Brain-Body Connection of Chronic Drug Abuse

Marine Sevel

Abstract

Opioids have a longstanding history in medicine and are also the subject of the ongoing substance abuse epidemic in the United States. In addition to strong analgesic (pain-relief) properties, synthetic opioids also have high addiction potential and their long-term abuse can result in fatal outcomes. The mechanisms and outcomes associated with the long-term abuse of synthetic opioids involve both the body and mind. In this review article, key organ systems and brain areas affected by long-term opioid use are summarized. Additionally, possible mechanisms that underlie the effects mediated by long-term opioid abuse are included. Lastly, this review article provides an overview of interventional approaches under current investigation for the treatment and management of opioid use disorders. It is important research on opioids is continued to better help those suffering from opioid use disorders.

Introduction

Opioids have been used for millions of years as a medication to relieve pain from wounds and injuries. In the 18th century, opioids were used as anesthetics. They were used in large numbers on the battlefield of the civil war in the U.S., due to opium's ability to quickly relieve a gunshot wound's pain. The influx of soldiers prescribed opioids for pain largely resulted in an opioid epidemic and the death of thousands (Boysen et al., 2023). Later in the 19th century, a spike in the prescription of opioids led the number of overdose deaths in the U.S. to increase dramatically. Since then, over 500,000 people have overdosed due to opioids and died in the United States alone (Federal Communications Commissions). Another layer of complexity is added to the epidemic with polysubstance use in efforts to balance, counteract, or potentiate the effects of another high.

What is important to note about opioids are their binding affinity and their potency. Opioids have a high affinity for the receptors they bind to which include mu-opioid receptors (MORs), delta opioid receptors (DORs), and kappa opioid receptors (KORs). These are known as GPCRs, or G-protein coupled receptors and are found everywhere in the body but mostly in the brain and the respiratory system. When a person takes opioids, the opioids bind to these opioid receptors within the body. Most commonly, they will bind to MORs. Activation of this type of receptor sends descending inhibitory impulses which decreases the transmission of pain from the periphery to the central nervous system, effectively causing analgesia (Dhaliwal A, Gupta M. 2023). Furthermore, activation of MORs results in a discontinuance of GABA (Gamma-aminobutyric acid) secretion. VTA (ventral tegmental area) GABA neurons specifically influences the release of dopamine in the brain, thus when less GABA is put out in the brain, there is an influx of dopamine leading to a euphoric sensation or a high.

The brain contains natural opioid-like molecules (endogenous opioids), that work on the same receptor systems as synthetic opioids. One major difference between endogenous and synthetic opioids is the dopaminergic release caused by each substance, where the former leads to a significantly smaller amount than that of a synthetic drug. The constant intake of synthetic opioids leads to the output of dopamine, eventually leading to a phenomenon called tolerance. As tolerance builds, the need for a larger quantity of synthetic opioids appears, and eventually an addiction is formed.

Besides the aforementioned analgesic effects of opioids, the presence of opioid receptors in other areas of the body causes other adverse effects. The chronic use of synthetic opioids leads to respiratory depression, constipation, hypotension, endocrine abnormalities, anti-diuretic hormone (ADH) secretion from the posterior pituitary, and immune dysfunction in the body. These effects of opioids have been studied, but they still have large pieces of information about them missing. Similarly, there are still many questions remaining regarding opioids' effects on the brain and mind. Currently, it is known that chronic opioid use weakens GABAergic inhibition of VTA DA neurons . Decreases in dendritic branching as well as spine density in NA MSNs (nucleus accumben's medium spiny neurons) and mPFC (medial prefrontal cortex) pyramidal cells also occur. These lead to impairments in the brain and its functions. In short, opioids can lead to permanent brain damage with irreversible effects on one's behavioral ability to function properly in response to cognitive stimulation.

The purpose of this study is to investigate the brain-body effects of opioids and their potentially lethal effects under chronic use. Here, specific organ systems within the body are reviewed, as well as specific brain areas affected by chronic opioid use. Moreover, an additional review of the effects of chronic cannabis use on the same central nervous system (CNS) structures is provided to issue additional details on the abuse potential of opioids relative to other substances of abuse.

Cardiac Effects

While uncommon, chronic opioid usage does lead to various adverse effects in the cardiovascular system. Intake of morphine may lead to immoderate levels of histamine release, thus leading to vasodilation and hypotension (Benyamin et al., 2008). This effect can be partially blocked by an H1 antagonist, a class of drug blocking histamine's attachment to H1 receptors, and can be completely reversed by naloxone (Benyamin et al., 2008). Notably, only mu, delta, and kappa receptors are present in the heart (Zimlichman et al., 1996) (Headrick et al., 2015).

Opioid use can also increase parasympathetic cardiac activity and bradycardia (Benyamin et al., 2008). The mechanisms for this effect are unclear, however one study provided a possible explanation. This study on rats used immunolabeling methods and found that MORs are located postsynaptically on premotor cardiac parasympathetic nucleus ambiguus (PCPNA) neurons, which are a subset of neurons in the nucleus ambiguus that control cardiac function (Irnaten et al., 2003). Seventy-eight percent of dendrites and the whole of the perikarya of PCPNA neurons housed MORs. The same study also found that the activation of MORs inhibited voltage-gated calcium currents in PCPNA neurons (Irnaten et al., 2003). Specifically, the MOR agonist endomorphin-1 elicited this effect rather than the MOR agonist endomorphin-2. The two agonists are differentiated by only one amino acid in their amino acid sequence (Geracioti et al., 2009). The calcium currents in question were mostly made up of omega agatoxin-sensitive P/Q type voltage-gated calcium currents. The study concludes it is possible that the inhibition of these calcium currents may indirectly encourage activity of PCPNA neurons through disinhibition. In other words, the less active calcium currents indirectly caused an increase in nucleus ambiguus neurons. This slowed the rats' heart rate. It is possible the same mechanism is what causes slowed heart rates in humans following opioid consumption.

Methadone (a type of opioid) was also found to block the ether-a-go-go-related-gene (hERG) channel in humans, which encodes the potassium channel IKr (Benyamin et al., 2008). This block causes a prolonged QT interval, and can thus lead to torsades de pointes (TdP), a change in the heart's rhythm known as ventricular tachycardia (Cohagan & Brandis, 2024). As

reported by the FDA, between 1969 and 2002 there were 59 cases of methadone-induced long QT syndrome (LQTS) or Tdp (Del Rosario et al., 2010). Tachycardia-correct QT prolongation (QTc) was also found to be caused by methadone, as it prolongs the cardiac action potential through inhibition of cardiac potassium channels (Benyamin et al., 2008). QTc greater than 500 milliseconds is generally associated with twice the increased risk of TdP (Li & Ramos, 2017). In a group of heroin addicts who were being treated with methadone, 16% developed prolonged QTc. Of that group, 3.5% experienced TdP (Benyamin et al., 2008). Review of data concluded QTc prolongation in significant patients was found in those taking a total daily dose of more than 30 mg of methadone. TdP on the other hand was observed in those taking 40-120 mg of methadone. In these studies, a significant correlation between QTc and the addition of CYP3A4 inhibitors like fluoxetine and clarithromycin to methadone treatments (Benyamin et al., 2008). In yet another study of seventeen patients receiving methadone who developed TdP, the mean daily dose was 397 +/- 283 mg, a higher average than the previous study (Krantz et al., 2002). Fourteen of those patients had a predisposing risk factor for arrhythmia. In conclusion, high dose methadone increases the likelihood of developing TdP, especially in those with predisposing risk factors. Treatment of drug-induced QT prolongation includes removal of the administration of the drug causing QT prolongation and looking into alternate treatment methods (Li & Ramos, 2017). If TdP fails to be prevented, direct-current cardioversion (DCCV) may be needed (Li & Ramos, 2017).

In line with the aforementioned effects of opioid usage, it is generally understood that heart function decreases as a function of chronic opioid usage. There is a strong correlation between the use of opioids and a dangerous drop in heart rate and blood pressure. A pattern is also present in the use of high doses of opioids and QTc and TdP which can be fatal. Due to the discovery of MORs on cardiac neurons, it is possible there are many more adverse effects of opioids on the heart that have not yet been identified.

Gastrointestinal Effects

Gastrointestinal effects of opioid use are pervasive. The most frequent effects include constipation, nausea, vomiting, and narcotic bowel syndrome. In a three year study of 200 patients receiving oxycodone, the most frequent adverse effect was constipation and nausea (Smith & Laufer, 2014). In cancer patients, 40-60% of those taking medically prescribed opioids experience constipation (Sizar et al., 2024). Opioid-induced constipation (OIC) is caused by the inhibition of gastric emptying and peristalsis by opioid stimulation. The increase in absorption of fluid leads to the hardening of stool and thus constipation. Other mechanisms through which opioids cause constipation is the increase of the anal sphincter tone, impairing defecation reflexes, and a decrease in the emptying of pancreatic juice and bile which hinders digestion (Sizar et al., 2024). While dietary fiber and fluid intake may help with OIC, traditional laxatives are more efficient at helping to resolve constipation. Newer agents like peripherally acting MOR antagonists (PAMORAs), selective 5-H antagonists, and intestinal secretagogues have also gained popularity and are widely used to treat OIC (Crockett et al., 2019). The National Cancer Institute (NIH) explains methylnaltrexone bromide (Relistor) as a drug that is a type of peripheral opioid antagonist. It binds to receptors outside the brain, letting the opioids relieve pain but is still able to block certain side effects of opioids.

Narcotic bowel syndrome (NBS) is a significant side effect of opioid use that has seemingly no cure. NBS causes abdominal pain, but when opioid dosages increase to alleviate this, the pain progresses and even gets worse, countering its purpose of analgesia.

(Grunkemeier et al., 2007). While pain is the dominant symptom of NBS, nausea, vomiting, bloating, and weight loss are also common symptoms. Unfortunately, there are not many studies on NBS or these counterintuitive effects of opioids. Certain studies suggest that NBS is caused because neural and opioid pathways can both inhibit and facilitate pain (Grunkemeier et al., 2007). Other studies explain NBS is due to neuroplasticity in the brain (Grunkemeier et al., 2007). The known mechanisms of NBS include the activation of excitatory anti-analgesic pathways within the excitatory and inhibitory opioid regulation system (Grunkemeier et al., 2007). Descending facilitation of pain and pain facilitation through dynorphins and cholecystokinin activation may also add to NBS, as well as glial cell activation that produces morphine tolerance and enhances opioid-induced pain (Grunkemeier et al., 2007). To treat NBS, opioid administration needs to be withdrawn slowly, and other medicines are sometimes taken for other symptoms of NBS such as antidepressants and laxatives.

As seen in NBS, opioids may also cause nausea and vomiting. Opioid-induced nausea and vomiting (OINV) is a significant issue for patients taking opioids, because it can cause complications like pulmonary aspiration, dehydration, and electrolyte imbalance (Khansari et al., 2013). As with NBS, OINV's mechanisms are not exactly clear. Opioids can affect vestibular function in various ways with different types of opioids. A recent randomized control trial hypothesized that opioids affect semicircular canal function, which leads to an imbalance between canal input and other sensory information thus causing nausea and vomiting. However, after the trial, the study concluded this wasn't the relevant trigger for OINV (Heuser et al., 2017). The study did however prove that movement triggered nausea independently of visual input, indicating that head-rest is more important to prevent OINV than sleep or eye closure (Heuser et al., 2017). For OINV, antidopaminergic, digestive tract movement-enhancing agents and antihistaminergic agents are usually the first choice for treatment (Hirakawa, 2013). Opioid antagonists like naloxone and naltrexone may also be used to alleviate nausea and vomiting, and for some patients, a different method of opioid administration may help too (Smith & Laufer, 2014).

Many of the issues opioids cause in the GI tract are due to the prevalence of opioid receptors within this organ system. In the GI tract, MORs and DORs are the most expressed (Galligan & Sternini, 2017). MORs are found specifically in the small intestine and proximal colon while KORs are found in the stomach and small intestine, as seen in rats (Galligan & Sternini, 2017). As such, it can be appreciated that systemic administration/availability of various opioids can lead to off-target effects in organ systems such as the GI tract.

Endocrine System Effects

In the endocrine system, KORS, DORs, and MORs are present. MORs are found in particularly high numbers (Jaschke et al., 2021). Within the endocrine system, opioids cause opioid endocrinopathy (OEI), opioid-induced androgen deficiency (OIAD), cortisol deficiency, and hyperprolactinemia.

OEI covers a variety of effects opioids have on the hypothalamic-pituitary-gonadal axis (HPG axis), which regulates the secretion of gonadal hormones in males and females. Common symptoms include fatigue, depression, hyperalgesia, decreased libido, anemia, and immune suppression. The hypothalamus secretes gonadotropin releasing hormones or GnRH which through follicle-stimulating hormones (FSH) and luteinizing hormones (LH) increases levels of testosterone and estrogen in the body (Medina II & Conermann, 2024). Thus, inhibition of GnRH further causes the inhibition of many hormones involved in the HPG axis, which includes not

only FSH and LH but also dehydroepiandrosterone (DHEAS) and growth hormones (GH) (Medina II & Conermann, 2024). Hypogonadism, the production of little or no hormones by the gonads, is a part of opioid endocrinopathy. It occurs in over half of male opioid users (De Vries et al., 2020). As previously said, opioids inhibit GnRH secretion, lowering levels of testosterone and estrogen. Opioids in addition inhibit oxytocin secretion from magnocellular neurons by blocking R-type Ca2+ channels (Morris et al., 2010). Low levels of oxytocin are linked to mental health disorders like depression. Opioids slow bone metabolism, leading to low bone mineral density and the impeding of fracture healing in animal models (Coluzzi et al., 2020). These effects are connected to opioid induced endocrine effects. As such, these effects may also be present in humans. Concerning OEI and hypogonadism, testosterone therapy is extremely common for men. It can include buccal, gel, cream, and transdermal patch release formulation (Medina II & Conermann, 2024). However, there is not much evidence supporting hormone therapy treatment in women. Hormone replacement in the form of estrogen-methyltestosterone is the only form of hormone treatment that is approved for women. DHEAS supplementation has shown promise in hormone therapies but is still less well-established than testosterone therapy (Medina II & Conermann, 2024). Other possible treatments include switching opioid classes while maintaining the same dosages, in efforts to mitigate their effects on the endocrine system.

OIAD is a manifestation of OEI and is characterized by low levels of gonadotropins, causing low levels of androgen. As well as OIAD, opioids can inhibit corticotropin-releasing hormones (CRH) and antidiuretic hormone (ADH) secretion (Smith & Elliott, 2012). This results in low levels of the adrenocorticotropic hormone (ACTH), causing hypoadrenalism. Opioids, specifically morphine and methadone, can cause hyperprolactinemia where there are high levels of prolactin in the blood. MORs, DORs, and KORs mediate tuberoinfundibular dopaminergic neurons. When stimulated, they reduce the activity of these neurons which leads to an increase in prolactin release (Kolnikaj et al., 2000). Treatment for drug-induced hyperprolactinemia includes switching doses or drug class, and the addition of a dopamine agonist (Molitch, 2005).

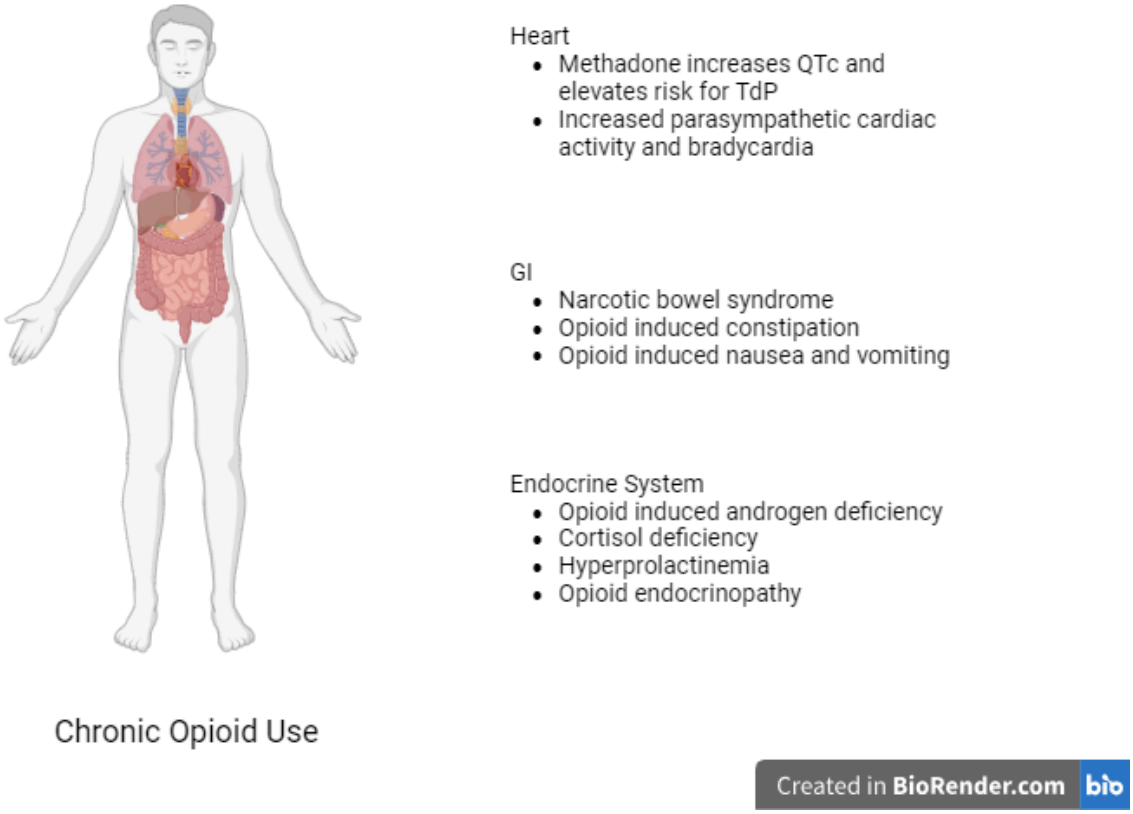

Figure 1. Effects of chronic opioid use on different areas of the body including the heart, the endocrine system, and the gastrointestinal tract. Created in BioRender.com

Brain Mechanisms

Nucleus Accumbens

The nucleus accumbens (NAc) is a brain structure located in the basal forebrain that plays a major role in the reward pathway of the brain. It mediates goal-directed behavior, thus it plays a major role in addiction. Structurally, the NAc consists of a shell and a core.

The NAc houses GABAergic medium spiny neurons (MSNs), different types of interneurons, and glial cells. 90% of the NAc's neurons are GABAergic MSNs (Scofield et al., 2016). These can either have D1 or D2 receptors. D1 dopamine receptors couple to a subtype of G proteins that activate adenylate cycles, thus stimulating cAMP production and other proteins dependent on cAMP. D2 dopamine receptors however couple to a different subunit of G proteins that has the opposite effect of D1 receptors, inhibiting adenylate cyclase and cAMP production (Scofield et al., 2016). Just as D1 and D2 receptors work differently, they contribute differently to drug-associated behaviors and drug-induced alterations in the structure and function of the two cell types (Scofield et al., 2016). Interneurons also have different cell types, three of the GABAergic interneurons being in the striatum. Those expressing parvalbumin generate gamma frequency and aid in the inhibition of cortical pyramidal neurons projecting to striatal neurons (Mannekote Thippaiah et al., 2022). The second type of interneurons co-express somatostatin, neuropeptide Y, and neuronal nitric oxide synthase. The third type expresses calretinin (Scofield et al., 2016). The fourth type of interneuron is cholinergic and is

maximally responsive to stimulus detection and context recognition in contrast to dopamine rigid neurons (Scofield et al., 2016). They are regulators of striatal network activity and output. Cholinergic interneurons have been shown to hold an essential role in motivation and mood regulation. For example, one study found a correlation between a reduction in cholinergic interneurons and depressive behavior (Warner-Schmidt et al., 2012). Astrocytes, a type of glial cell, regulate glutamatergic synaptic plasticity in the NAc through the control of glutamate concentration and coordinated uptake and release (Scofield et al., 2016). Other than the cells, core, and shell, the NAc also accounts for the extracellular matrix, a network of proteins and molecules that make up 20% of the total volume in our brains (Scofield et al., 2016). The extracellular matrix consists of 2 main proteins. It essentially provides support for the brain's cells, as well as regulates neurotransmission and cellular growth (Scofield et al., 2016).

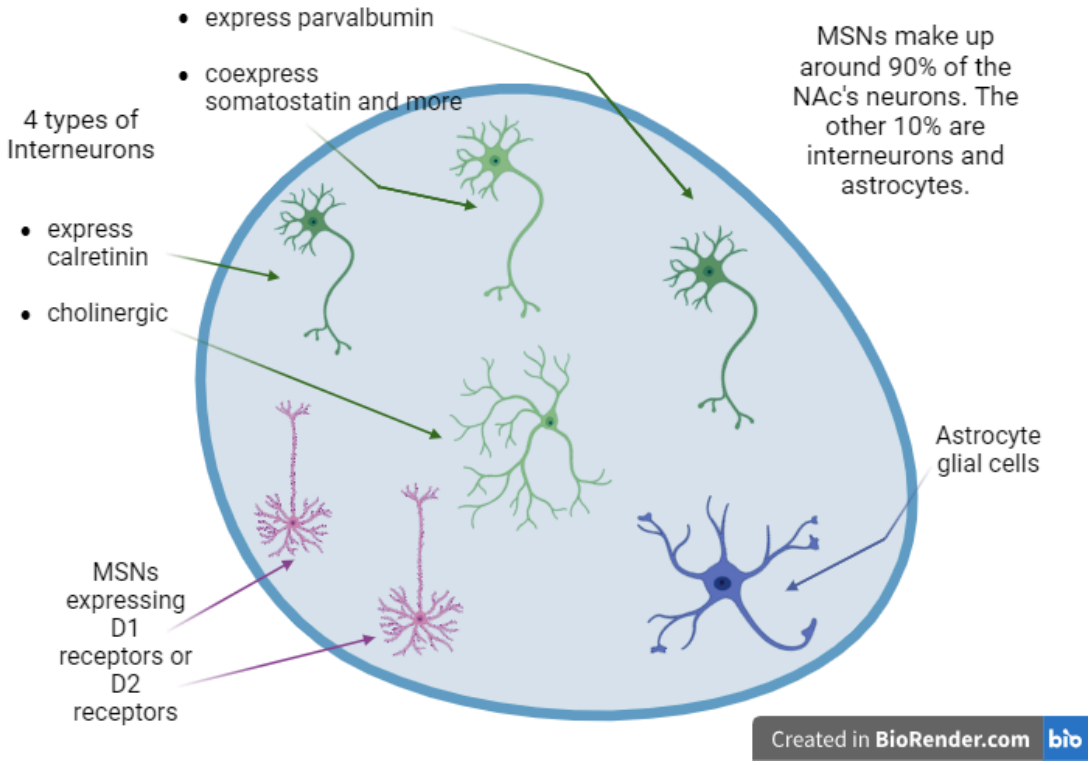

Figure 2. Different types of cells within the NAc. Created in BioRender.com

The NAc is a key structure regarding all drug use disorders. As chronic use of opioids continues in a person, the connection between neurons within the brain weakens or strengthens depending on the brain area. In the NAc, connections increase in size, number, and strength, contributing to enhanced synaptic connectivity between neurons (LearnGenetics, 2013). Connectivity changes cause drug-seeking behaviors to morph into habits, which thus lead to addictions or substance use disorders. These changes in neuronal connection are not permanent but can still take months to years to fully recover from and return to a normal state. Drugs of abuse, like opioids, induce neuroplasticity in the NAc, leading to drug-seeking behaviors, and are reflected in connectivity changes.

The NAc overlooks withdrawal and drug-seeking behaviors, as evidenced by multiple clinical reports and studies. Specifically, the paraventricular nucleus of the thalamus' inputs to

the nucleus accumbens plays a major role in the physical aspects of opioid withdrawal (Zhu et al., 2016). The NAc is such a major component of OUD that it may also be the key to a possible treatment for OUD. A 2023 clinical trial found through neuro imagery that in patients with OUD, deep brain stimulation of the NAc ventral capsule could reduce opioid cravings and therefore use (Rezai et al., 2024). As the deep brain stimulation surgery had no serious complications, research should be continued into the NAc regarding OUD, to find a dependable treatment for it and possibly other drug use disorders. Studies have recently also linked KORs in the NAc to behaviors regarding opioid withdrawal (Zhu et al., 2023). The study suggests that since KORs are abundantly expressed in the NAc, and the NAc overlooks stress-induced cocaine-seeking as well as motivation for heroin and opioid-withdrawal-related behavior, the addition of KOR antagonists in the NAc could reduce stress-induced cocaine-seeking and reduce motivation to consume opioids (Zhu et al., 2023).

In rats, cannabinoid receptor 1 (CB1) receptors within the NAc were found on the plasma membrane and in the cytoplasm of neuronal and glial profiles (Pickel et al., 2004). Additionally, structural analysis of synapses within the NAc indicates CB1 and opioid receptors participate in similar, if not the same, synapses within the NAc, potentially indicating shared neuronal signaling pathways between cannabinoids and opioids (Pickel et al., 2004). These receptors were generally more abundant in the shell rather than the core of the NAc. Interestingly, only 3% of the MORs found in the NAc using the same technique as the CB1 receptors overlapped with where CB1 receptors were found (Pickel et al., 2004).

Regarding long-term use, a study on 108 young adults found that those using greater quantities of marijuana had delays concerning non-drug reward anticipation in the NAc (Martz et al., 2016). In adolescents, marijuana use was found to lower NAc functional connectivity to the prefrontal cortex, which was also linked to depressive symptoms and anhedonia (Lichenstein et al., 2017). For long-term marijuana users, these adverse effects and symptoms may transform into real complications surrounding reward processing in the NAc, which can unfortunately further encourage future drug use disorders. Similarly, THC was found to impede responses to rewards in the NAc specifically in people with nicotine addictions.

The study concluded that nicotine addiction may be linked to altered endocannabinoid modulation of reward processing in the NAc (Jansma et al., 2013). Human MRI scans have also found that cannabinoid users had higher gray matter densities than those who didn't use cannabinoids in the left nucleus accumbens (Gilman et al., 2014). A higher density of gray matter in the NAc means the NAc itself has a higher density, which could potentially induce more activity. This increase in activity may lead to more drug-seeking behaviors, furthering drug addiction and repeating a harmful cycle. These effects of cannabis, specifically THC, can be found in Figure 3.

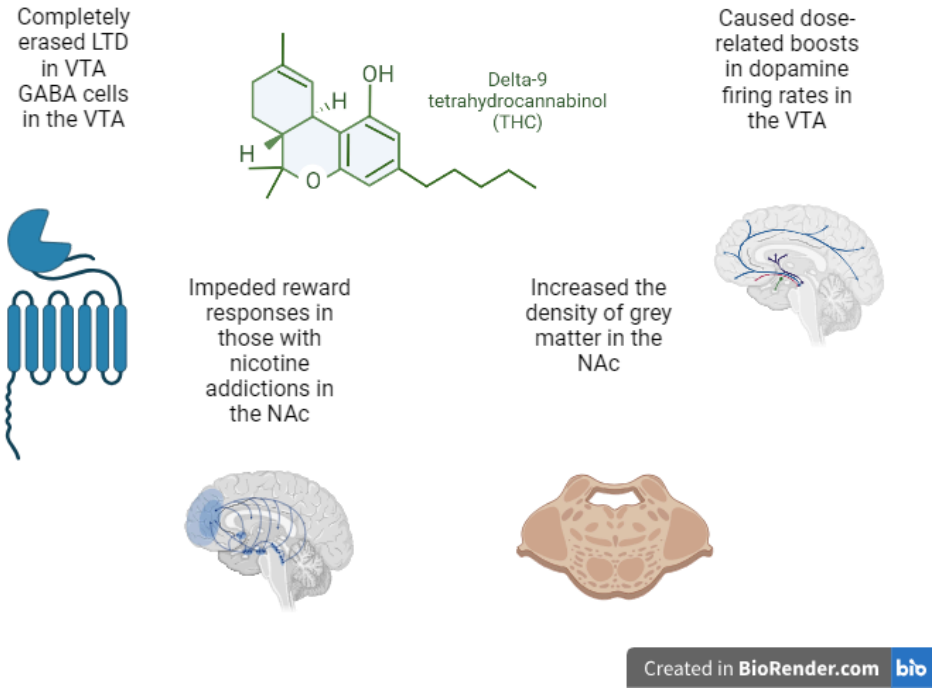

Figure 3. Effects of THC in the brain. Created in BioRender.com

Cannabis and opioids both elicit different effects that ultimately encourage drug-seeking behaviors and the formation of addictions. Both substances were correlated with depressive behavior and induced connectivity changes that further led to other harmful effects on the brain after prolonged use of the substances. These different substances have overlapping effects on the NAc.

Ventral Tegmental Area

The ventral tegmental area (VTA), consisting of the anterior lateral VTA and posterior medial VTA, regulates reward consumption, learning, memory, and addiction-inducing behaviors through the mediation of dopamine (DA) release. It consists of a group of neurons located in the midbrain. These neurons are made of 60% DA neurons, 35% GABAergic neurons, and 5% glutamate neurons (Cai & Tong, 2022).

In the VTA, dopamine relic neurons express tyrosine hydroxylase (TH), dopamine transporter (DAT), and vesicular monoamine transporter 2 (VMAT2) (Mannekote Thippaiah et al., 2022). These DA neurons either fire in a stable tonic pattern or in a high-frequency pattern. The latter releases more dopamine quicker into the NAc, driving reward (Mannekote Thippaiah et al., 2022). In contrast, a stable tonic firing pattern releases less dopamine and therefore has a smaller reward. GABAergic neurons in the VTA respond to aversive stimuli, while glutamate neurons express vesicular glutamate transporter 2, VGlu2, both of which contribute to reward and motivation signaling (Cai & Tong, 2022). This is through the local release of glutamate in the VTA from distal axons such as the NAc (Cai & Tong, 2022).

Similar to the NAc, chronic drug use is often followed by an increase in excitatory synaptic strength in VTA DA neurons. In a study covering cocaine's effect on the VTA, cocaine

causes synaptic changes to surface onto VTA DA neurons. This led to long-lasting increases in their burst firing causing major changes in the DA system (Creed et al., 2016). Changes in synaptic plasticity by all drugs of abuse in VTA DA neurons further induce the development of inhibitory synaptic plasticity and enhancement of excitatory synaptic strength (Creed et al., 2016). All these changes in the VTA DA cells induce behavioral changes. Because neuroplasticity regulates the structural regulation of neuronal spines as well as signal transduction, changes in neuroplasticity leads to many issues in the brain, contributing to the development of neurological and psychiatric disorders (Duman, 2004).

During cannabis use, the VTA releases excessive amounts of dopamine neurons into the brain, just as with other drugs. Systemic administration of delta 9-THC, a chemical found in cannabis, along with the synthetic cannabimimetic aminoalkyl indole WIN 55,212-2 created dose-related boosts in the firing rate of dopamine neurons in the VTA (French et al., 1997). This increase encourages further drug-taking and therefore the development of a drug use disorder. Recently, an age-dependent neural plasticity caused by THC has been discovered in the VTA. In young mice, VTA GABA cells in the VTA display long-term depression, or LTD, which is a state of synaptic plasticity (Ostlund et al., 2023). After regular exposure to THC, LTD was found to have been erased in the VTA. A seven-day withdrawal from THC resulted in restored LTD, but adult mice needed double the synaptic stimulation the younger mice required. The result of this study suggests as people get older, the brain's natural ability to heal itself from the negative effects of drugs one consumes wears down, and eventually may not function properly anymore. While the young mice are able to heal quickly, the adult mice take longer to do so, and this effect can only get worse as chronic drug use continues.

Mesolimbic Pathway

The mesolimbic pathway consists of the NAc, VTA, amygdala, hippocampus, and prefrontal cortex. It is the central reward pathway of the brain. When dopaminergic neurons are activated in the VTA, dopamine is released from the VTA and into the NAc synapses. When a natural amount of dopamine arrives in the NAc, the brain is able to elicit a behavioral response from cues (Becker-Krail et al., 2022). Studies of animals receiving dopamine receptor antagonists in the NAc were not able to perform operant behaviors in response to different cues (Nicola et al., 2005). It is important to note that all substances of abuse modulate the mesolimbic pathway through dopamine.

When the brain and mesolimbic pathway are exposed to chronic drug use, neuroplasticity changes occur in both the VTA and NAc, driving reward-seeking behaviors. The first most common example of neuroplasticity changes in the brain is tolerance and physical dependence (O'Brien, 2009). Over time, the brain counteracts high stimulation through mechanisms to reduce excitability. One mechanism by which this is mediated is through reduced expression of synaptic dopamine receptors and increasing expression of dopamine transporters (DATs), effectively reducing dopamine transmission. Over time, this makes the brain less responsive to the drugs it is receiving, which unfortunately also applies to endogenous reward signaling naturally occurring in the brain. In short, this phenomenon is called tolerance and causes the user to feel less rewards or less of a 'high' over time even with a continued use of the same dosages. To combat this, users take higher doses of drugs to get the same feeling repeating the cycle. In addition, activities releasing endogenous opioids and natural dopamine would be similarly affected, felt less by the user. This cycle leads to addiction. The second most common example of changes in neuroplasticity is compulsive drug-seeking behaviors as previously

mentioned. Compulsive drug-seeking behaviors due to neuroplasticity can be irreversible, making recovery difficult (O'Brien, 2009). These two phenomena increase risks for addiction and are what make drug use dangerous.

Conclusion

Understanding the bodily and brain effects of opioids is of great importance particularly now, as the U.S. faces a currently ongoing opioid epidemic. Rising rates of early-onset cancer facilitate the further increase in the use of opioids as pain relievers. Regarding the body, there are clear connections between opioids and the heart, with opioids inducing TdP, parasympathetic cardiac activity, and QTc prolongation. There are still likely effects on the heart by opioids that have not yet been discovered, suggested by the presence of MORs on cardiac neurons. In addition, opioids give rise to adverse effects in the gastrointestinal system including NBS, OINV, and OIC. NBS in particular has no cure and not much is known about the symptom. Lastly, opioids cause a wide variety of issues in the endocrine system, coined OEI. OEI covers OIAD, cortisol deficiency, and hyperprolactinemia. Many of these effects of opioids generally have no widespread cure but instead generally result in the prescription of additional drugs.

In the brain, the mesolimbic pathway and specifically the NAc and VTA have been covered. Drug use in the NAc induces neuroplasticity, resulting in an increase of neuronal connections, morphing drug-seeking behaviors into habits and addictions. This pattern of increasing excitatory synaptic strength is found again in VTA DA neurons, causing an influx in synaptic plasticity, which leads to neurological disorders. Regarding cannabis use, dose-related boosts in the firing rate of dopamine neurons happened in the administration of opioids as well as delta-9 THC. Cannabis use was found to cause an age-dependent neural plasticity, LTD which differs from the plasticity caused by opioids in the brain. Within the NAc, CB1 receptors and opioid receptors were found to participate in similar synapses, which could mean they share neuronal signaling pathways. Cannabinoid users were also found to have higher gray matter density, leading to drug-seeking behaviors. Cannabis and opioids overlap greatly in the fact that they both are addictive drugs that induce tolerance and dependence with permanent effects on the brain, particularly as one gets older.

As mentioned previously, there is still a significant lack of information regarding opioids and their effect on the brain and body. Effects of opioids on the heart have yet to be discovered, as well the mechanisms for NBS. There currently are not enough studies on how NBS works, and thus there is no cure for the painful syndrome. Within the brain, there are a multitude of ongoing studies aiming to help those with OUD, such as a trial overlooking the effects of deep brain stimulation of the NAc ventral capsule on opioid cravings that shows significant promise. There are still aspects of opioids and their mechanisms in the brain that remain unknown, which links to potential treatment methods for those with OUD. Treatment of OUD includes replacement or substitution therapy, rehabilitation, group therapy, reward cooperation, and cognitive behavioral therapy. With these therapies in mind however, relapse rates remain high. Medication-assisted-treatment has a success rate of over 50% and is another step towards the end of the opioid epidemic. Still, it is of great importance that research continues in the area of opioid use disorder, furthering our understanding of its effect on the body, brain, and mind. Certain genes are linked to addictions, increasing specific peoples' risks of becoming addicted to different substances. Professor Brian Anderson explains in an article that attentional biases for drug cues are a normal cognitive process that everyone undergoes (Anderson, 2016). Essentially, everyone has a form of addiction or exhibits addictive behaviors because of our

biases within reward learning. Addiction in some form will always be present in humans. Thus, it is profoundly imperative that research is continued into the psychology and scientific mechanisms of addiction. Through this, more efficacious treatments may be created to better the lives of currently almost 50 million people battling addiction in the U.S.

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