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Cannabidiol attenuates catalepsy induced by distinct pharmacological mechanisms via 5-HT_{1A} receptor activation in mice

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ABSTRACT

Cannabidiol (CBD) is a non-psychotomimetic compound from *Cannabis sativa* plant that produces antipsychotic effects in rodents and humans. It also reverses L-dopa-induced psychotic symptoms and improves motor function in Parkinson's patients. This latter effect raised the possibility that CBD could have beneficial effects on motor related striatal disorders. To investigate this possibility we evaluated if CBD would prevent catalepsy induced by drugs with distinct pharmacological mechanisms. The catalepsy test is largely used to investigate impairments of motor function caused by interference on striatal function. Male Swiss mice received acute pretreatment with CBD (5, 15, 30 or 60 mg/kg, ip) 30 min prior to the D_2 receptor antagonist haloperidol (0.6 mg/kg), the non-selective nitric oxide synthase (NOS) inhibitor L-nitro-N-arginine (L-NOARG, 80 mg/kg) or the CB_1 receptor agonist WIN55,212-2 (5 mg/kg). The mice were tested 1, 2 or 4 h after haloperidol, L-NOARG or WIN55,212-2 injection. These drugs significantly increased catalepsy time and this effect was attenuated dose-dependently by CBD. CBD, by itself, did not induce catalepsy. In a second set of experiments the mechanism of CBD effects was investigated. Thirty minutes before CBD (30 mg/kg) the animals received the 5-HT_{1A} receptor antagonist WAY100635 (0.1 mg/kg). The anticataleptic effect of CBD was prevented by WAY100635. These findings indicate that CBD can attenuate catalepsy caused by different mechanisms (D_2 blockade, NOS inhibition and CB_1 agonism) via 5-HT_{1A} receptor activation, suggesting that it could be useful in the treatment of striatal disorders.

1. Introduction

While Δ^9-tetrahydrocannabinol (Δ^9-THC) is the main active compound from *Cannabis sativa* plant, cannabidiol (CBD) is another cannabinoid generally found in relatively high concentrations in this plant that was initially proposed as devoid of psychopharmacological activity (Mechoulam, 1970). Δ^9-THC produces a combination of four typical behavioral changes (the tetrad) that include antinociception, hypolocomotion, hypothermia and catalepsy (Compton et al., 1992). These effects are blocked by cannabinoid CB_1 receptor antagonism (McMahon and Koek, 2007), indicating that they are mediated by these receptors. CBD, however, does not share this typical cannabinoid behavioral profile. On the contrary, it attenuates the psychotomimetic effects of high doses of Δ^9-THC (Zuardi et al., 1982), suggesting an antipsychotic activity.

Clinical trials and preclinical studies have confirmed that CBD can induce antipsychotic-like effects (for review see Campos et al., 2012; Zuardi et al., 2006). In humans, for example, CBD reduced psychotic symptoms induced by L-dopa in Parkinson's disease patients (Zuardi et al., 2009). Results from this study indicated that CBD could also improve motor function. This latter effect raised the possibility that CBD could have beneficial effects on motor related striatal disorders. Thus, the aim of the present study was to further investigate this possibility in mice submitted to the catalepsy test. The induction of catalepsy, defined as a failure to correct an externally imposed posture, is widely used to investigate impairments of motor function in rodents caused by interference on striatal function (Hauber, 1998; Sanberg et al., 1988). Thus, we investigated if CBD could prevent catalepsy induced by drugs with distinct pharmacological mechanisms that include dopamine receptor blockade, nitric oxide synthase (NOS) inhibition and CB1 receptor agonism. Since several pieces of evidence indicate that some CBD behavioral effects depend on facilitation of 5-HT_{1A}

Abbreviations: CBD, cannabidiol; L-NOARG, L-nitro-N-arginine; NO, nitric oxide; NOS, nitric oxide sinthase; Δ^9-THC, Δ^9-tetrahydrocannabinol.

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receptor-mediated neurotransmission (Gomes et al., 2011; Rock et al., 2012; Russo et al., 2005), we also tested whether the possible anticataleptic effect of CBD would be mediated by these receptors.

2. Material and methods

2.1. Animals

The experiments were performed using male Swiss mice weighting 25–35 g. The animals were housed in groups of 6 mice/cage under 12 h light cycle (lights on at 7 am) with free access to food and water. Procedures were conducted in conformity with the Brazilian Society of Neuroscience and Behavior guidelines for the care and use of laboratory animals, which are in compliance with international laws and policies and were approved by the local Ethical Committee (protocol number: 056/2012). Each animal was used twice with a week period between the tests and a multiple-treatment counterbalanced design was used.

2.2. Drugs

The following drugs were used: cannabidiol (CBD; THC Pharm, Germany), WIN55,212-2 (a CB_1 receptor agonist, Tocris, USA), haloperidol (a dopamine receptor antagonist, Haldol®, Janssen-Cilag Farmacêutica Ltda., Brazil), L-nitro-N-arginine (L-NOARG; a non-selective NOS inhibitor, Sigma-Aldrich, USA), and WAY100635 maleate (a 5-HT_{1A} receptor antagonist; Sigma-Aldrich, USA). CBD and WIN55,212-2 were diluted in 2% Tween 80 in sterile saline (vehicle), while haloperidol, L-NOARG and WAY100635 were diluted in sterile saline. The drugs were injected intraperitoneally (ip) in a 10 mL/kg volume.

2.3. Catalepsy test

Catalepsy was evaluated by placing the animal with both forelegs over a horizontal glass bar (diameter = 0.5 cm) elevated 4.5 cm from the floor. The time (s) during which the mouse maintained this position was recorded up to 300 s (Del Bel et al., 2002; Nucci-da-Silva et al., 1999). Catalepsy was considered finished when at least one forepaw touched the floor or when the mouse climbed upon the bar.

2.4. Experimental design

Catalepsy was induced by ip administration of haloperidol (0.6 mg/kg). Thirty minutes before haloperidol administration the animals received CBD (5, 15, 30 and 60 mg/kg; experiment 1). In another set of experiments, catalepsy was induced by L-NOARG (80 mg/kg; experiment 2) or WIN55,212-2 (5 mg/kg; experiment 3) and the animals were pretreated, 30 min before, with CBD (5, 15, 30 and 60 mg/kg). The mice were tested 1, 2 and 4 h after haloperidol, L-NOARG or WIN55,212-2 injection.

After that, to investigate the possible mechanism of action of CBD, mice were divided into groups receiving a first ip injection of the 5-HT_{1A} receptor antagonist WAY100635 (0.1 mg/kg) or saline followed, 30 min later, by an injection of CBD (30 mg/kg) or vehicle. Thirty minutes later, the animals received haloperidol, L-NOARG or WIN55, 212-2 injection and the time of catalepsy was measured 2 h after (experiment 4). The latter interval was chosen based on results from experiments 1 to 3, reflecting the time CBD was able to attenuate catalepsy induced by haloperidol, L-NOARG or WIN55,212-2. The intervals between drug injections and testing were based on CBD pharmacokinetics (Deiana et al., 2012) and previous studies that have investigated the behavioral effects of this compound (Casarotto et al., 2010; Zanelati et al., 2010). The doses of the drugs employed were also based on previous results from the literature (Del Bel et al., 2002; Moreira and Guimaraes, 2005; Pava et al., 2012; Zanelati et al., 2010).

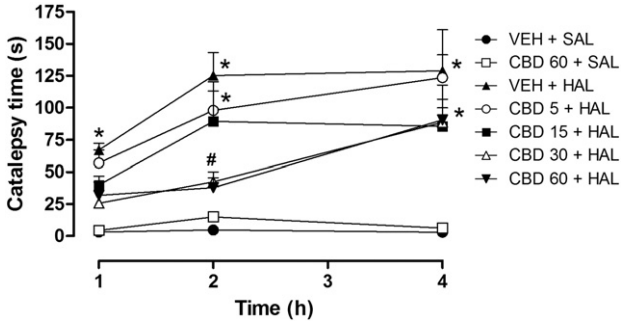

Fig. 1. Effects of CBD (5, 15, 30 and 60 mg/kg) or vehicle (VEH) on catalepsy induced by haloperidol (HAL, 0.6 mg/kg; n = 5–10/group). Data expressed as mean ± SEM of catalepsy time. * P < 0.05 from VEH + VEH group and # P < 0.05 from VEH + HAL, Bonferroni test.

2.5. Statistical analysis

Experiments 1, 2 and 3 were analyzed by two-way ANOVA, with treatment as the main independent factor, and time as a repeated measurement. An one-way ANOVA was used to analyze experiment 4. Post-hoc analysis were performed using the Bonferroni test. $P < 0.05$ was considered significant.

3. Results

3.1. Experiment 1: CBD effects on haloperidol-induced catalepsy

There were significant effects of time ($F_{2,82} = 16.95$, $P < 0.001$), treatment ($F_{6,82} = 11.44$, $P < 0.001$) and time X treatment ($F_{12,82} = 1.97$, $P < 0.05$). Haloperidol induced catalepsy throughout the experiment (Bonferroni post-hoc, $P < 0.05$ from VEH + VEH group; Fig. 1). CBD (30 and 60 mg/kg) attenuated the cataleptic effect of haloperidol 2 h after injection (Bonferroni test, $P < 0.001$ from VEH + HAL group), but not 1 and 4 h (Bonferroni test, $P > 0.05$ from VEH + HAL group). Moreover, as it was expected, CBD by itself did not induce catalepsy (Bonferroni test, $P > 0.05$ from VEH + VEH group; Fig. 1).

3.2. Experiment 2: CBD effects on L-NOARG-induced catalepsy

There was a significant effect of treatment ($F_{6,68} = 6.43$, $P < 0.001$), but no time ($F_{2,68} = 1.21$, $P > 0.05$) and time X treatment effects ($F_{12,68} = 0.71$, $P > 0.05$). L-NOARG induced catalepsy throughout the experiment (Bonferroni test, $P < 0.001$ from VEH + VEH group; Fig. 2). CBD (30 and 60 mg/kg) attenuated the cataleptic effect of L-NOARG 1, 2 and 4 h after injection (Bonferroni test, $P < 0.01$ from VEH + L-NOARG group), while CBD, at the dose of 15 mg/kg, attenuated the

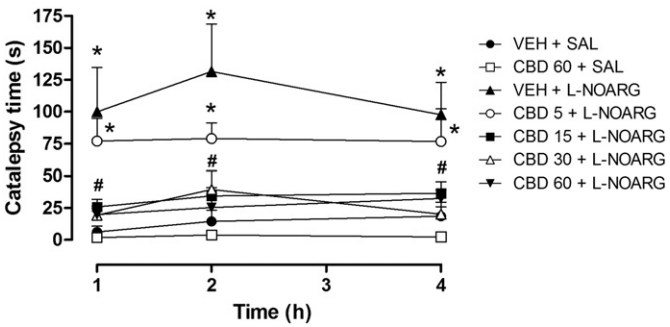

Fig. 2. Effects of CBD (5, 15, 30 and 60 mg/kg) or vehicle (VEH) on catalepsy induced by L-NOARG (80 mg/kg; n = 5–7/group). Data expressed as mean ± SEM of catalepsy time. * P < 0.05 from VEH + VEH and # P < 0.05 from VEH + L-NOARG group, Bonferroni test.

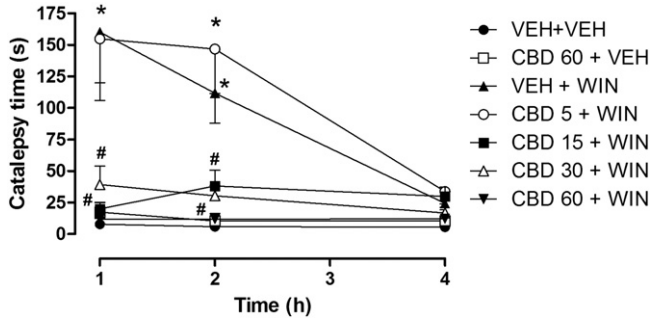

Fig. 3. Effects of CBD (5, 15, 30 and 60 mg/kg) or vehicle (VEH) on catalepsy induced by WIN55,212-2 (WIN, 5 mg/kg; n = 5–7/group). Data expressed as mean ± SEM of catalepsy time. * P < 0.05 from VEH + VEH and # P < 0.05 from VEH + WIN group, Bonferroni test.

cataleptic effect of L-NOARG 1 and 2 h after injection (Bonferroni test, P > 0.05 from VEH + L-NOARG group, Fig. 2).

3.3. Experiment 3: CBD effects on WIN55,212-2-induced catalepsy

There were significant effects of time ($F_{2,68}$ = 16.24, P < 0.001), treatment ($F_{6,68}$ = 10.01, P < 0.001) and time X treatment ($F_{12,68}$ = 5.82, P < 0.001). WIN55,212-2 induced catalepsy 1 and 2 h after injection (Bonferroni test, P < 0.001 from VEH + VEH group; Fig. 3), an effect attenuated by pretreatment with CBD (15, 30 and 60 mg/kg; Bonferroni test, P < 0.01 from VEH + WIN55,212-2 group; Fig. 3).

3.4. Experiment 4: effects of pretreatment with WAY100635, a 5-HT_{1A} receptor antagonist, on the anticataleptic effects of CBD

Confirming results from experiments 1 to 3, CBD (30 mg/kg) attenuated the catalepsy induced by haloperidol ($F_{5,55}$ = 17.80, P < 0.001; Bonferroni test, P < 0.01 from VEH + VEH + HAL group), L-NOARG ($F_{5,38}$ = 5.90, P < 0.01; Bonferroni test, P < 0.05 from VEH + VEH + L-NOARG group) and WIN55,212-2 ($F_{5,50}$ = 11.69, P < 0.001; Bonferroni test, P < 0.001 from VEH + VEH + WIN55,212-2 group). Moreover, pretreatment with WAY100635 was able to antagonize CBD effects on catalepsy induced by those three drugs (Bonferroni test, P > 0.05). WAY100635 by itself did not induce catalepsy (Bonferroni test, P > 0.05). The ability of the 5-HT_{1A} receptor antagonist WAY100635 to block CBD effects on drug-induced catalepsy is shown in Fig. 4.

4. Discussion

The present study shows that CBD attenuates the catalepsy induced by drugs with three distinct pharmacological mechanisms: D_2 receptor antagonist haloperidol, non-selective NOS inhibition (L-NOARG) and the CB_1 receptor agonism (WIN55,212-2). By itself, CBD did not induce catalepsy. This latter result agrees with the findings of Zuardi et al. showing that CBD, even at doses as high as 480 mg/kg, does not induce catalepsy in rats (Zuardi et al., 1991). In addition, a double-blind controlled clinical trial with 42 acute schizophrenic and schizophreniform psychosis patients comparing the effects of CBD with those of amisulpride, an atypical antipsychotic, showed that both treatments were equally effective in reducing acute psychotic symptoms after two and four weeks of treatment but CBD caused a much lower incidence of extrapyramidal symptoms, weight gain and increases in prolactin (Leweke et al., 2012). CBD also reduced psychotic symptoms induced by L-dopa in patients with Parkinson's disease without impairing motor function (Zuardi et al., 2009).

Since CBD attenuated catalepsy induced by drugs with different pharmacological mechanisms, a possible stimulatory effect of the drug would be suggested. However, there are several studies indicating that CBD does not change the locomotor activity (Casarotto et al., 2010; Hayakawa et al., 2008; Moreira and Guimaraes, 2005; Zanelati et al., 2010). Also, although it is not possible to discard the involvement of pharmacokinetic interactions as a possible explanation for the present results, this seems unlikely. CBD can actually inhibit CYP450 enzymes, what would potentiate, rather than inhibit, drug effects (Klein et al., 2011).

CBD can produce its effects through several pharmacological mechanisms (Izzo et al., 2009) such as facilitation of endocannabinoid signaling through their ability to inhibit the cellular reuptake and hydrolysis of endocannabinoid anandamide (Bisogno et al., 2001) and enhancement of adenosine signaling through inhibition of its uptake (Carrier et al., 2006). In 2005, Russo and colleagues reported that CBD can also displace the 5-HT_{1A} receptor agonist [^{3}H]8-OH-DPAT from cloned human 5-HT_{1A} receptors expressed in Chinese hamster ovary cultured cells and act as an agonist at these receptors (Russo et al., 2005). In addition, 5-HT_{1A} receptor antagonists were able to prevent several behavioral effects of CBD, including antidepressive (Zanelati et al., 2010), anti-nausea (Rock et al., 2012) and anxiolytic-like (Campos and Guimaraes, 2008; Gomes et al., 2011). The present results indicate that its anticataleptic effects also depend on 5-HT_{1A} receptors, although the exact mechanism by which CBD facilitates this neurotransmission is still unclear (Rock et al., 2012).

5-HT_{1A}-mediated neurotransmission had already been involved in catalepsy induced by D_2 receptor antagonists. For example, 5-HT_{1A}

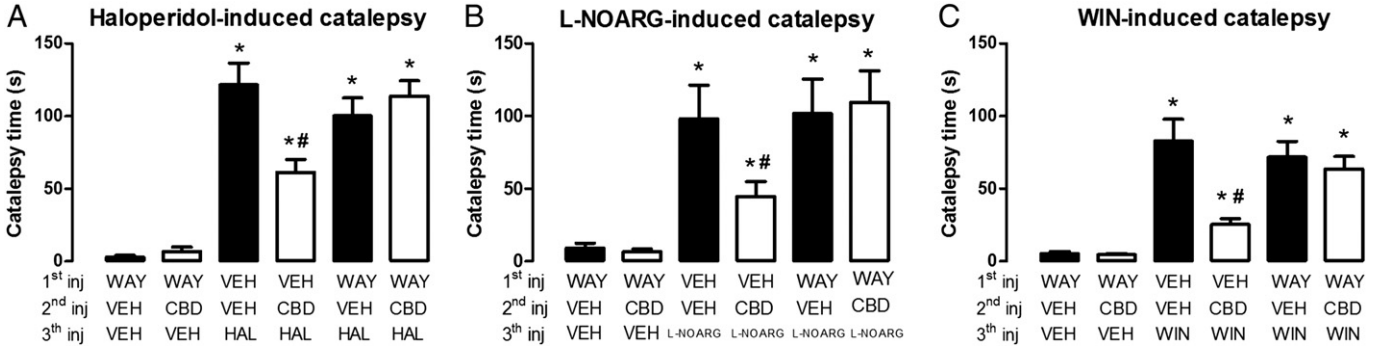

Fig. 4. Effects of pretreatment with saline (VEH) or WAY100635 (WAY, 0.1 mg/kg) followed by a second injection of vehicle (VEH) or CBD (30 mg/kg) on the catalepsy induced by haloperidol (**A**, HAL, 0.6 mg/kg; n = 6–12/group), L-NOARG (**B**, 80 mg/kg; n = 5–8/group) or WIN55,212-2 (**C**, WIN, 5 mg/kg; n = 6–10/group). The catalepsy was measured 2 h after these drugs. Data expressed as mean ± SEM of catalepsy time. * P < 0.05 from WAY + VEH + VEH and WAY + CBD + VEH; # P < 0.05 from (A) VEH + VEH + HAL, (B) VEH + VEH + L-NOARG or (C) VEH + VEH + WIN; Bonferroni test.

receptor agonists attenuate the catalepsy induced by haloperidol and risperidone (Hicks, 1990; Invernizzi et al., 1988; Neal-Beliveau et al., 1993; Prinssen et al., 2002). Also, the anticataleptic effect of 8-OH-DPAT is antagonized by the selective 5-HT_{1A} receptor antagonist WAY100635 (Bartoszyk et al., 1996). Moreover, WAY100635 enhances haloperidol-induced catalepsy (Prinssen et al., 2002).

Several studies have shown that NOS inhibitors induce catalepsy (Del Bel et al., 1998, 2002; Marras et al., 1995), an effect centrally mediated once it is also observed after intraventricular or intrastriatal administration of these drugs (Del Bel et al., 2004; Echeverry et al., 2007). The mechanisms of this effect are not known, but they suggest that nitric oxide (NO) plays an important modulatory role in the basal ganglia. NOS positive cells are found in the striatum (Vincent and Kimura, 1992) and antagonism of NO formation decreases dopamine release in this structure (Sandor et al., 1995). Similar to haloperidol-induced catalepsy, 5-HT_{1A} receptor antagonism facilitates the cataleptogenic effect of L-NOARG (Nucci-da-Silva et al., 1999). Our results corroborate this finding, indicating that 5-HT_{1A}-mediated neurotransmission is also involved in catalepsy produced by NOS inhibition.

Concerning the CBD effects on WIN55,212-2-induced catalepsy, a number of studies suggest that CBD can influence the pharmacological activity of CB_1 receptor agonists (Thomas et al., 2007; Zuardi et al., 1981, 1982). For example, CBD attenuates the psychotomimetic and anxiogenic effects of high doses of Δ^9-THC in humans (Karniol et al., 1974; Zuardi et al., 1982) even if it potentiates some positive effects of Δ^9-THC, such as antinociceptive (Varvel et al., 2006). Few studies, however, have investigated the effects of CBD on Δ^9-THC-induced catalepsy, and the results are contradictory. The cataleptic effects of Δ^9-THC were reversed CBD in two studies (Formukong et al., 1988; Karniol and Carlini, 1973) and potentiated in another one (Fernandes et al., 1974), while still other studies found that much higher doses of CBD failed to have any effect (Hayakawa et al., 2008; Jones and Pertwee, 1972; Varvel et al., 2006). Recently, it was observed that an extract of cannabis (containing Δ^9-THC, CBD and other phytocannabinoids) reduced the catalepsy induced by haloperidol in mice (Abdel-Salam et al., 2012). Since Δ^9-THC can induce catalepsy by itself and, in addition, potentiate the motor impairment caused by haloperidol (Marchese et al., 2003), it is possible that the anti-cataleptic effect of this cannabis extract is due to the presence of CBD.

The catalepsy induced by the CB_1 receptor agonist WIN55,212-2 is consistent with the abundant expression of CB_1 receptors in motor-related brain structures such as the basal ganglia (Herkenham et al., 1990). Similar to the present results with WIN55,212-2, other studies show that the behavioral changes triggered by CB_1 receptor agonists such as Δ^9-THC, HU-210 and CP55,940 were maximal from 1 to 2 h after a single intraperitoneal injection and were not longer detected after 4 h (Martin-Calderon et al., 1998; Mauler et al., 2002; McMahon and Koek, 2007).

It has been suggested that the catalepsy induced by CB_1 receptor agonist is mediated by a decrease in 5-HT neurotransmission in the nucleus accumbens due to the action of glutamate-containing neurons (Sano et al., 2008). Therefore, the activation of 5-HT_{1A} receptors in this structure could explain the anti-cataleptic effect of CBD against CB_1 receptor agonists. Corroborating this possibility, this effect was also prevented by the 5-HT_{1A} receptor antagonist WAY100635. Furthermore, similar to CBD, the 5-$HT_{1A/7}$ receptor agonist 8-OH-DPAT and the 5-HT_{1A} receptor partial agonist buspirone inhibit the Δ^9-THC-induced catalepsy, an effect blocked by a 5-HT_{1A} receptor antagonist (Egashira et al., 2006).

The mechanisms responsible for the 5-HT_{1A} agonist-induced anticataleptic activity are not yet clear. 5-HT_{1A} autoreceptors or heteroreceptors can influence several neurotransmitters that contribute to the activity of the extrapyramidal system. For example, activation of 5-HT_{1A} autoreceptors in the dorsal raphe attenuates haloperidol-induced catalepsy (Invernizzi et al., 1988). Indeed, Kapur and Remington (1996) proposed that serotonergic projections from the dorsal raphe inhibit dopaminergic nigrostriatal neuronal function in the midbrain and striatum. Agreeing with this proposition, in the midbrain the firing of dopaminergic cells projecting from the substantia nigra is inhibited by serotonin (Kapur and Remington, 1996). Thus, activation of the 5-HT_{1A} receptors, an inhibitory G-protein linked receptor, could disinhibit dopaminergic transmission in the nigrostriatal pathway by reducing serotonergic transmission through raphe autoreceptor activation. Interestingly, intracerebroventricular administration of CBD enhanced extracellular levels of dopamine in the nucleus accumbens (Murillo-Rodríguez et al., 2006), although there is no study evaluating its effects on dopamine levels in the dorsal striatum.

In addition to interfere with catalepsy, studies using animal models of Parkinson's disease CBD could also provide neuroprotection against the progressive degeneration of nigrostriatal dopaminergic neurons (Garcia-Arencibia et al., 2007; Lastres-Becker et al., 2005). Taken together, these results indicate that CBD could be useful in the symptomatic treatment of motor impairments observed in Parkinson's patients. Clinical data regarding this possibility, however, is limited and the results are contradictory. In the aforementioned work by Zuardi et al. (2009) CBD induced an apparent improvement of motor function in these patients (Zuardi et al., 2009). Also, a preliminary open pilot study showed that treatment with CBD for 6 weeks improved motor symptoms in all 5 patients with dystonic movement disorders. However, in 2 patients with coexisting Parkinsonian features, CBD exacerbated the hypokinesia and resting tremor (Consroe et al., 1986). Further clinical studies, with larger samples and more doses of CBD are clearly needed to evaluate possible therapeutic properties of CBD in Parkinson's disease.

In summary, we have shown that CBD attenuates catalepsy induced by drugs with different mechanisms through facilitation of 5-HT_{1A} receptor-mediated neurotransmission, suggesting that it could be useful in the treatment of striatal disorders.

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