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Review Article

Neuroinflammation as a possible link between cannabinoids and addiction

Rodrigues LCM, Gobira PH, de Oliveira AC, Pelição R, Teixeira AL, Moreira FA, Campos AC. Neuroinflammation as a possible link between cannabinoids and addiction.

Objective: Substance dependence disorder is a chronically relapsing condition characterised by neurobiological changes leading to loss of control in restricting a substance intake, compulsion and withdrawal syndrome. In the past few years, (endo)cannabinoids have been raised as a possible target in the aetiology of drug addiction. On the other hand, although the exact mechanisms of the genesis of addiction remain poorly understood, it is possible that neuroinflammation might also play a role in the pathophysiology of this condition. Studies demonstrated that (endo) cannabinoids act as immunomodulators by inhibiting cytokines production and microglial cell activation. Thus, in the present review, we explore the possible role of neuroinflammation on the therapeutic effects of cannabinoids on drug addiction.
Methods: We conducted an evidence-based review of the literature in order to assess the role of cannabinoids on the neuroinflammatory hypothesis of addiction (terms: addiction, cannabinoids and inflammation). We searched PubMed and BioMedCentral databases up to April 2014 with no date restrictions.
Results: In all, 165 eligible articles were included in the present review. Existing evidence suggests that disruption in cannabinoid signalling during the drug addiction process leads to microglial activation and neuroinflammation.
Conclusion: The literature showed that inflammation and changes in endocannabinod signalling occur in drug abuse; however, it remains uncertain whether these changes are causally or coincidentally associated with addiction. Additional studies, therefore, are needed to elucidate the contribution of neuroinflammation on the behavioural and neuroprotective effects of cannabinoids on drug addiction.

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Summations

- Psychostimulants induce microglia activation and the expression of different pro-inflammatory cytokines.
- Modulation of the endocannabinoid system is involved in the control of drug abuse and neuroinflammation.
- In the present review, we explore the hypothesis that a disruption in endocannabinoid signalling and CB_2 activation lead to microglial activation and neuroinflammation, which might contribute to the process of addiction.

Considerations

- Evidence suggests the involvement of neuroinflammatory mechanisms mediated by endocannabinoids in the process of drug addiction, but this possibility has not been tested extensively.
- CB_1 receptors play a role in the potentiation of reward and drug intake, and this receptor is highly expressed in the brain. Therefore, its participation in the present hypothesis should carefully studied.

Cannabinoids and addiction

The Diagnostic and Statistical Manual of Mental Disorders in its fourth edition defines substance dependence as a chronically relapsing disorder that is characterised by neurobiological changes that lead to the loss of control in restricting the intake of a substance, compulsion and negative emotional states that are induced by motivational withdrawal syndrome when drug taking is prevented (1,2).

Marijuana (*Cannabis sativa*) is the most widely used illicit drug worldwide. The 2006 Annual Report on Drug Abuse estimates that 4% of the adult world's population consumes Cannabis regularly (3). Cannabis can induce transient psychotic symptoms in healthy individuals (4,5) and possibly increase the risk of psychotic disorders, such as schizophrenia, in a dose-dependent manner in individuals with special vulnerability (6). The primary psychoactive ingredient, Δ^9-tetrahydrocannabinol (THC), is largely responsible for the subjective effects of *C. sativa*, but other phyto- and synthetic cannabinoids may also induce psychotomimetic effects (7). Lower doses of THC (e.g. 1.0 mg/kg) enhance electrical brain stimulation reward in laboratory animals with electrodes implanted in the ventral tegmental area-medial forebrain bundle-nucleus accumbens reward axis (8–11).

The very first hypothesis regarding the mechanism underlying the subjective effects of THC was based on the ability of this substance to perturb the membrane permeability of neural cells (12). However, a specific receptor for cannabinoids was proposed in the late 1980s (13), and this receptor was later cloned and termed cannabinoid CB_1 receptor (14). The CB_1 receptor is the major pharmacological target that is responsible for cannabinoid effects, including the subjective effects related to THC abuse (6,15). CB_1 receptors are widely expressed in pre-synaptic terminals where they regulate excitatory and inhibitory transmission in the brain (e.g. GABAergic, glutamatergic, serotonergic, cholinergic and dopaminergic neurotransmission) (16,17). Endogenous ligands for the CB_1 receptor (termed endocannabinoids) have been identified, and the most extensively studied ligands are the arachidonic acid derivatives arachidonoyl ethanolamide (anandamide – AEA) and 2-arachidonoyl glycerol (2-AG). The activity of these ligands is terminated by the enzymes fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL), respectively (18). A second cannabinoid receptor (CB_2) has also been characterised, and it was initially proposed to be absent in the central neurons. However, later research changed this notion (19).

The reward circuitry of the mammalian brain consists of synaptically interconnected neurons that link several brain regions through mainly by dopaminergic circuitries (20). GABAergic and glutamatergic neural inputs also contribute to the core reward system, which have come to be recognised as critically important in the regulation of reward processes and reward-driven behaviours. Cannabinoids were largely considered a separate class from other addictive drugs in terms of addictive potential and the neurobiological substrates that are involved during cannabinoid drug abuse effects (11,20). However, accumulating evidence now implicates brain endocannabinoid signalling in the aetiology of drug addiction (21), and several studies support the view that the endocannabinoid system represents a new candidate for the control of drug rewarding properties (22), because there is dense CB_1 receptor expression in brain regions that are involved in the motivational and addictive properties of abused drugs, including the ventral tegmental area, nucleus accumbens and prefrontal cortex (23). The endocannabinoids AEA and 2-AG (12), and the enzymes responsible for their catabolism (24), are expressed in dopaminergic neurons. Moreover, endocannabinoids can be released following the depolarisation of neurons in brain areas related to reward circuitry (25).

CB_1 receptors are abundant in the brain reward circuitry, and they participate in the addictive properties of different drugs of abuse (26). CB_1 receptors in these circuits are expressed on glutamatergic and GABAergic interneurons in the reward circuitry of the mesolimbic system, which modulate the firing of dopaminergic neurons. *In vivo* microdialysis experiments showed that CB_1 receptor activation increases dopamine (DA) release in the nucleus accumbens (27). The CB_2 receptor, which is believed to control neuroinflammatory mechanisms, is also expressed in microglia and neurons (25) in the striatum and midbrain, which are areas related to reward and addiction (19). However, the presence of CB_2 receptor in neurons is controversial because of questions regarding the specificity of CB_2R antibodies (28).

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It has been difficult to establish sensitive paradigms to evaluate the reward properties of cannabinoids. In contrast to other drugs, cannabinoids produce false negative results in some behavioural methods for investigations of abused drugs (7). For example, some investigations failed to establish cannabinoid intravenous self-administration in non-human primates (29). However, a new reliable method was developed recently to induce self-administration of the phytocannabinoid Δ^9-THC (30) and the endocannabinoids AEA or 2-AG by monkeys (31,32). Justinova et al. (31) trained monkeys with no history of exposure to other drugs to learn to press a device connected to pump that delivered THC intravenously in a constant ratio. The self-administered THC doses in these studies are comparable to doses found in human marijuana users (33,34). The effects of cannabinoid self-administration were prevented by pretreatment with rimonabant, which shows involvement of CB_1 receptors in reward. Intravenous AEA administration increases extracellular DA levels in the nucleus accumbens of rats in a CB_1 receptor-dependent manner (35), which contributes to the reinforcing effects of exogenous AEA.

The abuse liability of drugs that inhibit endocannabinoid hydrolysis has also been investigated. Mice given daily injections of the FAAH inhibitors, URB597 or PF-3845, for 6 days and challenged with the CB_1 antagonist SR141716A displayed no withdrawal symptoms (36). However, treatment for 6 days with high doses of the selective MAGL inhibitor JZL184 significantly reduced CB_1 function and expression and SR141716A-induced somatic withdrawal symptoms (36). These findings suggest that inhibitors of endocannabinoid hydrolysis may present a lower abuse liability compared with direct CB_1 agonists (21,22,37).

In addition to the obvious role of the endocannabinoid system on *C. sativa* abuse, this system may also been involved in the control of the intake of other drugs of abuse (e.g. cocaine, alcohol). Moreover, evidence in the literature support the modulation of the endocannabinoid system as a possible target for the treatment of drug abuse. The present review summarised the evidence that supports the hypothesis that neuroinflammatory mechanisms promote an integrative concept that links cannabinoids to the addictive properties of different drugs.

Cannabinoids and alcohol

The endocannabinoid system may play a role in addictive properties of different drugs of abuse. Alcohol (or ethanol) is a widely abused substance that is associated with diverse social problems. A growing body of biochemical and pharmacological evidence has established a role for the endocannabinoid system in the neurobiology of alcohol (38). Rats exposed chronically to alcohol had increased AEA content in the limbic forebrain, which is a key area for the reinforcement of psychoactive drugs (39–41). FAAH knockout (KO) mice display increased preference for alcohol and consume more ethanol than wild type mice (42). These studies suggest that CB_1 receptors are involved in ethanol addiction. Acute CB_1 receptor agonist exposure increases motivation for drinking beer (43). Similarly, the genetic deletion of CB_1 receptors reduces alcohol consumption in rodents. CB_1 receptor KO mice exhibit reduced voluntary alcohol consumption and do not release DA in the nucleus accumbens after alcohol consumption (44). Further, there is a reduction in ethanol self-administration and ethanol conditioned place preference in mice lacking CB_1 receptors (45).

Preclinical evidence indicates that the CB_1 antagonist rimonabant suppresses alcohol-related behaviours, such as alcohol drinking and seeking behaviour, and alcohol self-administration in rats and mice (38,46,47). In constrast, clinical studies reveal controversial data. Subjects in one study were treated with rimonabant (20 mg/day for 12 weeks), and no significant benefits were observed, except a delayed time to have a first drink and relapse were noted (48). Another study showed that rimonabant in the same treatment regimen did not change alcohol self-administration or endocrine measures during a laboratory session in non-treatment-seeking heavy alcohol drinkers (49). However, all clinical trials of rimonabant were discontinued due to adverse psychiatric effects.

As an alternative, CB_2 receptors have also emerged as a potential target for alcohol abuse. CB_2 receptor activation enhances alcohol intake in stressed mice, and a CB_2 antagonist may induce the opposite behaviour (19). However, a more recent work shows that deletion of the CB_2 receptor gene increased preference for and vulnerability to ethanol consumption (50).

Therefore, the picture is not entirely clear, and the endocannabinoid system may favour or counteract neural changes that mediate alcohol abuse through a mechanism that is dependent on a predominant activity of CB_1 or CB_2 receptors.

Cannabinoids and psychostimulants

Several studies suggest the involvement of the endocannabinoid system in behaviours related to psychostimulants (51,52). CB_1 and CB_2 receptors are

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expressed in glutamatergic and GABAergic interneurons in the reward circuitry of the mesolimbic system, which modulates dopaminergic neurons that are responsible for most effects of cocaine and amphetamine (25,53–55).

One important animal model that is currently used to study the addictive behaviour of psychostimulants is behavioural sensitisation (56). This test is characterised by a progressive increase in a particular response, such as locomotion, after repeated exposures to a drug (56). Motor sensitisation to cocaine is impaired in CB_1-deficient mice or after pharmacological blockade of these receptors (57,58). Furthermore, genetic ablation of CB_1 receptors decreases cocaine self-administration (45). Treatment with antagonists impairs self-administration behaviour and inhibits cocaine-enhanced brain stimulation reward (59,60). The stress-induced reinstatement of cocaine seeking is also prevented by blockade of CB_1 receptors (61). Reductions in CB_1 receptor expression and signalling in the prefrontal cortex from human cocaine addicts and animal rodents have also been reported (39,62).

Evidence also suggests that CB_2 receptors modulate processes related to cocaine addiction. Recent studies showed a decrease in cocaine motor sensitisation and self-administration in mice overexpressing cannabinoid CB_2 receptors, which suggests that this receptor is involved in cocaine-evoked behaviours (62,63). Moreover, Xi et al. (64) demonstrated that CB_2 receptors modulate the rewarding and locomotor activity of cocaine via a dopaminergic neurotransmission-dependent mechanism in KO mice. However, new studies are necessary to investigate the mechanisms of the role of CB_2 receptors in cocaine reward, and whether this mechanism is applicable to other drugs of abuse.

Acute and chronic cocaine administration also promotes alterations in levels of AEA and 2-AG (65–67). These data suggest that the cannabinoid system attempts to modulate cocaine-induced changes. However, pharmacological interventions that culminate with increases in endocannabinoids levels have yielded controversial results. For example, inhibition of MAGL or FAAH does not alter sensitisation behaviour to cocaine. Furthermore, blockade of FAAH does not affect self-administration (67,68). However, inhibition of AEA hydrolysis prevented reinstatement of cocaine-seeking behaviours (68).

The involvement of endocannabinoid systems in the reinforcing effects of amphetamines has also been studied. Analogous to the results with cocaine, pharmacological blockade of CB_1 receptors reduces amphetamine self-administration and decreases the reinstatement of drug seeking (69,70). Depletion of CB_1 receptors also attenuates drug-induced acute hyperlocomotion. Furthermore, CB_1 KO mice did not sensitise to the locomotor stimulant effects of amphetamine (6). Results with CB_1 antagonists in motor sensitisation were controversial because both inhibition and potentiation of this behaviour occurred (71,72).

Acute or chronic amphetamine treatment increase anandamide concentrations in the dorsal striatum and decrease AEA and 2-AG levels in the ventral striatum (71). In contrast, methamphetamine administration reduced MAGL activity and increased 2-AG levels in the limbic forebrain 7 days after neurotoxic doses (73). A recent study also showed that facilitation of anandamide neurotransmission attenuated amphetamine-induced behavioural sensitisation (74).

Cannabinoids and opiates

Several studies demonstrated that the endocannabinoid system modulates distinct opioid-induced responses, such as pain, anxiety and reward (75,76). A functional and bidirectional interaction between the endocannabinod and the opioid system is observed for reward (75). Blockade of opioid receptors reverses the effects of THC, and conversely, blockade of cannabinoid receptors prevents the development of morphine self-administration and conditioned place preference in rodents (77,78). Consistent with these findings, the CB_1 receptor antagonist, rimonabant, reduces the reinforcing effects of self-administered heroin and inhibits reinstatement to this opiate (79,80). A very similar panorama is found in CB_1 KO mice, which show reduced behavioural sensitisation, conditioned place preference and self-administration induced by opiates (81,82). The pharmacological and genetic blockade of CB_1 receptors also attenuates opioid withdrawal syndrome (82).

Interestingly, one recent study suggested that facilitation of endocannabinoid signalling also reduces withdrawal in morphine-dependent mice (83). Although this effect might seem controversial, a clinical study noted that moderate cannabis use is associated to better naltrexone treatment adherence in opiate-dependent patients (84). These data demonstrated that enhancement of endocannabinoid levels and blockade of CB_1 receptors ameliorate reward, reinstatement and withdrawal promoted by opiates.

Cannabinoids and nicotine

Nicotine is the main psychoactive constituent of tobacco, and it is responsible for the development of dependence (85). Notably, frequent concomitant

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consumption of marijuana and tobacco is reported (86), which may reflect a possible interaction between these systems. Preclinical studies revealed that co-administration of non-effective doses of nicotine and THC produced significant conditioned place preference in mice (87). In addition, alterations in endocannabinoid levels in distinct brain regions was observed in animals chronically treated with nicotine (3).

Cross-talk between nicotine addiction and the endocannabinoid system was confirmed in experiments that showed that treatment with a CB_1 antagonist reduced nicotine self-administration and place preference in rodents that was associated with a decrease in DA release in the nucleus accumbens (88,89). In agreement with these results, CB_1 KO mice do not express behaviours related to nicotine-induced CPP or nicotine self-administration (90,91). Similar responses were observed with pharmacological and genetic blockade of CB_2 receptors (92).

One clinical study also suggested rimonabant as a potential therapeutic tool for relieving the symptoms of smoking cessation. Rates of smoking cessation for subjects who received a major dose of rimonabant were double the rates of patients who received placebo (93). Another study suggested that rimonabant and nicotine patch treatment also decreases smoking compulsion (94).

Facilitation of endocannabinoid signalling may also impact nicotine reward. Pharmacological and genetic FAAH disruption in mice enhances nicotine reward and withdrawal (95). However, pharmacological blockade of FAAH significantly inhibits nicotine reward but has no effect on nicotine withdrawal in rats (95). These latter symptoms were not modified after blockade of cannabinoid receptors (27).

Neuroinflammation and addiction: role of (endo)cannabinoids

The exact mechanisms of the genesis of addiction are not well understood, but it is possible to speculate that neuroinflammation plays a role in the pathophysiology of this condition. In fact, evidence in the literature suggests that psychostimulants induce microglia activation and the expression of different cytokines, such as tumour necrosis factor (TNF)α and interleukins (IL) and nitric oxide in animal models, and these results may also be present in humans (96–98). Moreover, these cytokines could, *per se*, facilitate addiction development. For example, IL-1β increases mRNA expression and activity of serotonin transporters in human JAR choriocarcinoma cells. This increased activity of serotonin transporters could enhance the effect of psychostimulants that target these transporters.

Five-day intraperitoneal (i.p.) injections of IL-2 in male BALB/c mice enhance the sensitivity of animals to a selective DA uptake inhibitor 5 weeks after cytokine treatment (99). These long-lasting changes induced by IL-2 might be important for central nervous system (CNS) abnormalities that are induced by addictive drugs. Similar to the long-lasting effect observed with IL-2 treatment, 5-day treatment with IL-6 increased the sensitivity to the locomotor-stimulating effects of an amphetamine administered 14 days after the last i.p. administration of IL-6 (100). Moreover, IL-2 and interferon (IFN)-α potentiated the response induced by a psychostimulant drug in a protocol of drug discrimination behavioural effect using D-amphetamine (101,102). In contrast, TNF-α might play a different role in addiction. Methamphetamine increases the expression of this cytokine, which could attenuate the rewarding effects and discriminative stimulus effects of this psychostimulant in rats (103,104). Serum levels of IL-10 are decreased in human cocaine abusers but TNF-α expression is increased (77). Cocaine infusions rapidly increase the production of IFN-γ and decrease IL-10 secretion from polymorphonuclear cells (105). Cocaine withdrawal in rats is associated with increases in plasma levels of corticoids (106). Amphetamine increases the number of circulating neutrophils but decreases circulating lymphocytes (107).

Psychostimulants may also increase the activation of transcription factors. For example, methamphetamine increases the activation of nuclear factor kappa B (NF-κB) and activator protein 1 (AP-1) in endothelial cells (108). Activation of these transcription factors induces the expression of different inflammatory mediators, which might be important for the development of drug dependence.

The immune system is also altered in chronic alcohol abusers. Changes in circulating immunoglobulin (Ig) levels were the first described immune system link with alcohol use disorder (109). Alcohol alters immune function in part by its effects on neurotransmitter, neuroendocrine, behavioural and autonomic pathways (110–114). However, many studies reported that cytokine levels were altered in alcohol user disorder patients with or without liver disease (115–117). Alcohol consumption in moderate or higher levels is also associated with increased IL-10, type 1 helper T cell (Th1) activation, decreased macrophage-derived chemokine concentrations and suppression of the NF-κB (118–120).

The connection between the immune system and alcohol abuse is even more pronounced in animal models. Chronic alcohol administration in rodents increases TNF-α, IL-1β and IL-6 levels in the brain (121). Chronic alcohol consumption is also associated with increases in pro-inflammatory cytokines in glial

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cells for the activation of toll-like receptor 4 (TLR-4). One study in mice lacking TLR-4 showed that this receptor prevents neuroinflammation-induced damage after chronic alcohol consumption (122). Apparently, these receptors are responsible for the recognition of several molecules derived from microorganisms and by stimulation of innate immune responses (123). Receptor recognition triggers the execution of a sequence of signals, and genes that encode the pro-inflammatory cytokines TNF-α, IL-1β and IL-2 are expressed (124).

Another possible link are microglial cells. Microglia are an important source of inflammatory mediators in the CNS, and these cells might be associated to addiction-related processes. Importantly, it has been hypothesised that primed microglia could release inflammatory mediators that are induced by different stressors during the early recovery period from addiction, which induces sickness behaviour syndromes that could function as a first step for relapse behaviour (96). Microglia activation and the production of inflammatory mediators might also play important roles in the plasticity that accompanies the development and maintenance of drug abuse (125–127). Moreover, increases in dopaminergic neurotransmission are also involved in microglial activation. DA depletion caused by α-MPT prevented the activation of mesencephalic microglia and the subsequent TH neuron loss induced by an intranigral injection of LPS. Moreover, psychostimulants, such as methamphetamine, induce neurotoxic effects by increasing microglial activation and inflammation that is dependent on DA release (128,129).

Recently, Zhao et al. (121) suggested that exposure to short cycles of alcohol administration (4 days) and periods of withdrawal (6 days) increases the activation of microglia, and the neurodegeneration that is associated with declines in learning and memory processes. In addition, methamphetamine increases the production of IL-6 and IL-18 in cultures of human foetal glial cells (130). However, this result is not clear and deserves further investigation.

Therefore, it could be assumed in this context that (endo)cannabinoids could modulate addiction through its effects on microglia activation and the production of inflammatory mediators. Importantly, different papers have demonstrated the presence of CB_1 and CB_2 receptors on immune cells (131) and that cannabinoids reduced the binding of the respective transcription factors to CRE and NF-κB in these cells (132). Cannabinoids may act as immunomodulators by inhibiting cytokine and chemokine production, the cell proliferation and expansion of regulatory T cells, and the induction of apoptosis in these cells (133,134).

Evidence has been presented that 2-AG protects neurons exposed to harmful insults, such as inflammation, by acting as an endogenous inhibitor of cyclooxygenase-2 (135). AEA inhibits TNF-α-induced NF-κB activation by direct inhibition of the IκB kinase (136). However, AEA and 2-AG degradation increased the production of prostaglandins in activated glial cells (137,138). This effect might be due to the hydrolysis of AEA and 2-AG to arachidonic acid, which leads to enhanced levels of substrate for the formation of prostaglandins (138). The apparent contradictory pro-inflammatory effect of endocannabinoids seems to be mediated by a CB_1/CB_2 receptor-independent mechanism, and it is prevented by endocannabinoid hydrolysis inhibitors (FAAH and MAGL inhibitors) (137,138). In addition, it is important to stress that the enhanced levels of prostaglandins in the brain should not be interpreted as a mere pro-inflammatory signal, because these mediators also possess anti-inflammatory effects (139).

Treatment with WIN55,212-2, a CB_1/CB_2 receptor agonist, reduced mRNA expression of pro-inflammatory cytokines, TNF-α, IL-1β, IL-6 and IFN-γ, in the CNS in a viral model of multiple sclerosis (140). The pharmacological inhibition of AEA hydrolysis reduces microglial activation, nitric oxide levels and the production of several inflammatory mediators, such as TNF-α, IL-6, IL-1β and IL-12, most likely due to the activation of CB_2 receptors (141–143).

Another possible mechanism of inhibition of cannabinoid receptor-dependent inflammatory response might involve the activation of peroxisome proliferator-activated receptors (PPARs). Several studies in the last decade reported non-CB_1 and non-CB_2-mediated cannabinoid effects, and several cannabinoids interact with PPARs but in a complex manner (144). The PPAR family (PPARα, PPARβ and PPARγ) plays important roles in the maintenance of lipid metabolism, peroxisomal enzyme expression, insulin sensitivity, glucose homoeostasis, cell proliferation, apoptosis and inflammation (145). Indeed, a large body of evidence suggests that PPAR-γ mediates some of the modulatory effects of cannabinoids on neuroinflammation (146,147). Activation of PPARs inhibits the transcription of pro-inflammatory genes that prevent the signalling pathway of NF-κB (147–150). In particular, several protective effects of PPARγ have been demonstrated in the brain (151,152). For example, it was demonstrated recently that neuroinflammatory mechanisms and PPAR-γ are involved in the behavioural sensitisation that is induced by the synthetic cannabinoid WIN55,212-2 (147). In addition, the endocannabinoid 2-AG may decrease

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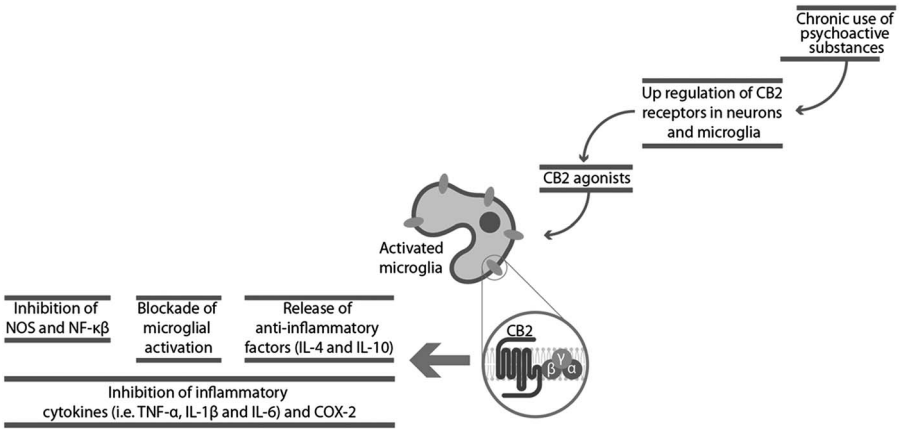

Fig. 1. Role of microglial CB_2 receptor in the possible mechanism linking neuroinflammation, (endo)cannabinoids and addiction.

IL-2 production via PPAR-γ activation (153). The PPAR receptors may also play a role in addiction. Coincidentally, major findings of the putative role of PPARs in addiction come from studies conducted with cannabinoids (154). Currently, several pieces of evidence suggest that PPAR-α and PPAR-γ agonists play a role in relapse, sensitisation, conditioned place preference, withdrawal and drug intake induced by psychostimulants (154).

It has been proposed that chronic activation of microglia plays a major role in disorders that are characterised by nervous tissue inflammation (155). CB_1 is expressed constitutively in microglia, and CB_2 is expressed in microglia during activation states (143,155,156). However, CB_1 receptors have been suggested to modulate inflammation (157,158), but it could also play a role in potential addictive properties of *C. sativa*, which is a potential contradiction. However, CB_1 activation by *Cannabis* consumption would increase dopaminergic neurotransmission, which could lead to the activation of microglia via a CB_1-independent mechanism (128).

CB_2 is predominantly expressed in the immune system and, in our opinion, it might be a key mediator of cannabinoid regulation of immune functions during addiction via microglia activation (159–161). Primed microglia could release inflammatory mediators and contribute to the maintenance of drug abuse (125,126,147), and cannabinoids would be involved in the attenuation of this effect. However, CB_1 activation would control DA release due to its primarily pre-synaptic location, and CB_2 activation would affect DA neurotransmission by decreasing inflammatory responses (pro-inflammatory cytokines, nitric oxide, etc.) (162).

CB_2 receptor stimulation reduced morphine-induced production of inflammatory mediators from activated microglia (163). Deletion of the CB_2R gene increases the preference for ethanol consumption. This effect could be mediated by the increase in mRNA expression of tyrosine hydroxylase and μ opioid receptors in the ventral tegmental area and nucleus accumbens, respectively (50). However, other mechanisms might also contribute to this action. Moreover, activation of CB_2 receptors also reduced the rewarding and locomotor-stimulating effects of cocaine. One possibility to explain this effect is that activation of CB_2 receptors on astrocytes or microglia could alter the production of pro-inflammatory mediators, which would inhibit DA release from the nucleus accumbens (164). Therefore, we speculate that impaired CB_2 receptor signalling would contribute to the reinforcing effects of different drugs because CB_2 receptors regulate the expression of inflammatory mediators, which possess important roles in addiction. Therefore, it is reasonable to suggest that the effects of cannabinoids on drug abuse might be mediated by neuroinflammatory mechanisms via CB_2 receptors on microglia.

Perspectives and conclusions

The present paper reviewed the possible role of neuroinflammation in the mechanism of cannabinoids on drug addiction. We explored the hypothesis that a disruption in cannabinoid signalling during drug addiction processes would involve microglial activation and a consequent neuroinflammation (Fig. 1).

Several pieces of evidence suggested that abused drugs, such as psychostimulants drugs or alcohol, induce microglia activation and the expression of inflammatory mediators, such as cytokines and transcription factors. (Endo)cannabinoids may act as immunomodulators by inhibiting cytokine production and microglia activation. This latter mechanism seems particularly important because

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CB_2 receptors on activated microglia might play a major role in neuroinflammatory processes related to addiction. Notably, several studies support a role of PPAR receptors in the anti-inflammatory effects of cannabinoids, mainly in the CNS. Activation of PPARs exerts anti-inflammatory effects by inhibiting the expression of pro-inflammatory genes and reducing the production of cytokines, metalloproteases and acute-phase proteins. An increasing body of evidence shows that (endo) cannabinoids activate PPARs, which have anti-inflammatory activities, and the activation of these nuclear receptors may represent a novel mechanism by which cannabinoids modulate inflammatory conditions. However, additional studies designed to test this hypothesis are needed to elucidate the contribution of neuroinflammation on the behavioural and neuroprotective effects of cannabinoids on drug addiction.

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Conflicts of Interest

The authors declare no conflicts of interest.

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