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Roles of cannabinoid CB1 and CB2 receptors in the modulation of psychostimulant responses

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Review Article

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Abstract

Addiction to psychostimulant drugs, such as cocaine, D-amphetamine, and methamphetamine, is a public health issue that substantially contributes to the global burden of disease. Psychostimulant drugs promote an increase in dopamine levels within the mesocorticolimbic system, which is central to the rewarding properties of such drugs. Cannabinoid receptors (CB_1R and CB_2R) are expressed in the main areas of this system and implicated in the neuronal mechanisms underlying the rewarding effect of psychostimulant drugs. Here, we reviewed studies focusing on pharmacological intervention targeting cannabinoid CB_1R and CB_2R and their interaction in the modulation of psychostimulant responses.

Summation

The search identified studies that evaluated the rules of pharmacological and genetic modulation of CB1 and CB2 cannabinoid receptors in the regulation of psychostimulant responses. Most studies demonstrated that activation of CB2R and inhibition of CB1R inhibited behavioural and molecular effects induced by distinct psychostimulants.

Considerations

Although studies reported that blockade of CB1R inhibits psychostimulant effects, the incidence of serious psychiatric adverse events, limits the use of selective CB1R antagonists for treating psychostimulant addiction disorders. Drugs targeting CB2R signalling might represent a more promising approach.

Moreover, preclinical studies only have focused on male mice and rats, excluding female animals. As sexual dimorphism has been demonstrated in behavioural and molecular responses correlated to cannabinoid receptors, the role of CB1R and CB2R in regulation of psychostimulants in female animals should be explored in future studies.

Introduction

Psychostimulants are a broad class of drugs that englobe cocaine, amphetamine, and its derivatives [i.e., methamphetamine, N-methyl- 3,4-methylenedioxymethamphetamine (MDMA)]. Psychostimulant addiction is a public health issue that substantially contributes to the global burden of disease (UNODC, 2021). This chronic pathology is characterised by complex behavioural and neurobiological phenomena entailing the compulsive use of a substance (Wise and Koob, 2014, Volkow and Morales, 2015). The mechanisms for the addictive properties of drugs, including psychostimulants, involves the facilitation of reward centres in the brain, particularly the mesocorticolimbic dopaminergic pathways connecting the ventral tegmental area (VTA) with various limbic structures, such as nucleus accumbens (NAcc), prefrontal cortex (PFC), and hippocampus (Koob and Volkow, 2010). Acute and chronic exposure to psychostimulants cause both transient and persistent adaptations in regions of the mesocorticolimbic neurocircuitry, resulting in altered behavioural responses, ultimately, leading to drug addiction (Rothman and Baumann, 2003, Howell and Kimmel, 2008).

Several pieces of evidence show that the endocannabinoid system modulates the reward-related effects of dopamine and that this system might be involved in the neurobiological mechanism underlying psychostimulant addiction (Wiskerke *et al.*, 2008, Manzanares *et al.*, 2018). The endocannabinoid system comprises the endogenous ligands anandamide (AEA) and 2-arachidonoylglycerol (2-AG), the enzymes responsible for their synthesis and degradation and the cannabinoid receptors (Hillard, 2015). AEA and 2-AG are the main

endocannabinoids, whose effects are mediated mainly by two metabotropic receptor termed CB_1R and CB_2R (Hillard, 2015, Lu and Mackie, 2016). Both cannabinoid receptors are expressed in mesolimbic pathways and can modulate excitability of dopaminergic neurons (Howlett *et al.*, 1990, Onaivi *et al.*, 2006, Covey *et al.*, 2017). In accordance with their localisation, accumulating reports have pointed to the involvement of CB_1R and CB_2R in the main behavioural effects of psychostimulants (Wiskerke *et al.*, 2008, Vlachou and Panagis, 2014). Moreover, cannabinoid receptors also display an important role in regulating molecular responses of these drugs (Wiskerke *et al.*, 2008, Vlachou and Panagis, 2014, Parsons and Hurd, 2015). Interestingly, these studies suggest that cannabinoid receptors work with opposing functions to modulate certain behavioural- and molecular-related effects of these drugs, since an activation of CB_2R leads to similar results as compared to CB_1R blockade.

The focus of the present review is to discuss the distinct behavioural responses induced by psychostimulants and how a differential modulation of CB_1R and CB_2R can regulate them. The molecular mechanisms through which CB_1R and CB_2R change the neuroadaptations promoted by psychostimulants will also be explored. Finally, we will propose an overarching hypothesis integrating both receptors in the pharmacological modulation of psychostimulant effects.

Psychostimulants: mechanisms of action and behavioural responses

Psychostimulants are a broad class of psychotropic substances with the capacity to stimulate various functions of the central nervous system, including attention, vigilance, alertness, arousal, and locomotion (Favrod-Coune and Broers, 2010). Intense hedonic feelings characterised as a "rush" are also described (Boutrel and Koob, 2004, McCreary *et al.*, 2015). Most of them act by directly facilitating mesocorticolimbic terminals by either inhibiting the dopamine transporter (DAT) or facilitating the release of dopamine (Harris and Baldessarini, 1973, Nestler, 2004). While cocaine binds predominantly to DAT and inhibits dopamine reuptake, amphetamine has two more complementary action mechanisms to elevate dopamine levels (Sulzer *et al.*, 2005). This drug can act by reversing the vesicular monoamine transporter, leading to a large release of the cytoplasmic and vesicular stores of dopamine (Robertson *et al.*, 2009). An additional mechanism of action for amphetamines is the facilitation of the output of dopamine from vesicles into the cytoplasm (Sulzer *et al.*, 2005). Both mechanisms also lead to an enhanced dopaminergic signalling in the mesocorticolimbic circuitry.

The use of experimental animal models is an important strategy to obtain direct insights into the molecular and behavioural effects promoted by psychostimulants (McCreary *et al.*, 2015). Administration of cocaine and amphetamine in laboratory animals induces a dose-dependent increase in locomotor activity. Moreover, repeated exposure to these drugs leads to the development of behavioural sensitisation, which is characterised by a progressively increasing behavioural response to repeated drug exposure (Sanchis-Segura and Spanagel, 2006, Steketee and Kalivas, 2011). This phenomenon is observed, for example, as an increase in locomotor activity, which becomes even more pronounced in animals previously exposed to single or repeated administration of the same psychostimulant (Shuster *et al.*, 1977, Steketee and Kalivas, 2011).

The rewarding properties of cocaine and amphetamine are largely assessed using the conditioned place preference (CPP) paradigm (Bardo and Bevins, 2000, Wiskerke *et al.*, 2008). CPP is generally performed in a box containing two distinct compartments with different contextual cues, which are equally explored by the rodents in a pre-test session. The conditioning phase is performed by administering the psychostimulants and keeping the animal confined to one compartment (the conditioned stimulus), whereas vehicle injection is paired with the other compartment, in alternate periods. After the conditioning phase, the test session is performed in the absence of the drug, and the animals can explore both sides of the box. An increase in the time exploring the drug-paired compartment, compared to time spent in the vehicle-paired side, is suggestive of the rewarding effect of the drugs (Bardo and Bevins, 2000, Sanchis-Segura and Spanagel, 2006).

Drug self- administration has been one of the most direct approaches to study the rewarding properties of cocaine and amphetamine in experimental animals (Gardner, 2000). In this behavioural model, rodents are trained to perform an operant response (e.g., a lever press or nose poke) for an infusion of drug, typically accompanied by a concurrently-delivered, discrete cue such as a light and a tone. Different kinds of schedule might be used to obtain the drug, being the most largely used the fixed ratio (FR) schedule and progressive ratio (PR) schedule (Gardner, 2000, Farrell *et al.*, 2018). Briefly, under a FR schedule, the psychostimulant is delivered every time that a pre-selected number of responses are completed. Conversely, under a PR schedule, the required ratio increases following a predefined progression, which usually is an arithmetic one. Breakpoints in this schedule, which reflects the motivation for the drug, can be defined as the maximum response rate achieved to obtain a single infusion of psychostimulant before the animal fails to complete the next ratio requirement (Gardner, 2000, Panagis *et al.*, 2014).

Both CPP and self-administration paradigms can be used to assess relapse, another important property of psychostimulants. Once self-administration and place preference behaviours are established, animals undergo extinction training during which they are re-exposed to the drug environment in the absence of psychostimulants. After these extinction processes, animals can be tested for reinstatement, which are often precipitated by exposure to a small priming dose of drug, experiencing acute stress, or encountering discrete or contextual cues previously paired with drug use (Shaham *et al.*, 2003, Farrell *et al.*, 2018).

Over the years, the use of preclinical models has helped to elucidate the cellular and molecular aspects regarding the neurobiology of psychostimulant drugs, as well as new potential strategies for the pharmacological modulation of psychostimulant actions including, compounds targeting CB_1R and CB_2R.

Overview of CB_1R and CB_2R

Cannabis is one of the first plants to be used as a medicine and a drug of abuse by the humankind (Zuardi, 2006). This plant is the source of a set of more than 100 compounds, among which is Δ9-tetrahydrocannabinol (Δ9-THC), the main responsible for the psychoactive effects of the plant (Mechoulam and Hanus, 2000, Hanus *et al.*, 2016). After the identification of Δ9-THC, researchers focused their efforts in elucidating the pharmacological mechanism underlying its effects (Mechoulam and Hanus, 2000, Pertwee, 2006). Complementary studies with Δ9-THC synthetic derivatives, including radioactive ligands, provided convincing evidence regarding the existence of specific cannabinoid receptors

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(Devane *et al*., 1988, Pertwee, 2006). Currently, two major types of receptors have been characterised and cloned, CB_1R and CB_2R (Devane *et al*., 1988, Munro *et al*., 1993, Pertwee, 2010).

The CB_1R is one of the most abundant Gi protein alpha subunit (Gi/o) protein-coupled receptors in the brain (Howlett *et al*., 2002). The activation of these presynaptic receptors leads to inhibition of neurotransmitter release by a mechanism that involves inhibition of voltage-gated calcium (Ca^{2+}) channels and activation of inwardly rectifying potassium (K^+) channels via the stimulated cyclic adenosine monophosphate-protein kinase A (cAMP-PKA) signal pathway (Kano, 2014, Howlett and Abood, 2017). CB_1R expression was described in distinct regions of mesocorticolimbic dopaminergic pathways, including hippocampus, PFC, and NAcc (Howlett *et al*., 2002). These regions are involved in motivational and reward processes, which are modulated by endogenous and exogenous CB_1R ligands (Koob and Volkow, 2010, Wenzel and Cheer, 2018).

Regarding the CB_2R, early evidence suggested that this receptor might be absent in brain and restricted to peripheral tissues. However, after the development of more selective and sensitive tools, it was possible to identify CB_2R in the central nervous system (Van Sickle *et al*., 2005, Onaivi *et al*., 2006). Indeed, CB_2R is distributed extensively in different brain areas, such as hippocampus, PFC, amygdala, olfactory nucleus, striatum, and thalamus (Chen *et al*., 2017). The CB_2R shares 44% homology with the CB_1R and also is coupled to Gi/o protein (Howlett *et al*., 2002). CB_2R also modulates the activity of Ca^{2+} and K^+ channels, and recent electrophysiological and biochemistry findings confirmed the functionality of these receptors in mesocorticolimbic pathways (Zhang *et al*., 2014, Howlett and Abood, 2017, Jordan and Xi, 2019).

This convergence of cannabinoid receptors in the central nervous system, especially in mesolimbic circuitry, is consistent with the reward effects of synthetic and natural cannabinoids (Gessa *et al*., 1998, Zhang *et al*., 2014, Li *et al*., 2021). In addition, CB_1R and CB_2R are crucial mediators of synaptic plasticity in mesolimbic pathways, an important component in the control of motivated behaviour promoted by drugs that promote addiction (Xi *et al*., 2011, Garcia-Gutierrez *et al*., 2013, Zlebnik and Cheer, 2016). Therefore, CB_1R and CB_2R not only underlie the rewarding effects of cannabis, but can also interact with other drugs of abuse, including psychostimulants (Wiskerke *et al*., 2008, Zhang *et al*., 2014).

Role of CB_1R in psychostimulant responses

Activation of CB_1R is essential for the establishment of addiction to cannabinoid drugs (Wenzel and Cheer, 2018). Moreover, both genetic and pharmacological approaches strongly suggest a role for CB_1R signalling on responses to other drugs of abuse, including psychostimulants (Wiskerke *et al*., 2008).

CB_1R and psychostimulant motor effects

Acute administration of cocaine or amphetamine induces a robust increase in locomotor activity (hyperlocomotion) in animals exposed to an open field. Administration of rimonabant, a CB_1R antagonist/inverse agonist, dose-dependently inhibits the hyperlocomotion induced by d-amphetamine and cocaine in rodents previously exposed to the open field (Poncelet *et al*., 1999, Gobira *et al*., 2019). A similar effect has been observed after pharmacological blockade of CB_1R by AM251, a more selective CB_1R antagonist/inverse agonist (Corbille *et al*., 2007). Accordingly, locomotor responses to cocaine were also significantly reduced in CB_1R knockout mice (Li *et al*., 2009).

Converging evidence also supports that blockade of CB_1R regulates behavioural sensitisation induced by psychostimulants. The development of single-trial cocaine- and amphetamine-induced locomotor sensitisation was impaired in CB_1R knockout (KO) mice or after CB_1R pharmacological blockade in wild-type mice (Corbille *et al*., 2007, Mereu *et al*., 2015, Delis *et al*., 2017, Lopes *et al*., 2019). The sensitised locomotor response to a single cocaine challenge was also reduced in rats pretreated with rimonabant (Filip *et al*., 2006). These pharmacological studies evaluated the expression of psychostimulant locomotor sensitisation, since the blockade of CB_1R was performed before the cocaine challenge. By injecting the CB_1R antagonism on the first day of test, a recent work demonstrated that the acquisition of motor sensitisation also was impaired by blockade of these receptors (Lopes *et al*., 2019).

Despite this evidence, other studies have demonstrated that neither genetic silencing nor pharmacological inhibition of CB_1R altered psychostimulant ability to induce motor sensitisation (Martin *et al*., 2000, Lesscher *et al*., 2005). In addition to distinctions in animal species and strains, these discrepancies might result from differences in the dose of psychostimulant and number of injections during acquisition phase (single or repeated drug injection). The context of CB_1R antagonist administration also appears to be important in the regulation of behavioural sensitisation. For instance, Gerdeman and co-workers observed that rimonabant did not diminish the established cocaine sensitisation if delivered in the home cage, but only if the rimonabant-injected mice were exposed to activity chambers previously paired with cocaine (Gerdeman *et al*., 2008).

In accordance with behavioural responses, CB_1R also appears to be relevant in psychostimulant-activated signalling pathways. cAMP-dependent phosphorylation of glutamate receptor 1, promoted by cocaine, was altered in the striatum of CB_1R -null mice (Corbille *et al*., 2007). Moreover, phosphorylation of extracellular signal-regulated kinase (ERK) promoted by cocaine and D-amphetamine were prevented in the dorsal striatum, as well as in the NAcc core and shell of CB_1R mutant mice (Corbille *et al*., 2007). Corroborating these findings, blockade of CB_1R prevented cocaine-induced increased in c-Fos expression in the shell and core portions of NAcc, and (Gobira *et al*., 2018). Altogether, these results provide evidences that CB_1R is essential for biochemical responses to psychostimulants that are intrinsically correlated with locomotor behavioural effects.

CB_1R and psychostimulant reward and reinforcement

The endocannabinoid signalling has also been implicated in the modulation of psychostimulant-induced reward, as evaluated in the CPP test. Administration of CB_1R antagonist before cocaine or methamphetamine injections, in the conditioning phase, impaired dose-dependently the acquisition of CPP (Yu *et al*., 2011, Delis *et al*., 2017, Lopes *et al*., 2019). CB_1R antagonist also decreased the expression of cocaine-induced CPP. Blockade of CB_1R also prevented neuronal activation in the hippocampus of animals exposed to cocaine-CPP (Lopes *et al*., 2019). Interestingly, no effect was observed when the CB_1R blockade was performed only on the test day (Chaperon *et al*., 1998, Lopes *et al*., 2019). These data suggest that CB_1R might be important in the consolidation of psychostimulant-paired memories, but is not involved in the retrieval of these memories (Lopes *et al*., 2019). Despite pharmacological findings indicating that CB_1Rs

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are involved in psychostimulant reward memory, cocaine-induced CPP was unaffected in CB1R KO mice (Martin *et al.*, 2000, Houchi *et al.*, 2005). These differences are not clear, but might be explained by compensatory changes in the CB1R KO mice, since CB1R is important during development for establishing proper neuronal connectivity in brain regions related to memory and reward (Berghuis *et al.*, 2007).

Intravenous drug self-administration is one of the most used approaches for studying drug reinforcement. Experiments using this paradigm also provide evidence that CB_1Rs play a critical role in psychostimulant-induced reinforcing properties. A significant reduction in acquisition of cocaine self-administration was observed in CB_1R KO mice compared with wild type (Soria *et al.*, 2005). The number of sessions required to CB_1R null mice to achieve this behaviour was increased (Soria *et al.*, 2005). Pharmacological blockade of CB_1R with SR141716A in wild-type mice promoted similar effects (Soria *et al.*, 2005). Evidence also pointed that the maximal effort to obtain a cocaine infusion, in PR reinforcement schedule, was significantly reduced after the genetic and pharmacological ablation of CB_1R (Soria *et al.*, 2005, Xi *et al.*, 2008). Treatment with CB_1R antagonists, in a dose-dependent manner, lowered the break point for cocaine self-administration under a PR reinforcement schedule in rats (Xi *et al.*, 2008). Similarly, the blockade of CB_1R suppressed the intake of methamphetamine in rats trained to self-administer this drug (Vinklerova *et al.*, 2002).

Intriguingly, these reports are countered by studies which demonstrated that pharmacological and genetic inactivation of CB_1R were ineffective to modulate cocaine and amphetamine self-administration under FR schedules (Cossu *et al.*, 2001, Lesscher *et al.*, 2005). Besides the differences in ratio schedule, the extension in the period of cocaine self-administration also appears to be important to the effect of CB_1R in modulation of drug-intake. For example, blockade of CB_1R reduces the breakpoint for cocaine self-administration in rats that had 6 h to access the drug. On the other hand, a lower efficacy of CB_1R antagonist was observed in rats that access cocaine only 1 h daily (Orio *et al.*, 2009). In accordance with those findings, the levels of both phosphorylated and total CB_1R protein were increased only in the NAcc of rats given extended daily access to cocaine (Orio *et al.*, 2009). In the extended access regimen, the intake of the drug gradually increases over days, on the other hand the consume of cocaine remains stable in animals under short access protocol (Ahmed and Koob, 1998, Wee *et al.*, 2007). This escalated drug intake also is associated with increased breakpoints or responding for cocaine under a progressive ratio (PR) schedule of reinforcement, both processes that demonstrated pivotal role of CB_1R in modulating psychostimulant behaviour (Wee *et al.*, 2007). Therefore, this evidence suggested that the capacity of CB1R to regulate the rewarding properties of psychostimulants might influence the motivation to obtain these drugs.

Increases in dopamine extracellular levels in the NAcc have been related to the primary reinforcing effects of psychostimulants (Di Chiara, 1998). Similar to observed in the modulation of self-administration, the importance of silencing of CB_1R in regulation of levels of dopamine in the NAcc also appears to be complex. Striatal extracellular dopamine response to acute cocaine was reduced in CB_1R KO mice (Li *et al.*, 2009). A similar result was obtained after the pharmacological blockade of these receptors in wild-type mice (Li *et al.*, 2009). Although this is consistent with findings that rimonabant inhibits cocaine- and amphetamine-induced dopamine release in rats (Cheer *et al.*, 2007, Covey *et al.*, 2016), both basal and cocaine-induced increase in extracellular levels of dopamine in the NAcc were unaffected in CB_1R KO mice (Soria *et al.*, 2005) or after treatment with CB_1R antagonist (Caille and Parsons, 2006). Differences in the genetic background of the KO animals and methods to evaluate dopamine levels might explain these discrepant results. For example, while no changes in cocaine-enhanced dopamine release were observed in KO mice from CD1 background (Soria *et al.*, 2005), alterations in dopamine levels following cocaine injections were obtained in CB_1R -null mice with a C57BL/6J genetic background (Li *et al.*, 2009).

A recent study, using modern molecular tools to selectively ablate CB_1R on specific subtypes of neurons, provided interesting novel insights that clarified the role of these receptors in the regulation of dopamine levels in the NAcc in animals submitted to self-administration paradigm. A lower training dose was required to acquire cocaine self-administration for the mutant mouse lines with CB_1R deletion targeted in forebrain GABAergic (GABA-CB1-KO) neurons, suggesting an increased sensitivity to the aversive effect of high unit drug doses (Martin-Garcia *et al.*, 2016). Conversely, at low doses, GABA-CB_1R-KO mice self-administered more than the wild type, confirming an increased sensitivity to the positive reinforcing effects of cocaine (Martin-Garcia *et al.*, 2016). A dopaminergic mechanism appears to be involved in this behavioural response, since naïve GABA-CB_1R-KO mice showed increased cocaine-induced dopamine release in the NAcc (Martin-Garcia *et al.*, 2016). Authors also observed that silencing of cortical glutamatergic neurons did not change cocaine's primary reinforcing effects as revealed by the similar dose-response curves for cocaine self-administration in this genotype compared to wild type (Martin-Garcia *et al.*, 2016).

Overall, blockade of CB_1R might curb behavioural and dopaminergic responses correlated to psychostimulant reward. However, these effects are sensitive to variations in the experimental protocol, such as dose of psychostimulant, ratio schedule, and the extension in the period of drug self-administration. Moreover, recent evidence demonstrated that CB_1R located on glutamatergic and in GABAergic neurons contribute differentially to the effect of psychostimulants.

CB_1R and psychostimulant reinstatement

A major feature of psychostimulants use disorder is the risk of relapse in drug use even after long periods of withdrawal (Le Moal and Koob, 2007, Wise and Koob, 2014). Reinstatement episodes might be triggered by re-exposure to the drug itself or even to previously drug-associated contextual cues, as well as exposure to stressful stimuli (Shaham *et al.*, 2003, Steketee and Kalivas, 2011). De Vries and co-workers provided evidence for a pivotal role of CB_1R signalling in psychostimulant reinstatement. They found that a single injection of the CB_1R agonist HU-210 reinstated drug-seeking following the extinction of cocaine self-administration, an effect reversed by co-administration of a CB_1R antagonist (De Vries *et al.*, 2001). The authors also showed that rimonabant by itself prevented drug-induced reinstatement of cocaine seeking (De Vries *et al.*, 2001). These findings were replicated by other studies using AM251 (Xi *et al.*, 2006, Adamczyk *et al.*, 2012) and ORG 27,569, a CB_1R negative allosteric modulator (Jing *et al.*, 2014). Similarly, methamphetamine- and MDMA-induced

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reinstatement were prevented by both CB_1R antagonism and by allosteric modulation of these receptors (Jing *et al.*, 2014, Nawata *et al.*, 2016). Accordingly, CB_1R antagonism also impaired cocaine and methamphetamine-induced reinstatement in the CPP paradigm (Yu *et al.*, 2011).

CB_1R has also been found to play a critical role in mediating reinstatement of previously extinguished drug-seeking behaviour upon re-exposure to the drug-associated cues. The increase in operant self-administration response induced by re-exposure to cues previously paired with methamphetamine, MDMA, and cocaine infusion was blocked by CB_1R antagonist (Anggadiredja *et al.*, 2004, Ward *et al.*, 2009, Adamczyk *et al.*, 2012, Nawata *et al.*, 2016). Reinstatement to psychostimulant-seeking induced by different types of stressors was also inhibited by blockade of CB_1R. For instance, forced swim or restraint stress-induced reinstatement of extinguished cocaine-CPP was suppressed by systemic CB_1R antagonism (Vaughn *et al.*, 2012, Tung *et al.*, 2016, Guzman *et al.*, 2021). Moreover, restraint stress-induced cocaine seeking was not observed in CB_1R-deficient mice (Tung *et al.*, 2016). Reinstatement to cocaine-seeking promoted by injection of pharmacological stressor corticotrophin-releasing factor also was prevented by blockade of CB_1R (Kupferschmidt *et al.*, 2012). The exposure to various types of stress events potentiated other relapse-promoting stimuli (e.g., cues, drug re-exposure), augmenting their proneness to elicit drug seeking (Mantsch *et al.*, 2016, McReynolds *et al.*, 2018). CB_1R played an important role in both stress- and drug-induced reinstatement, blockade of these receptors prevented the ability of stress to potentiate low-dose cocaine-induced reinstatement (McReynolds *et al.*, 2016). In addition, a similar modulatory role of CB_1R has consistently been found with respect to cocaine- and amphetamine reinstatement induced by exposure to cues previously associated with these drugs.

Although it is recognised that CB_1Rs are important to the behavioural effects of psychostimulants-seeking, few studies have focused on understanding the neural substrates involved in these processes. The NAcc is an important neuroanatomical locus of the reinstatement-preventing effects of CB_1R antagonists. Local injections of this CB_1R antagonist into the NAcc inhibited cocaine-induced reinstatement of drug-seeking behaviour (Xi *et al.*, 2006). The antagonism of CB_1R in the portion core of the NAcc, but not in the shell, dose-dependently prevented restraint stress-induced reinstatement of cocaine-CPP, while activation of CB_1R potentiated this behaviour (Guzman *et al.*, 2021). Alteration of glutamate release within NAcc appears to be involved in these effects of CB_1R, since pharmacological modulation of CB_1R in the NAcc regulates extracellular levels of this neurotransmitter under cocaine-reinstatement conditions (Xi *et al.*, 2006, Guzman *et al.*, 2021). CB_1R expressed in VTA and in prelimbic (PL) cortex also appear to be involved on stress-induced cocaine reinstatement. CB_1R antagonist microinjected bilaterally into the VTA inhibited the capacity of the restraint stress to reinstate extinguished cocaine CPP (Tung *et al.*, 2016). The activation of CB_1R inhibits GABA release leading to VTA dopaminergic disinhibition and reinstatement of cocaine CPP (Tung *et al.*, 2016). Regarding PL, both stress- and corticosterone-potentiated cocaine reinstatement were prevented by intra-PL administration of the CB_1R antagonist in this region (McReynolds *et al.*, 2018). Similarly, to observed in the VTA, a CB_1R-dependent attenuation of GABAergic neurotransmission in the PL seems to be involved in this process (McReynolds *et al.*, 2018).

In summary, although the effect of CB_1R blockade in modulation of psychostimulant reward is still controversy, more robust behavioural and molecular evidence indicate that CB_1R is a required element in the ability of drug, stress and cue to reinstate psychostimulants seekingbehaviour.

Role of CB_2R in psychostimulant responses

Early evidence suggested that expression of CB_2R could be absent in encephalic structures and restricted to peripheral tissues (Munro *et al.*, 1993). More recently, their expression and function were detected in the brain through molecular, genetic, behavioural, and pharmacological approaches (Gong *et al.*, 2006, Jordan and Xi, 2019). Among other regions, CB_2Rs have been identified in the cell bodies of dopaminergic neurons in mesocorticolimbic pathway, indicating that these receptors might modulate the effects of psychostimulant drugs (Gong *et al.*, 2006, Chen *et al.*, 2017). Indeed, the presence of the CB_2R in mesocorticolimbic neurocircuitry is in conformity with findings that modulation of these receptors regulates behavioural and molecular responses to cocaine and amphetamine (Xi *et al.*, 2011, Canseco-Alba *et al.*, 2019, Jordan and Xi, 2019). Interestingly, the roles for CB_2R in the effects of psychostimulants seem to be opposite to those ascribed to CB_1R.

Systemic administration of the CB_2R agonist, JWH133, dose-dependently inhibited cocaine-enhanced locomotion in wild-type mice, but not in CB_2R KO animals (Xi *et al.*, 2011, Gobira *et al.*, 2019, Lopes *et al.*, 2019). Local administration of CB_2R agonist into NAcc also resulted in attenuation of cocaine hyperlocomotion, confirming that this effect is mediated by activation of brain CB_2R (Xi *et al.*, 2011). Consistently with these pharmacological data, findings obtained with genetically modified mice also support the importance of CB_2R to regulate psychostimulant responses. Transgenic mice overexpressing CB_2R were less responsive to cocaine-induced motor hyperactivity than wild-type mice (Aracil-Fernandez *et al.*, 2012). Corroborating these findings, specific deletion of CB_2R in dopamine neurons increased the responsivity to acute administration of amphetamine, methamphetamine, and cocaine (Canseco-Alba *et al.*, 2019).

CB_2R also is involved in regulation of behavioural sensitisation induced by psychostimulants. A decrease in motor sensitisation to cocaine was observed in mice overexpressing the CB_2R and after treatment with an agonist of these receptors during the acquisition phase of sensitisation (Aracil-Fernandez *et al.*, 2012, Delis *et al.*, 2017, Lopes *et al.*, 2019). Similarly, when a CB_2R agonist was injected on the test day, the expression of cocaine sensitization in both mice and rats also was inhibited (Delis *et al.*, 2017). Interestingly, compared to the wild type, mice with a selective deletion of CB_2R in dopamine neurons did not develop behavioural sensitisation when exposed to repeated treatment with cocaine, amphetamine, and methamphetamine (Canseco-Alba *et al.*, 2019).

CB_2R seems to be also involved in the regulation of psychostimulant-rewarding responses. Transgenic mice overexpressing CB_2R show an impairment in the acquisition of cocaine self-administration (Aracil-Fernandez *et al.*, 2012). Similarly, both acquisition and expression of cocaine-induced CPP were inhibited by previous pharmacological treatment with CB_2R agonist (Delis *et al.*, 2017, Lopes *et al.*, 2019). These effects, were inhibited by blockade of CB_2R, supporting the involvement of these receptors in regulation of cocaine rewarding (Lopes *et al.*, 2019).

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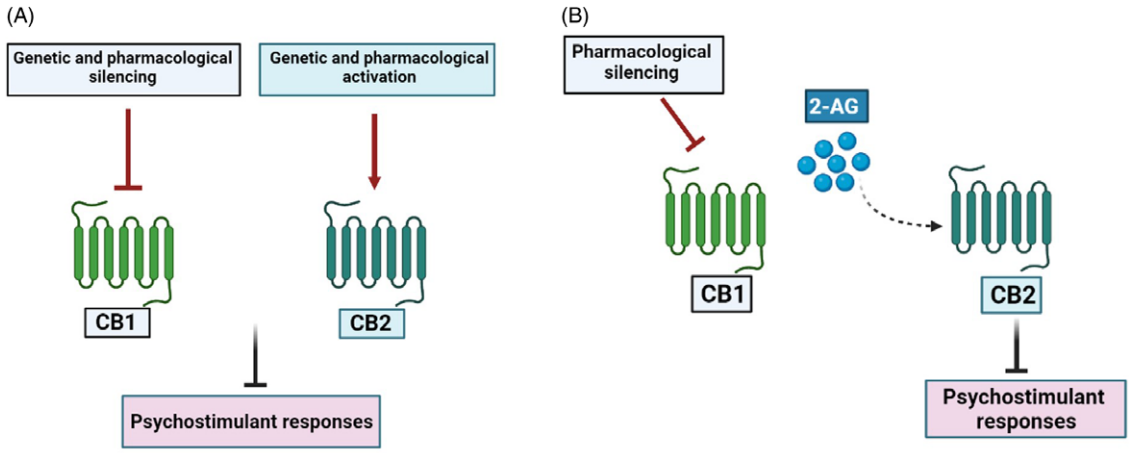

Fig. 1. CB1 and CB2 receptors differentially regulate the effects of psychostimulant drugs. Both CB_1R blockade and CB_2R activation inhibits the molecular and behavioural responses to psychostimulant drugs (Panel A). Blockade of CB_1R redirects 2-AG effects to predominantly facilitate CB2R signalling (Panel B).

Intriguingly, some studies have observed opposite results. For example, systemic blockade of CB_2R inhibited intravenous cocaine self-administration and shifted cocaine dose-response curves downward in rats and wild type, but not in CB_2R KO, mice (Jordan *et al.*, 2020). Similarly pharmacological silencing of CB_2R reduced the reinstatement of cocaine-seeking behaviour (Adamczyk *et al.*, 2012). Although the reasons for these discrepancies remain unclear, species difference in CB_2R expression could play a role. For instance, activation of CB_2R inhibited cocaine self-administration under a FR in mice, but not in rats (Zhang *et al.*, 2015). However, under a PR schedule of reinforcement, activation of CB_2R increased breakpoint for cocaine self-administration in rats (Zhang *et al.*, 2015). Beyond differences between species, the multifaceted pattern of CB_2R suggested by these studies may be due to the doses and the pattern of psychostimulants administration as well as by the differences in behavioural protocol used in the experiments.

Evidence from molecular assays suggests that brain CB_2R modulates the effects of psychostimulants by a dopaminergic mechanism. Indeed, while activation of these receptors reduces the cocaine-induced enhancement of dopamine levels in the NAcc, the blockade of CB_2R elevated basal extracellular dopamine levels in this brain region (Xi *et al.*, 2011, Zhang *et al.*, 2014). Moreover, electrophysiological studies showed that treatment with CB_2R agonists leads to a decrease in VTA's dopamine neuronal firing (Zhang *et al.*, 2014). Finally, a reduction in dopamine active transporter gene expression and enhanced in tyrosine hydroxylase activity were observed in the midbrain after selective deletion of CB_2R in dopamine neurons (Canseco-Alba *et al.*, 2019).

In summary, the data reviewed here provided evidence that CB_2R modulates behavioural and molecular responses to psychostimulants. Considering the important limitation for the therapeutic development of CB_1R antagonists, which cause unwanted serious psychiatric adverse events, modulation of CB_2R might be an interesting target to treat psychostimulant addiction (Moreira and Crippa, 2009).

Integrating CB_1R and CB_2R functions in the modulation of psychostimulant effects

As discussed throughout this review, either CB_1R blockade or CB_2R activation inhibits the molecular and behavioural responses to psychostimulant drugs. Their diametrically opposite roles might be explained by differences in the expression patterns in mesolimbic pathways modulating drug reward and reinforcement. CB_1Rs are expressed in GABAergic neurons and glutamate presynaptic terminals in the VTA, while CB_2Rs are located direct in dopaminergic VTA neurons (Kortleven *et al.*, 2011, Zhang *et al.*, 2014, Wang *et al.*, 2015). This differential expression leads to a distinct regulation in the function of dopamine neurons. CB_1R might fine-tune GABA and glutamate inputs onto mesolimbic dopaminergic neurons, predominantly increasing dopaminergic activity, whereas CB_2R might directly inhibit VTA neurons and reduce dopamine release (Zhang *et al.*, 2014, Wang *et al.*, 2015).

A major challenge consists in tying together studies focusing on each cannabinoid receptor to postulate an integrative hypothesis on endocannabinoid modulation of psychostimulant effects. Recently, we found that CB_1R antagonists and CB_2R agonists prevent the hyperlocomotion and the CPP induced by cocaine in mice, as expected. More importantly, the ameliorating effects of CB_1R antagonism could be reversed by previous administration of CB_2R antagonist. Therefore, CB_1R antagonists could inhibit cocaine effects possibly because endocannabinoid actions are diverted predominantly to CB_2R. Moreover, although inhibition of the endocannabinoid hydrolysing enzymes FAAH (fatty acid amide hydrolase) and MAGL (monoacylglycerol lipase) failed to interfere with cocaine effects, inhibition of MAGL, which preferentially hydrolysis 2-AG, did prevent cocaine hyperlocomotion when combined with a low, ineffective dose of a CB_1R antagonist (Gobira *et al.*, 2019). Accordingly, cocaine inhibition of norepinephrine uptake stimulates 2-AG release in the VTA, with subsequent inhibition of GABAergic terminals and facilitation of dopaminergic activity (Wang *et al.*, 2015). Moreover, modulation of 2-AG levels in VTA and in prelimbic cortex also regulate cocaine-related responses (Tung *et al.*, 2016, McReynolds *et al.*, 2018). In summary, a distinct functional localisation of cannabinoid receptors in the mesocorticolimbic system might explain how CB_1R blockade and CB_2R activation exert opposite effects upon cocaine responses. In addition, the ameliorating effects of CB_1R antagonists might occur by redirecting 2-AG effects to predominantly facilitate CB_2R signalling (Fig. 1).

The integrative response promoted by CB1R blockade and CB2R activation in modulation of other drugs of abuse have not been performed yet. However, the individual role of cannabinoid

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Table 1. Cannabinoid receptors influence on psychostimulant-related behaviours

Modulation of cannabinoid receptor	Behavioural Test	Results	Sex/Specie/ Background	Reference
Pharmacological blockade of CB_1R	Psychostimulant motor effects	Inhibition of the hyperlocomotion	Male Mongolian gerbils Male Swiss mice	Poncelet *et al.*, 1999 Gobira *et al.*, 2019
Genetic CB_1R deletion	Psychostimulant motor effects	Inhibition of the hyperlocomotion	Male C57BL/6J mice Male C57BL/6J mice	Corbille *et al.*, 2007 Li *et al.*, 2009
Pharmacological activation of CB_2R	Psychostimulant motor effects	Inhibition of the hyperlocomotion	Male C57BL/6J mice Male Swiss mice Male Swiss mice	Xi *et al.*, 2011 Gobira *et al.*, 2019 Lopes *et al.*, 2019
Overexpression of CB_2R	Psychostimulant motor effects	Inhibition of the hyperlocomotion	Male C57BL/6J mice	Aracil-Fernandez *et al.*, 2012
*Genetic CB_2R deletion	Psychostimulant motor effects	Potentiation of the hyperlocomotion	Male C57BL/6J mice	*Canseco-Alba *et al.*, 2019
Pharmacological blockade of CB_1R	Psychostimulant motor effects	Impaired the locomotor sensitisation	Male Wistar rats Male C57BL/6J mice Male C57BL/6J mice Male Swiss mice Male Sprague-Dawley rats Male Swiss mice	Filip *et al.*, 2006 Corbille *et al.*, 2007 Gerdeman *et al.*, 2008 Mereu *et al.*, 2015 Delis *et al.*, 2017 Lopes *et al.*, 2019
		No changes in the locomotor sensitisation	Male C57BL/6J mice	Lesscher *et al.*, 2005
Genetic CB_1R deletion	Psychostimulant motor effects	Impaired the locomotor sensitisation	Male C57BL/6J mice	Corbille *et al.*, 2007
		No changes in the locomotor sensitisation	Male CD1mice	Martin *et al.*, 2000
Pharmacological activation of CB_2R	Psychostimulant motor effects	Impaired the locomotor sensitisation	Male Sprague-Dawley rats Male Swiss mice	Delis *et al.*, 2017 Lopes *et al.*, 2019
Overexpression of CB_2R	Psychostimulant motor effects	Impaired the locomotor sensitisation	Male C57BL/6J mice	Aracil-Fernandez *et al.*, 2012
Pharmacological blockade of CB_1R	Psychostimulant reward	Impaired the CPP Impaired the CPP Impaired the CPP No changes in the CPP	Male Kunming mice Male Sprague-Dawley rats Male Swiss mice Male Wistar rats	Yu *et al.*, 2011 Delis *et al.*, 2017 Lopes *et al.*, 2019 Chaperon *et al.*, 1998
Genetic CB_1R deletion	Psychostimulant reward	No changes in the CPP No changes in the CPP	Male CD1mice Male CD1mice	Martin *et al.*, 2000 Houchi *et al.*, 2005
Pharmacological activation of CB_2R	Psychostimulant reward	Impaired the CPP Impaired the CPP	Male Sprague-Dawley rats Male Swiss mice	Delis *et al.*, 2017 Lopes *et al.*, 2019
Pharmacological blockade of CB_1R	Psychostimulant reinforcement	Decreased drug self-administration	Male Wistar rats Male CD1 mice Male Long-Evans rats Male Wistar rats	Vinklerova *et al.*, 2002 Soria *et al.*, 2005 Xi *et al.*, 2008 Orio *et al.*, 2009
		No changes in drug self-administration	Male C57BL/6J mice Male Long–Evans rats	Lesscher *et al.*, 2005 He *et al.*, 2019
Genetic CB_1R deletion	Psychostimulant reinforcement	Decreased drug self-administration	Male CD1 mice	Soria *et al.*, 2005
		No changes in drug self-administration	Male CD1 mice	Cossu *et al.*, 2001
Pharmacological activation of CB_2R	Psychostimulant reinforcement	Decreased drug self-administration	Male C57BL/6J mice Male C57BL/6J mice	Xi *et al.*, 2011 Zhang *et al.*, 2015
Overexpression of CB_2R	Psychostimulant reinforcement	Decreased drug self-administration	Male C57BL/6J mice	Aracil-Fernandez *et al.*, 2012
Pharmacological blockade of CB_2R	Psychostimulant reinforcement	Decreased drug self-administration	Male Long-Evans rats	Jordan *et al.*, 2020

(*Continued*)

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Table 1. (*Continued*)

Modulation of cannabinoid receptor	Behavioural Test	Results	Sex/Specie/ Background	Reference
Pharmacological blockade of CB_1R	Psychostimulant reinstatement	Prevented drug-induced reinstatement	Male Wistar rats Male Wistar rats Male Long–Evans rats Male Kunming mice Male Wistar rats Male Sprague-Dawley rats Male Wistar rats	De Vries *et al.*, 2001 Anggadiredja *et al.*, 2004, Xi *et al.*, 2006 Yu *et al.*, 2011 Adamczyk *et al.*, 2012 Jing *et al.*, 2014 Nawata *et al.*, 2016
		Prevented cue-induced reinstatement	Male Wistar rats Male C57BL/6J mice Male Wistar rats Male Wistar rats	Anggadiredja *et al.*, 2004, Ward *et al.*, 2009 Adamczyk *et al.*, 2012 Nawata *et al.*, 2016
		Prevented stress-induced reinstatement	Male C57BL/6J mice Male Long–Evans rats Male C57BL/6J mice Male Sprague-Dawley rats Male Sprague-Dawley rats Male Wistar rats	Vaughn *et al.*, 2012 Kupferschmidt *et al.*, 2012 Tung *et al.*, 2016 McReynolds *et al.*, 2016 McReynolds *et al.*, 2018 Guzman *et al.*, 2021

*DAT-Cnr2 conditional knockout, ** Deleted CB_1R in cortical glutamatergic neurons.

receptors in decreasing the effects induced by distinct classes of addictive drugs has already been demonstrated (Manzanares *et al.*, 2018). For instance, pharmacological and genetic silencing of CB_1R reduced the hyperlocomotion and rewarding effects induced by alcohol, opiates, and nicotine (Navarro *et al.*, 2001, Houchi *et al.*, 2005, Simonnet *et al.*, 2013, Marinho *et al.*, 2015, Guegan *et al.*, 2016). CB_1R also modulates the dopamine release in the NAcc elicited by these prototypical drugs (Cheer *et al.*, 2007, Parsons and Hurd, 2015). Moreover, similarly to observed with psychostimulants, the activation of CB_2R reduced ethanol consumption and the ethanol-induced CPP (Al Mansouri *et al.*, 2014). Treatment with CB_2R-agonist also decreases the responses promoted by opiates (Zhang *et al.*, 2018, Iyer *et al.*, 2020). Together these studies suggested that modulation of both cannabinoid receptors seems to be a common mechanism underlying the molecular and behavioural properties of different classes of drugs.

Concluding remarks and future perspectives

Preclinical studies implicate cannabinoid receptors in the modulation of behavioural and molecular responses induced by psychostimulant drugs. The consistent results showing that genetic and pharmacological blockade of CB_1R inhibits cocaine effects and could encourage the use of selective antagonists for treating psychostimulant addiction disorders. However, the incidence of serious psychiatric adverse events, such as anxiety and depression, limits the use of these compounds. In this context, drugs targeting CB_2R might represent a more promising approach. Thus, an increasing number of studies has focused on the effects of CB_2R agonists in modulation of psychostimulants responses. Combining inhibition of 2-AG hydrolysis with low doses of CB_1R antagonists and therefore favouring endocannabinoid facilitation of CB_2R signalling could also represent a new approach.

Despite this substantial evidence demonstrating the important roles of CB_1R and CB_2R in regulation of psychostimulant responses, so far the studies have focused on male mice and rats, excluding in female animals. Sexual dimorphism has been demonstrated in behavioural and molecular responses correlated to CB_1R and CB_2R. For example, expression and functionality of CB_1R were observed in the VTA and PFC of females compared to male animals, possibly providing a neural substrate for the existing sex differences to the rewarding effects of cannabinoids (Llorente-Berzal *et al.*, 2013, Castelli *et al.*, 2014). In fact, females self-administered more WIN55,212-2, a non-selective cannabinoid agonist, than male rats(Fattore *et al.*, 2010). Regarding responses correlated to CB_2R, Onaivi and co-workers demonstrated that treatment with CB_2R agonist alters mouse spontaneous locomotor activities in a sex-dependent fashion (Onaivi *et al.*, 2006). In the face with this evidence, the role of CB_1R and CB_2R in regulation of psychostimulants in female animals should be explored in future studies.

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