suffering from an addiction, the NAcc brings the extrinsic drive and desire for opioids and that characteristic compulsion to use. When facing withdrawal, the limbic system triggers the emotional symptoms of withdrawal, such as anxiety (Baik, 2020).

Effects of Usage

Due to the ubiquity of the EOS throughout the brain and various other parts of the body, the usage of opioids doesn't only affect the brain and behaviour, but also a variety of other physiological functions and organs. There are often lesser-known symptoms and side effects of opioid usage and are often seen in those who use opioids medically and are even seen with the activation of opioid receptors with endogenous peptides, although only to a limited extent (Dhaliwal & Gupta, 2020).

Short-Term Effects

The common side effect and the primary motive of medical usage of opioids is analgesia. When an opioid, whether exogenous or endogenous, attaches to MOR, the inhibition of the GABAergic interneurons triggers impulses from inhibitory neurons. This triggers the release of endorphins, from the dorsal horn, an area within the spinal cord consisting of grey matter. This production of endorphin reduces the nociceptive transmission from the peripheral afferent neurons containing pain signals to the thalamus. The activation of the MOR in the locus cerulus also inhibits the secretion of norepinephrine, leading to a decrease in stress (Dhaliwal & Gupta, 2020).

Opioid receptors are abundant and widely distributed throughout the autonomic nervous system, and thus their activation affects many physiological processes. There is an excessive abundance of opioid receptors within the GI tract, and their activation slows down peristalsis. This activation reduces passive water movement throughout the lumen of the small intestines, leading to constipation. Mechanoreceptors within the airways and lungs also have opioid receptors, and when activated, respiration is slowed, leading to the development of hypercapnia and hypoxia. Hypotension is also common in those who use opioids, as hyperpolarisation of the vagus nerve due to opioid receptor activation can cause bradycardia and vasodilation (Dhaliwal & Gupta, 2020).

The hypothalamus and the pituitary gland can also be affected by opioid usage. Activation within the hypothalamus inhibits gonadotropin-releasing hormone deliverance, leading to sexual dysfunction, infertility, and osteoporosis. The release of adrenocorticotropin is also inhibited, leading to low cortisol levels, which can cause a variety of symptoms, such as nausea, vomiting, abdominal pain, weakness, fatigue, lethargy, and fever. Certain cases have been shown to cause the release of anti-diuretic hormone, leading to reduced urination and possibly even hyponatremia. Opioid receptors present on phagocytes and other immune cells reduce the efficacy of these cells when activated, leading to a weakened immune system. The opioids can also affect the medium pontine reticular formation leading to decreased deep sleep and REM sleep durations coupled with longer light sleep durations (Dhaliwal & Gupta, 2020).

Long-Term Effects

Along with such symptoms of active opioid usage, long-term usage can dramatically alter the structure and chemical balance of the brain and nervous system. One of the primary reasons that opioids are not ideal for long-term usage is due to the development of tolerance. Tolerance is defined by the progressive diminishing of the analgesic or intoxicating effects of opioids when taking the same amounts consistently, thus requiring higher doses to achieve the "high" they desire. There are a variety of causes of tolerance development. With prolonged opioid use, the body could learn to metabolise drugs in the system sooner e.g. an increase in drug-decomposing enzymes within the body. The receptors could also become desensitised to opioids, due to their repeated stimulation. This is often done through the phosphorylation of receptors by kinases, hindering its ability to couple with G-proteins. Receptor downregulation is also possible, which is usually done by the binding of β-arrestins to receptors, triggering endocytosis. Alterations within the cell could also lead to tolerance, such as increased activity of cAMP pathways, making the inhibition of adenylyl cyclase by lower doses of opioids not as effective. These alterations also affect the EOS as well, leading to opioid dependency, where people are dependent on opioid usage to perform normally. If gone without opioids for too long, addicts will experience withdrawal symptoms, which prompts them to continue using, making detoxification extremely hard for addicts (Dumas & Pollack, 2008).

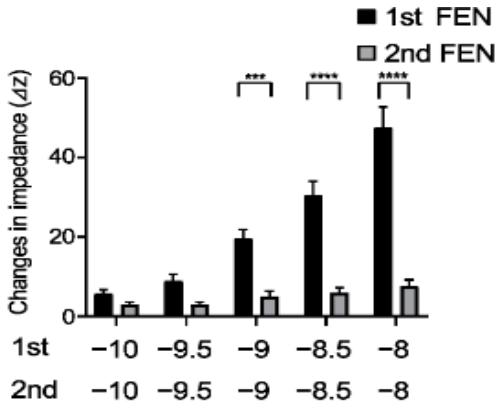

Figure 3. This graph shows the difference in signal strength between the first and second doses of fentanyl, based on the amount provided (the x-axis is logarithmic).

Opioid - Induced Disorders

The formal diagnosis for opioid addiction is opioid use disorder. It is characterised as a substance use disorder and is defined by a disruptive and threatening usage of opioids that causes significant distress. It is marked by an excessive usage of opioids that is either not used for medical purposes or is in larger quantities than prescribed. This can be accompanied by a variety of symptoms. The person could suffer from cravings or desires to use, and develop tolerance. The cravings can often drive people to use in conditions where it is inappropriate or even harmful. Addicts centre their daily routine around obtaining and using opioids, to the point where it causes problems with their social occupational, or recreational lives. Addicts often struggle with controlling or cutting down their opioid usage and tend to use it when it can be physically or psychologically hazardous. Those with opioid use disorder commonly have psychological comorbidities e.g. depression, PTSD, etc. or physiological comorbidities e.g. HIV, Hepatitis A, B, C, etc. (American Psychiatric Association, 2013).

Opioid use disorder is often coupled with opioid tolerance and dependency and when detoxing, opioid addicts can suffer from withdrawal symptoms. When stopping the usage of opioids or taking an antagonist, the lack of exogenous opioids within the system causes addicts to suffer from withdrawal symptoms. These tend to start around six to eight hours after the last use and progressively get worse. Acute withdrawal symptoms typically last up to a week, but many long-term symptoms can last for months or even are lifelong. Some of the acute symptoms include nausea, dysphoria, rhinorrhea, diarrhoea and piloerection, while some long-term symptoms include insomnia, anxiety and cravings. Treatment often includes being in an inpatient detoxification program or utilising methadone detoxification (Tengler, 2020).

Conclusion

Although opioids have proven to be an indispensable part of modern medicine, it is also well-understood how dangerous their use is. Nearly 565,000 Americans have died from opioid overdoses between 1999 and 2020, with the rates still on the rise. Despite congressional efforts to limit access to illicit drugs and stop opioid abuse, the number of overdoses continues to increase year after year, with the current concern benign the rise of synthetic opioids, primarily fentanyl and fentanyl analogues. Fentanyl is up to 50 times more potent than heroin and is actively laced into a variety of other drugs, often without the user's knowledge (Congressional Research Service, 2022).

The opioid epidemic within the United States continues to worsen year by year, And motions to stop the rise of deaths before it is too late are actively on the rise. But, there is only so much that can be done without a proper understanding of how these opioids work within us and we must understand these processes and how they are expressed physiologically and psychologically. Only then can we truly work to find the most beneficial relationship with this monumental discovery of opioids.

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