Cannabinoids in Opioid Addiction Treatment: Pharmacological Mechanisms

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Abstract

Opioid addiction, a chronic relapsing disorder, continues to impose great health and economic burden on our society. America’s opioid crisis has become an epidemic due in part to the lack of effective treatments for the negative physical and emotional states suffered by the individuals during withdrawal from chronic opioid use. These symptoms might be major contributing factors to relapse. Recently, cannabis and cannabinoids have emerged as a potential therapeutic strategy in the treatment of opioid addiction. This review differs from many other reports in the field by focusing on the possible mechanisms underlying the effects of cannabinoids on the negative physical and emotional states induced by opioid withdrawal. We start by briefly outlining the current opioid crisis and how both opioids and cannabinoids affect the mammalian central nervous system (CNS). Next, we present findings that illustrate how cannabinoids may be used to enhance opioid analgesia and to mitigate opioid withdrawal syndromes. Finally, we summarize these findings and propose directions for future research.

Keywords: Cannabis; Cannabinoids; Opioids; Addiction; Mechanisms

Introduction

Since morphine was first extracted in 1803 [1], opioids have grown to be the standard of care around the world for the treatment of pain [2]. Although opioid consumption has always posed the risk of addiction, opioid use disorders and opioid overdoses have rapidly increased since the late 1990s [3]. Today, prescription opioid dependency affects over 2.1 million Americans, and over 130 people in the United States die from opioid overdoses every day [4]. In 2017, these trends prompted the Department of Health and Human Services to declare the opioid overdose crisis an epidemic [5].

As the opioid epidemic continues to reach new heights in North America, the need to find viable alternatives to opioid treatment becomes increasingly urgent. Given its antinociceptive properties and lower potential for overdose, Cannabis has received increasing attention as both a substitute for opioid-based pain treatment and also as a treatment strategy for opioid addiction [6]. A growing amount of literature has been investigating whether cannabinoids can attenuate opioid withdrawal symptoms and compensate for the side effects of opioid treatment. Preclinical studies with cannabinoids have mitigated morphine withdrawal symptoms in animals, including jumping, weight loss, head shakes and paw tremors [7-9]. Furthermore, states that had legalized medicinal marijuana saw a 24.8% lower mean annual opioid overdose rate compared to states that had not [10], and the number of opioid abuse and dependence-related hospitalizations decreased by 23% without changes in the number of marijuana-related admissions [11]. These reports suggest that cannabinoids might be used by some opioid addicts to reduce the risk of overdose; however, due to its current status as a Schedule I substance in the US and a limited number of human trials, many of the underlying mechanisms and effects of cannabinoids on opioid addiction are not yet fully understood.

The clinical aspects of cannabinoids and opioid interactions have been recently reviewed by Scavone et al. [7]. This narrative review will examine the signaling pathways common to both cannabinoids' effects and several opioid withdrawal symptoms including hyperalgesia, anxiety, and depression. From the perspective of these shared pathways, this review aims to evaluate some of the mechanisms that may contribute to cannabinoids' potential therapeutic effects on opioid addiction and withdrawal.

Opioid signaling

Although opioids can bind to several types of receptors (kappa, delta, mu, nociceptin/orphanin FQ), [12] their analgesic [13] and rewarding [14] effects are primarily mediated by mu opioid receptors (MORs), a class of G protein-coupled receptors (GPCR) found in the CNS. MORs is present throughout the mammalian CNS but are concentrated in areas such as the ventral tegmental area (VTA), striatum, locus coeruleus, and spinal dorsal horn [15]. Activation of MORs by opiate ligands in the mesolimbic reward system produces a highly addictive euphoria [14], whereas activation in the brainstem is responsible for respiratory depression associated with opioid overdose [16,17].

Opioid-MOR signaling mediates a variety of intracellular functions through the Gi/o protein. One such function is the modulation of specific adenylyl cyclase (AC) isoforms. These cell membrane-bound enzymes convert adenosine triphosphate (ATP) into cyclic adenosine monophosphate (cAMP) via the cleavage of a pyrophosphate group [18]. There are nine different isoforms of AC (named with Roman numerals, AC-I through AC-IX). Upon acute MOR activation, the Gi/o protein associated with the GPCR inhibits AC-I, AC-V, AC-VI, and AC-VIII and activates AC-II, AC-IV, and AC-VII [19]. The net effect of these interactions inhibits the production of cAMP and its downstream
Cannabinoids and opioid-induced negative physical states

Cannabinoids and opioid-induced hyperalgesia: Despite being one of the most common strategies to treat chronic pain, opioid therapy may paradoxically lead to an increased sensitivity to noxious stimuli (opioid-induced hyperalgesia [OIH]) that contributes to the development of tolerance, addiction, and overdose [42]. While the susceptibility to, pathogenesis and severity of OIH depend on a variety of factors, it is generally considered that longer periods of opioid use, higher dosages of opioids, and use of opioids with higher potencies are associated with more severe OIH. However, as reported by Vanderah et al. [43], adult male Sprague Dawley (SD) rats with no visible signs of withdrawal can develop OIH after only a single dose as well. Although most of the underlying pathways of OIH remain enigmatic, there are some plausible theories as to why hyperalgesia is observed following opioid use.

One of the best-supported hypotheses for OIH is opioid-induced upregulation of excitatory signaling in the spinal cord [44] and areas of the brain that are involved in pain perception, such as the Nucleus Raphe Magnus (NRM) [37]. It has been demonstrated that morphine withdrawal increases NRM AC-VI and AC-III mRNA levels and AC-V and AC-VI immunoreactivity, reflecting increased cAMP levels and excitatory signaling to the nociceptive fibers in the spinal cord [37]. Mao et al. [44] also found that chronic morphine exposure downregulated glutamate transporters, EAAC1 and GLAST, in the spinal cord, further elevating glutamate levels after opioid exposure. This rise in glutamate levels leads to increased NMDAR activation and a subsequent influx of calcium and sodium ions and efflux of potassium ions. Not only do these ionic shifts contribute to the depolarization of the neuron, but the increased intracellular calcium also acts as a secondary messenger by stimulating PKC [45]. Multiple previous reports have shown that the upregulation of PKC activity can enhance OIH. PKC removes magnesium from NMDAR and phosphorylates NMDAR subunits, further increasing their sensitivity and activity [45,46]. This is consistent with the findings by Li and Clark [47] who reported an increase in NMDAR and Substance P (SP)-neurokinin 1 (NK-1) receptor signaling following opioid withdrawal. Increased levels of nitric oxide (NO) that diffuse from the postsynaptic membrane to the presynaptic membrane and stimulate the release of SP are produced through a PKC-dependent process. This increase in NO contributes to the development of sensitivity to noxious stimuli [48]. However, because morphine can increase NK-1 receptor-activated internalization [49] and capsaicin-evoked SP release, it is unclear to what degree the increased signaling is directly due to increased glutamate signaling and PKC activity. Moreover, chronic NMDAR activation may cause severe nerve injury or cell death [45,50], resulting in additional tolerance and hyperalgesia [51].

Cannabinoid signaling

Historically, the use of cannabis dates to before 500 B.C. in central Asia, where Cannabis sativa, the plant that produces cannabis, was used in herbal medicine [27] and spiritual practices [28]. Today, marijuana is one of the most abused recreational drugs around the world [29], with a plurality of Western nations and US states liberalizing or legalizing cannabis use in various forms. The psychoactive ingredients within cannabis bind to endogenous cannabinoid GPCR (CB1 and CB2) receptors. CB1 receptors (CB1R) are the most abundant GPCR in the CNS and are highly expressed in regions involved in reward, addiction, and cognition, including the amygdala, cingulate cortex, prefrontal cortex (PFC), ventral pallidum, caudate putamen, nucleus accumbens, VTA, and lateral hypothalamus [7,30,31]. The psychomimetic and rewarding effects of cannabis are generally attributed to the activation of CB1R in these areas [32]. CB1R activation by exogenous compounds, such as ∆9-THC, has been linked to cognitive dysfunction [29], dysregulated stress responses, psychosis, mania, and amotivated syndrome [33]. This article will focus more on the effects of cannabinoid-CB1R signaling since CB1R are the better studied of the two receptors. However, CB2 receptors (CB2R) may also play an essential role as recent reports indicate that they both are present in dopaminergic neurons in the VTA [34] and mediate immune responses, including those that contribute to inflammatory [35] or neuropathic hyperalgesia [36], which have been hypothesized to use the same mechanisms of opioid-induced hyperalgesia [37].

After CB1R activation by a cannabinoid (CB) or CB2R agonist, the coupled G11/0 protein dissociates and activates G protein-coupled inwardly rectifying potassium (GIRK) channels, inhibits specific AC isoforms [38], and closes voltage-gated P/Q- and L-type calcium channels, all like that of MORs [7,38-40]. While it may be tempting to infer from these findings that MORs and CB1R share the same G11/0 protein pools, reports by Shapira et al. [41] suggest otherwise. Using [35S] guanosine-5′-O-(3-thiotriphosphate) binding assays, it was shown that MOR and CB1R activation on N18TG2 cell membranes by etorphine and desacyl-levonantradol, respectively, resulted in a summative effect. Application of low concentrations of pertussis toxin to deplete the G protein reservoir did not alter this additivity, suggesting that the two receptors use different G11/0 protein pools that converge at the level of AC activity.

cAMP-mediated signaling cascades [7]. Protein kinase A (PKA), an enzyme that phosphorylates cAMP response element binding (CREB) proteins, is one of the many signaling molecules downregulated in the absence of cAMP. Under normal circumstances, CREB proteins diffuse through the nuclear membrane and activate transcription at cAMP response element (CRE) [7]. With chronic opioid use, prolonged downregulation of cAMP levels causes neurons to compensate for this decreased signaling activity through various allostatic adaptations including increased expression of AC-VIII, PKA precursors, and CREB, among other signaling proteins [7].

Additionally, an earlier study showed that protein kinase C (PKC), when activated by the influx of calcium ions from opioid-MOR binding, also catalyzes the in vitro phosphorylation of MORs and delta opioid receptors (DORs), representing another signaling pathway in agonist-induced receptor desensitization [20]. This is consistent with reports by Javier, et al. [21] who noted that morphine-induced tolerance involves several signaling proteins, including the N-methyl-D-aspartate acid glutamate receptor (NMDAR), nitric oxide synthase (NOS), PKC, PKA, calcium (Ca++)-calmodulin (CaM)-dependent kinase II (CaMKII), and the regulators of G-protein signaling (RGS) proteins. Furthermore, there is evidence of a physical association between MORs and NMDARs in post-synaptic structures, supporting the idea that the NMDAR/nNOS/CaMKII pathway plays a significant role in opioid tolerance. These studies showed that the associated NMDAR could be affected by various signals originating from the activated MOR and, in turn, exert a negative feedback effect on MOR signaling that result in MOR desensitization [21]. These adaptations, together with super-activation of AC-I, AC-VI, and AC-VIII, increase neuronal excitability, allowing the cell to act “normally” [22] in the presence of opioids [19]. Alterations to these signaling pathways are hypothesized to be the underlying molecular mechanisms for addiction, tolerance, and withdrawal [23-26].
Bie et al. [37] also showed that overproduction of cAMP is associated with the upregulation of the hyperpolarization-activated current (Ih), which contributes to neuron excitability and facilitates nociceptive signaling. Blockade of the cAMP pathway, NMDAR, NK-1 receptor, or PKC activity, as well as stimulation of glutamate transporters, have all been shown to reduce OIH.

A comprehensive meta-analysis showed that medicinal cannabis and cannabinoids effectively alleviate multiple types of pain such as fibromyalgia, multiple sclerosis, cancer-associated pain, and non-cancer-associated pain [52]. Furthermore, administration of cannabinoids effectively suppressed hyperalgesia and allodynia in inflammatory and neuropathic pain, which have been speculated to arise through the same physiologic mechanisms as OIH [53-57]. As described above, administration of CB₁R agonists results in hyperpolarization of neurons through regulation of various signaling pathways and cytosolic ion levels like opioids. By inhibiting N-, P/Q- and L-type calcium channels, [59] CB₁R may downregulate the A C pathway, PKC signaling cascade, neuron excitability, and ultimately nociceptive neurotransmitter release and signaling [60].

Additionally, cannabinoids may decrease glutamate signaling through the internalization of NMDAR NR1 subunits, thereby inactivating NMDAR. Sánchez-Blázquez et al. [61] reported that the C1 segment of the NR1 subunit could associate with the C-terminus of CB₁R through interactions with histidine triad nucleotide-binding protein 1. Upon activation and internalization of CB₁R, the NR1 subunit would also be co-internalized, leading to deactivation of associated NMDARs. Conversely, Hillard and Auchampach [62] found that 10 μM or above of Δ⁹-THC upregulated PKC activity in rat frontal cortices in vitro, possibly by facilitating the formation of enzyme/ phosphatidylycerine/calcium complexes and resulting in augmented OIH.

Consequently, cannabinoids may also protect against opioid-evoked NMDA-mediated neurotoxicity. Ryan et al. [63] found that cannabidiol (CBD), a cannabinoid with no psychomimetic properties, can regulate cytosolic calcium levels under conditions of high excitability by targeting mitochondria. This is consistent with the findings of Marsicano et al. [64] who showed that mice lacking CB₁R in forebrain neurons could not suppress kainic acid-induced seizures and potential excitotoxicity through anandamide-CB₁ signaling. Cannabinoids may also attenuate OIH through activation of glial cell CB₁R. Chronic morphine exposure stimulates the release of proinflammatory mediators such as NO, IL-1β, IL-6, and TNF-α from microglial cells in the spinal cord [35]. Therefore, activation of microglial CB₁R by cannabinoids may attenuate OIH by inhibiting the release of various inflammatory cytokines that facilitate nociceptive signaling [35].

Another possible mechanism of OIH is the modulation of the rostral ventromedial medulla (RVM). Activation of specific subsets of neurons in the RVM, termed on-cells, facilitates nociceptive signaling, whereas activation of “off-cells” inhibits it [42,50,65]. Morphine exposure elevates the release of cholecystokinin (CCK) and leads to tonic activation of RVM on-cells, which in turn increase spinal dynorphin levels and release of excitatory neurotransmitters and calcitonin gene-related peptides on primary afferent fibers [50,66]. These upregulations manifest as enhanced spinal nociceptive signaling and result in hyperalgesia. Both bilateral lesioning of the descending pathway (the dorsolateral funiculus) from the RVM and inhibition of RVM activity with lidocaine prevent increases in dynorphin [67], and excitatory neuropeptides, in addition to opioid tolerance, and OIH [43].

Regarding cannabinoids, Meng and Johansen [68] showed that microinjections of WIN55,212-2 in the RVM reduced activation of on-cells, shortened off-cell inhibition duration, and increased off-cell activity induced by tail-flicks. These findings are further supported by other investigators who have shown that CB₁R activation inhibits the RVM antinociceptive signaling pathway by suppressing presynaptic GABAergic input [69].

Cannabinoids and opioid withdrawal-induced locus coeruleus-noradrenaline circuit hyperactivity

Another region of the CNS affected by chronic opioid intake is the locus coeruleus (LC), which supplies noradrenaline (NA) to various parts of the brain responsible for cognition, pain, emotional state, anxiety, arousal, and stress [70,71]. During acute opioid administration, the decrease in CAMP and the closing of various ion channels inhibits LC neurons from releasing NA [7], resulting in somnolence, bradypnea, hypotension, and many other symptoms characteristic of opioid intoxication. However, upon repeated opioid exposure, the LC becomes increasingly excitable through allostatic adaptations. This results in increased NA signaling, causing many of the observed withdrawal symptoms associated with opioid abstinence [7,72]. These symptoms include hyperhidrosis [73], nausea and vomiting, oscillation, restlessness, anxiety and irritability, mydriasis, tremors, tachycardia, and a plethora of flu-like symptoms such as chills, pyrexia, and myalgia and arthralgia [7,74]. While these neuroendocrine adaptations are restored to normal levels after approximately two months of opioid abstinence [72], the symptoms that precipitate during this withdrawal period often require pharmacological therapy. Using drugs that target the NA circuitry, treatment strategies can attenuate many opioid withdrawal symptoms. However, because consumption of α2-adrenergic receptor agonists can result in hypotension, sedation, cognitive impairment, incomplete attenuation of withdrawal symptoms, and other negative side effects [7], the search for a more efficient therapeutic agent without these undesirable side effects remains imperative.

While there is a growing body of evidence that suggests CBs play a role in the treatment of opioid addiction, the effects of CBs on the LC remain equivocal. Various reports indicate that administration of anandamide [9] or Δ⁹-THC [75,76] abates opioid withdrawal symptoms in rodents, which may be the result of interactions with NA circuitry [7]. Furthermore, Δ⁹-THC administration in the LC reduces the symptoms of morphine withdrawal by facilitating enkephalin release, which is of particular importance because chronic opioid exposure decreases endogenous opioid levels in the LC [7]. Mendiguren and Pineda [77] showed that administration of WIN55,212-2 suppressed KCl-evoked firing in the LC, suggesting a regulatory role for CBs under conditions of pathological hyperexcitability. In contrast, Muntoni et al. [78] reported that WIN55,212-2 and Δ⁹-THC dose-dependently increased firing in the LC pathway by inhibiting release of gamma-aminobutyric acid (GABA). Additionally, administration of WIN55,212-2 and CP 55940 both elevated Fos expression in NA neurons of the LC, reflecting increased neuronal activity that may be associated with the unexpected increase in LC NMDAR activation [79-81]. The ambivalent nature of the effects of cannabinoids is further emphasized by the observation that intravenous WIN55,212-2 and CP 55940 increased LC neuron firing rates in a dose-dependent manner, directly contrasting that of in vivo local administration and in vitro bath application, which did affect LC neuronal firing rates [81].
Cannabinoids and opioid synergy and opioid-sparing effects

Cannabinoids’ analgesic properties have raised the question as to whether these substances can serve as substitutes for opioids in pain therapy or be taken concurrently with opioids [84]. Like MORs, CB1Rs are highly expressed in areas of the CNS involved with nociceptive signaling [85]. However, unlike MOR agonists, no preclinical studies and only a few clinical studies have reported hyperalgesia with chronic administration of cannabinoids [86]. Furthermore, previous reports showed that co-administration of cannabinoids and opioids, each at sub-analgesic levels, resulted in a synergistic effect that not only elicited successful analgesia but also prevented the development of tolerance [87,88]. A meta-analysis of six preclinical trials showed that when administered with Δ⁹-THC, the median effective dose of morphine was a 3.6-fold lower than that of morphine alone in rodent models [89]. Similar findings were observed using codeine where the median effective dose was 9.5-fold lower when co-administered with Δ⁹-THC than alone [89]. Similarly, human studies by Dr. Ziva Cooper and colleagues showed that cannabis might augment the analgesic effect of opioid oxycodone; however, it also slightly enhanced oxycodone’s abuse liability [90].

Although the underlying mechanisms for this phenomenon remain poorly understood, some possible explanations have been offered. Using kinetic binding studies, Kathmann et al. [91] found that Δ⁹-THC and CBD act as allosteric modulators for mu and delta opioid receptors. Additionally, the observed synergism may be the result of elevated synthesis and release of dynorphins that enhance the antinociceptive effects of MOR agonists by binding to kappa opioid receptors [88,92]. This possibility is supported by Cocher et al. [92] who found that Δ⁹-THC increases both prodynorphin and proenkephalin gene expression in rat spinal cords. Furthermore, Donvito et al. [52] suggested that CBs suppress the release of proinflammatory cytokines caused by opioids through activation of CB2Rs, as discussed earlier. These effects may account for the synergistic analgesic effects of cannabinoids and opioids and suggest that cannabinoids could be a viable adjunctive or even substitute therapy for opioids in pain management to reduce the likelihood of developing dependence, tolerance, or OIH. However, contrary to the above findings, various other groups have not been able to document synergism between opioids and Δ⁹-THC [93]. Some investigators have reported cross-talk and cross-tolerance [85,94-96] where chronic opioid exposure led to the development of tolerance to the antinociceptive effects of cannabinoids, just as chronic administration of cannabinoids does for opioids. The effects of opioid-cannabinoid synergy remain debatable and for future research to further elucidate [95,97-99].

Cannabinoids and opioid-induced negative emotional states

One common contributing factor to and symptom of chronic opioid use is the development of negative emotional states upon abstinence [100]. As detailed by Swift and Stout [101], these emotional symptoms are directly associated with heightened cravings for the drug since they promote a conditioned association between opioid use and symptomatic relief [100,102,103]. Furthermore, while many of the somatic withdrawal symptoms result from biological adaptations, some are modulated by emotional factors [104,105]. In a study of 60 males in heroin withdrawal, 20 in long-term abstinence, and 20 healthy controls, viewing images that elicited negative emotional states heightened sensitivity to cold pressor pain in all groups, but particularly so in the heroin withdrawal group [23]. Cannabinoids, given their antidepressant and anxiolytic properties, may interact with opioid addiction and withdrawal circuitry by affecting negative emotional states. Various authors have reported that activation of CB1Rs elicits anxiolytic and antidepressant effects in animal models [39,106,107]. In contrast, Wilson and Roberts [105] suggested that cannabis use strengthens the relationship between pain and negative affective states through self-efficacy (the confidence that a patient can manage their symptoms using MAT). The following discussion addresses how cannabis use affects anxiety and depression, the most often cited negative emotional states resulting from and contributing to opioid addiction [102].

Cannabis mitigates anxiety

Cannabis is widely associated with the ability to modulate anxiety, with data from case series, preclinical trials, and clinical trials typically confirming its anxiolytic effects [39,108,109]. A clinical study by Fabre and McLendon [110] found that anxiety levels drastically improved after 11 daily doses of nabilone, a synthetic cannabinoid with effects that mimic Δ⁹-THC and endogenous cannabinoids [111]; these effects also persisted for 17 days after discontinuation of nabilone. Likewise, inhibition of CB1Rs resulted in increased anxiety when rats were subjected to light/dark choice tests or elevated plus mazes (EPM) [106]. These effects, caused by CB1 and non-CB1 receptors such as the serotonin 5-HT1A receptor, [112] were also produced by blocking the degradation of anandamide using fatty acid amide hydrolase (FAAH) [106]. Crippa et al. [111] reported that patients with social anxiety disorder were significantly less anxious after 400 mg of CBD compared to placebo control subjects. Using 99mTc-ECD SPECT imaging, they also found that patients given CBD showed reduced ECD in the left amygdala-hippocampal complex and left posterior cingulate gyrus compared to the placebo group. These results are consistent with the findings that these limbic and paralimbic cortical areas are associated with the pathophysiology of anxiety. If the increased hippocampal activity is correlated with decreased anxiety levels, it seems reasonable to surmise that reduced activity may be associated with increased anxiety. Additionally, Gonzalez-Cuevas and colleagues reported in a 2018 study that rats with a history of prolonging alcohol or cocaine use significantly reduced stress and drug-seeking behavior after given CBD [113]. These improvements persisted for several months after CBD was no longer detectable and are consistent with the current research that shows CBD can reduce compulsions, anxiety, and nausea–symptoms associated with detoxification [113].
Conversely, one of the most common side effects of both acute and chronic cannabis use is anxiety [108, 114]. Approximately 20%-30% of all users experience brief anxiety after using marijuana, although the incidence depends on various contributing factors [115]. Chronic users of cannabis are associated with a 7% to 29% higher probability of having anxiety disorders than the general population [115]; other reports indicate an even higher incidence [116]. However, it remains unclear whether cannabis use leads to increased anxiety or individuals with preexisting anxiety conditions predispose them to cannabis use [117]. Other factors, such as a poor socioeconomic background, childhood adversity, or traumatic experiences, may all contribute to the development of both anxiety disorders and a higher likelihood of cannabis use [117].

**Cannabis alleviates depression**

Cannabinoids may also act as antidepressants, but much less is known regarding this effect of cannabis in opioid addiction than its anxiolytic properties [114]. Compounds such as AM404, URB597, oleamide, Δ9-THC [119], and HU-210 all evoke antidepressant behaviors in forced swim tests [120]. Additionally, genetic deletion [121] or pharmacological blockade of CB1Rs has been shown to increase depression-like phenotypes in mice [122]. Likewise, rimonabant was associated with severe depression and suicidal tendencies in clinical trials [123]. In a controlled 10-year-longitudinal study of 1310 subjects by Wittchen et al. [124], Cannabis use/cannabis use disorders were associated with mood and anxiety disorders. However, in another study, this association was not observed after accounting for demographics, neuroticism, and other drug use [125].

**Mechanisms of cannabinoids rescue opioid-induced negative emotional states**

One possible mechanism underlying the negative emotional states experienced during opioid withdrawal may be the elevated levels of corticotropin-releasing factor (CRF) due to hyperactivation of the hypothalamic-pituitary-adrenal axis (HPA-axis) and extrahypothalamic sources [126]. Genetic deletion of CRF1 and CRF2 receptors eliminated both the negative affective states and the elevated dynorphin levels that accompany opioid withdrawal, indicating an integral role for the CRF system in opioid addiction [127]. However, contrary to expectations, cannabinoid use results in escalated HPA-axis activity and CRF release, likely exacerbating dysregulation of the CRF system [126, 128]. This finding is corroborated by other studies showing that cannabinoids increase blood cortisol levels in a dose-dependent manner [128, 129]. High doses of the CB1R agonist HU-210 also activated the HPA-axis, but intriguingly, this effect was prevented by the 5-HT1A antagonist WAY 100635 and the 5-HT2A/2C antagonist ketanserin, and not by an NMDAR antagonist (MK 801) or an AMPA/kainate receptor antagonist (DNQX) [130]. Additionally, pretreatment with prazosin, an α1-adrenoceptor antagonist, abolished the withdrawal-induced increase in cortisol release [130]. Collectively, these findings suggest that cannabinoids activate the HPA-axis through upregulation of monoaminergic neurotransmitters such as 5-HT and NA. This hypothesis is directly supported by findings of high levels of FAAH [131] and CB1R expression in rodent dorsal raphe nuclei, a serotonergic center in the brain [85, 132]. Likewise, microinjections of CBD into the dorsal periaqueductal gray of SD rats seemed to decrease anxiety in the elevated plus maze and elevated T-maze studies [112]. As expected, 5-HT1A receptors contributed to the observed anxiolytic effects because they were reversed by the administration of a 5-HT1A receptor antagonist. Similarly, microinjections of CBD in the bed nucleus of the stria terminalis and the central nucleus of the amygdala also produced anxiolytic effects via 5-HT1A receptor activation [133].

CBD has demonstrated an agonistic potential for 5-HT1A receptors by increasing GTP binding to Gi protein [134]. Likewise, the antidepressant effects of cannabinoids appear to be dependent on the 5-HT system. Rodriguez Bambico et al. [135] found that low doses of WIN55,212-2 possessed antidepressant-like qualities that were blocked by both rimonabant and parachlorophenylalanine (a 5-HT-depleting agent) in forced swimming test. This increase in monoaminergic transmission may play a role in promoting neurogenesis in the hippocampus, a characteristic feature of many antidepressants [106, 136]. These results aside, it has also been shown that higher doses of cannabinoids decrease 5-HT signaling in the brain and are associated with anxiogenic and depressant-like behaviors [133, 137].

This phenomenon was documented by Katsidoni et al. [138], who reported that while low doses of Δ9-THC induced rewarding effects and reduced the frequency of intracranial self-stimulation, high doses of the drug resulted in an anhedonic effect that lasted for two hours post-injection. Phan et al. [139] also found the same biphasic response following ingestion of Δ9-THC in healthy human subjects, as monitored by behavioral scores and amygdala reactivity in fMRI. In addition to the heterogeneous responses of the 5-HT system to cannabinoids, the observed behavioral effects may also be the result of biphasic regulation of the metabolic rate in the cortical and limbic structures by cannabinoids [138]. Also, these effects may also be the result of transient receptor potential vanilloid one receptors (TRPV1) activation, which produces anxiogenic effects at high doses of CBD [133]. TRPV1 receptors are a natural target of the anandamide, and therefore a possible target for non-endogenous cannabinoids as well [106]. Other reports attribute the biphasic effects to CB1Rs on glutamatergic and GABAergic neurons, since genetic deletion of each of these receptors in C57BL/6N mice resulted in abrogation of anxiolytic and anxiogenic effects respectively[140-143]. Therefore, cannabis may influence anxiety levels via TRPV1, CB1R and 5-HT1A receptors with low acute doses of cannabinoids causing anxiolysis and high doses eliciting anxiogenic effects. Future studies surrounding the anxiogenic and anxiolytic effects of cannabis use will further clarify their underlying mechanisms [143-146].

**Conclusion**

Opioid addiction and relapse are complex biological and psychological processes that are partially fueled by the negative physical and emotional states that precipitate upon opiate withdrawal. Accumulating evidence suggests that cannabinoids have significant effects on a variety of negative physical and emotional states characteristic of opioid withdrawal through their shared use of various mechanisms. However, despite advancements in the understanding of cannabinoid pharmacology, the role of cannabinoids in mitigating symptoms of opioid withdrawal remains elusive. Because the current topography of the debate predominantly centers on Δ9-THC, WIN55,212-2, endocannabinoids, CBD, morphine, and heroin, there is a paucity of studies on the other 50+ cannabinoids found in the marijuana plant. Additionally, cannabis use poses severe risks for vulnerable demographics including adolescents and those genetically susceptible to its ramifications. As such, their therapeutic efficacy in managing opioid withdrawal remains to be fully elucidated in future studies.
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