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ORIGINAL ARTICLE

Cannabidiol reverses the mCPP-induced increase in marble-burying behavior

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ABSTRACT

Cannabidiol (CBD), one of the main components of *Cannabis* sp., presents clinical and preclinical anxiolytic properties. Recent results using the marble-burying test (MBT) suggest that CBD can also induce anticompulsive-like effects. Meta-chlorophenyl-piperazine (mCPP) is a nonspecific serotonergic agonist (acting mainly at 5HT1A, 5HT2C and 5HT1D receptors) reported to increase symptoms in OCD patients and block the anticompulsive-like effect of serotonin reuptake inhibitors (SRIs) in animal models. The aim of this study was to investigate the interference of CBD on mCPP effects in repetitive burying. Administration of mCPP showed dual effects in the MBT, increasing the number of buried marbles at lower (0.1 mg/kg) while decreasing it at higher doses (1 mg/kg), an effect not related to a general increase in anxiety-like behavior. As found previously, CBD (30 mg/kg) and the positive control fluoxetine (FLX; 10 mg/kg) decreased burying behavior without changing general exploratory activity. A similar effect was found when subeffective doses of CBD (15 mg/kg) and FLX (3 mg/kg) were administered together. These subeffective doses alone were also able to block mCPP-induced repetitive burying. The results, in addition to reinforcing a possible anticompulsive effect of CBD, also suggest that mCPP-induced repetitive burying could be a useful test for the screening of compounds with presumed anticompulsive properties.

INTRODUCTION

Obsessive-compulsive disorder (OCD), affecting 2–3% of the population, is characterized by recurrent intrusive thoughts recognized as mind-derived, known as obsessions, and compulsions: ritualistic behaviors aiming to alleviate the obsession-generated anxiety (for review see [1]). Serotonin reuptake inhibitors (SRIs) such as clomipramine, fluoxetine (FLX), and fluvoxamine are first choice drugs for this disorder (for review see [2,3]). Based on this observation, it was suggested that serotonin (5HT)-mediated neurotransmission is involved in OCD pathophysiology (for reviews see [3,4]). Decreased availability of 5HT could lead to an increased sensitivity of 5HT receptor subtypes [4]. Corroborating this proposal, there are reports of exacerbated OCD-related symptoms following pharmacological challenge with meta-chloro-phenyl-pyperazine (mCPP) administration [5–8]. This compound is a nonselective serotonergic agonist that acts in the central nervous system primarily through 5HT1A/D and 5HT2C receptors [9]. At higher doses, mCPP can also induce a general anxiogenic effect [10]. Preclinical models of OCD indicate that mCPP treatment blocks not only the effects of the clinically effective FLX [11] but also induces repetitive behaviors by itself [12].

Cannabidiol (CBD) is a nonpsychotomimetic component of *Cannabis* sp., with demonstrated antidepressant- and anxiolytic-like properties [13–15]. Recently, we also observed an anticompulsive-like effect of CBD in the marble-burying test – MBT. Contrary to what has been observed in other anxiety-related models, 5HT1A antagonism was not able to counteract CBD anticompulsive-like effects [16].

Thus, the aim of this study was to investigate the interference of systemically injected CBD on mCPP

effects in the MBT. This model was initially developed to assess anxiolytic-like effect, based on the observation that rodents tend to bury potentially harmful objects [17,18]. But contrary to other anxiety models, animals submitted to MBT show tolerance to repeated administration of diazepam [16] and exhibit no habituation on burying behavior following re-exposition to the marbles. These data supports the proposal that the MBT is more related to repetitive than to neophobic behavior [19].

Following the present observation of a dual effect at different doses of mCPP, we also evaluated whether the observed pro-repetitive effects on behavior were related to a general anxiogenic-like effect. After the determination of subeffective doses of CBD and FLX, we performed the interaction between these drugs and mCPP-induced burying behavior.

MATERIALS AND METHODS

Animals

Male Swiss mice, weighing 25–30 g, were used in all experiments. The animals were maintained in a 12-h light cycle with food and water available *ad libitum* except during the test. 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 (Ethical Committee protocol number: 146/2009). All efforts were made to minimize animal suffering.

Drugs

Cannabidiol (CBD; THC Pharm, Frankfurt, Germany) and fluoxetine (FLX; EMS, Campinas, Brazil) were suspended in 2% Tween 80 in sterile saline and mCPP (meta-chlorophenylpiperazine; Sigma-Aldrich, St. Louis, MO, USA, #125180) was dissolved in sterile saline. All drugs were injected intraperitoneally (ip) at a 10 mL/kg volume.

Apparatus

Marble-burying test

The marble-burying test (MBT) was performed in a square box (38 × 32 × 28 cm) containing a 5 cm sawdust layer on the floor and twenty-five green clear glass marbles (1.5 cm diameter) evenly spaced. One hour before the test the animals were left undisturbed in the experimental room. Depending on the experiment protocol (described below), the animals received injections 20 and/or 30 min before the test.

The test lasted for 30 min and, immediately after, the animals were taken from the box and the number of buried marbles was counted. Only marbles that had at least two-thirds of their superficies covered with sawdust were considered as buried [17].

Open field test

An open field was used to evaluate locomotor activity. It consists of a Plexiglas circular arena (40 cm diameter) with 40 cm high walls. The animals were placed in the center of the arena, and the total distance travelled was determined during 5 min using the ANY-MAZE software (Stoelting, Ireland).

Procedure

Experiment 1: effect of mCPP injection in the MBT and open field

Independent groups of experimentally naïve mice received ip injections of vehicle (n = 9) or mCPP at 0.1, 0.3 or 1 mg/kg dose (respectively, n = 10, 10 and 9). The animals were tested 20 min after drug injection in MBT. Independent groups of mice were also treated with the effective mCPP dose (0.1 mg/kg) or vehicle (n = 7/group) and submitted to the open field test 20 min after drug injection. The following parameters were considered in the open field test: total distance travelled and percent time spent in central and peripheral areas of the open field. The mCPP dose range was based on literature [18].

Experiment 2: effect of fluoxetine injection in the MBT

Independent groups of mice received ip injections of vehicle (n = 7) or FLX, at 1, 3 or 10 mg/kg dose (respectively, n = 6, 8 and 10) and tested in the MBT 30 min after the injection. The FLX dose range was based in literature [20].

Experiment 3: effect of cannabidiol (CBD) injection in the MBT

Independent groups of mice received vehicle (n = 11) or CBD, at 5, 15 or 30 mg/kg dose (respectively, n = 9, 10 and 9) and tested in the MBT 30 min after the injection. The CBD dose range was based in literature [16].

Experiment 4: effect of FLX and CBD combination in the MBT

The objective of this experiment was to investigate if subeffective doses of CBD and FLX could have additive and/or synergic effects in decreasing the number of buried marbles. Mice were divided into two groups

that received ip injections of vehicle ($n = 9$) or a combination of FLX (3 mg/kg) and CBD (15 mg/kg, $n = 10$). The test was performed 30 min after the injections.

Experiment 5: effect of FLX or CBD on mCPP-induced increase in the number of buried marbles

This procedure was performed to investigate if subeffective doses of FLX and CBD could prevent the mCPP-induced increase in repetitive behavior.

Experiment 5a: experimentally naïve animals received vehicle or FLX (3 mg/kg) followed, 10 min later, by an injection of mCPP (0.1 mg/kg) or saline. The following groups: vehicle/vehicle ($n = 13$), vehicle/mCPP ($n = 12$), FLX/ saline ($n = 11$), and FLX/mCPP ($n = 11$) were submitted to the MBT 20 min after the last injection.

Experiment 5b: experimentally naïve animals received vehicle or CBD (15 mg/kg) followed, 10 min later, by an injection of mCPP or saline. The following groups: vehicle/vehicle ($n = 7$), vehicle/mCPP ($n = 7$), CBD/ saline ($n = 7$), and CBD/ mCPP ($n = 6$) were submitted to the MBT 20 min after the last injection.

Experiment 6: effect of FLX, CBD or combination in the open field

Experimentally naïve mice received ip injections of vehicle ($n = 6$), FLX (3 or 10 mg/kg; $n = 6$/group), CBD (15 or 30 mg/kg; $n = 6$/group) or its combination (FLX 3 mg/kg and CBD 15 mg/kg; $n = 6$) and were submitted to the open field test for 5 min.

Statistical analysis

Experiments were analyzed by one-way ANOVA and *post hoc* analysis was performed using the Newman–Keuls test when appropriate. For results obtained in open field test and experiment 4, Student's *t*-test was used. A $P < 0.05$ was considered significant.

RESULTS

Experiment 1: effect of mCPP injection in the MBT

The one-way ANOVA indicated a significant effect of mCPP ($F_{3,34} = 35.03$; $P < 0.05$). As shown in the *Figure* 1*a*, at 0.1 mg/kg dose mCPP increased the number of buried marbles while 0.3 and 1 mg/kg doses reduced this parameter (Newman–Keuls, $P < 0.05$). No difference was observed in the total distance traveled ($t_{12} = 0.40$; nonsignificant – NS), percent time spent in center (t_{12}=0.11; NS) or in the periphery ($t_{12} = 0.18$; NS) of the open field, *Figure* 1*b,c*.

Experiment 2: effect of FLX injection in the MBT

The one-way ANOVA indicated a significant effect of FLX ($F_{3,27} = 5.29$; $P < 0.05$). As seen in the *Figure* 2*a*, FLX, at 10 mg/kg dose, reduced the number of buried marbles (Newman–Keuls, $P < 0.05$).

Experiment 3: effect of CBD injection in the MBT

The one-way ANOVA indicated a significant effect of CBD injection ($F_{3,35} = 4.01$; $P < 0.05$). CBD, at the dose of 30 mg/kg, was able to reduce the number of buried marbles (Newman–Keuls, $P < 0.05$). The 5 and 15 mg/kg CBD doses were not different from control (Newman–Keuls, NS), as seen in *Figure* 2*b*.

Experiment 4: effect of FLX and CBD combination in the MBT

The Student's *t*-test indicated a significant treatment effect ($t_{17} = 2.67$; $P < 0.05$), as seen in *Figure* 2*c*. The combined injections of subeffective doses of FLX (3 mg/

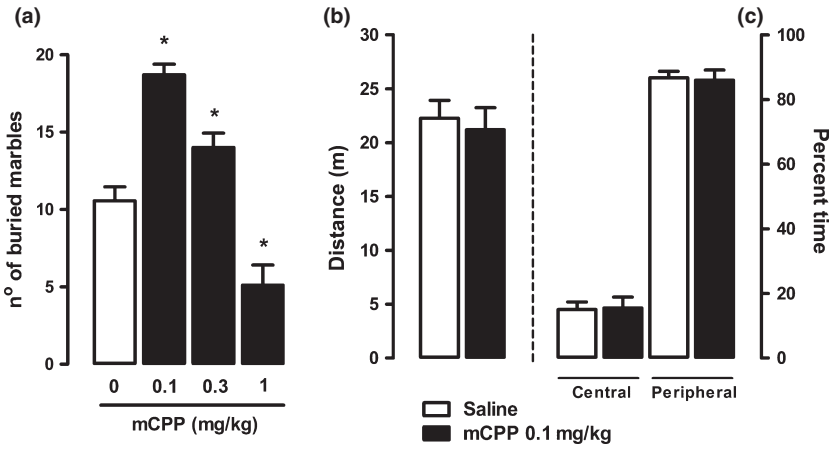

Figure 1 (a) Effect of a systemic (ip) injection of mCPP (0, 0.1, 0.3 or 1.0 mg/kg) on marble-burying test (MBT) ($n = 9$–10/group). Data represent the mean ± SEM of buried marbles. (b) Effect of mCPP (0, 0.1 mg/kg) on locomotor activity and (c) anxiety-related parameters ($n = 7$/group). Data represent the mean ± SEM of total distance traveled or percent time spent in open field areas. *$P < 0.05$ from respective control group.

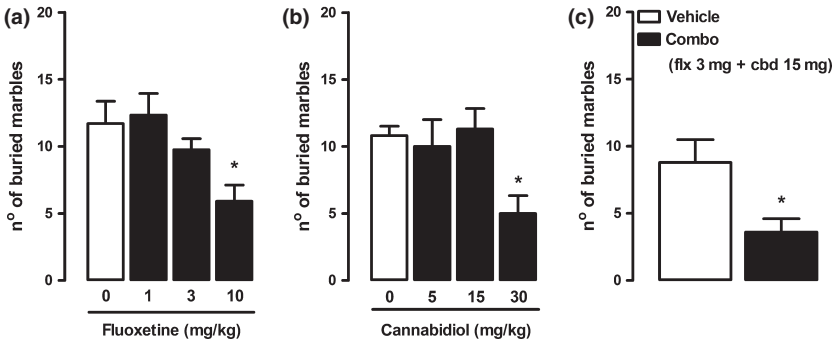

Figure 2 Effect of systemic (ip) injection of (a) fluoxetine (0, 1, 3 or 10 mg/kg), (b) cannabidiol (0, 5, 15 or 30 mg/kg) or (c) combination in animals submitted to marble-burying test (MBT). Data represent the mean ± SEM of buried marbles. *$P < 0.05$ from control group.

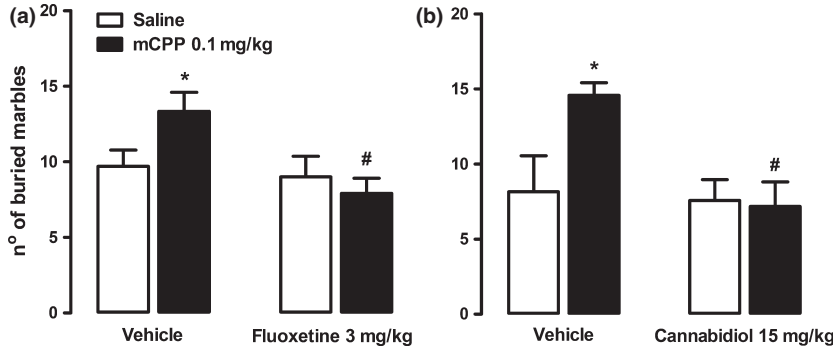

Figure 3 (a) Effect of a first systemic (ip) injection of vehicle or fluoxetine (3 mg/kg), followed by a second injection of saline or mCPP (0.1 mg/kg) on marble-burying test (MBT) (n = 11–12/group). (b) Effect of a first ip injection of vehicle or cannabidiol (15 mg/kg), followed by a second injection of saline or mCPP (0.1 mg/kg) on marble-burying test (MBT) (n = 6–7/group). Data represent the mean ± SEM of buried marbles. *$P < 0.05$ from vehicle/saline-treated group, #$P < 0.05$ from vehicle/mCPP-treated group.

kg) and CBD (15 mg/kg) reduced the number of buried marbles compared with the control group.

Experiment 5: effect of FLX or CBD on mCPP-induced increase in the number of buried marbles

Experiment 5a: as shown in *Figure* 3*a*, there was a significant difference between groups ($F_{3,43} = 3.88$; $P < 0.05$). Post hoc test indicated a significant difference between vehicle/mCPP-treated and all other groups (Newman–Keuls, $P < 0.05$). FLX pretreatment decreased the mCPP-induced increase in the number of buried marbles.

Experiment 5b: one-way ANOVA also found a significant difference between groups ($F_{3,23} = 4.43$; $P < 0.05$), as shown in *Figure* 3*b*. The vehicle/mCPP was different from all other groups (Newman–Keuls, $P < 0.05$). CBD pretreatment decreased the mCPP-induced increase in the number of buried marbles.

Experiment 6: effect of FLX, CBD and combination in the open field

One-way ANOVA found no significant drug effect on the total distance traveled ($F_{5,30} = 0.89$; NS). No difference was also observed in percent time spent in center ($F_{5,30} = 0.53$; NS) or in the periphery ($F_{5,30} = 0.55$; NS) of the open field, *Table* I.

DISCUSSION

The present study observed that mCPP systemic injection causes a dose-dependent dual effect in the burying behavior observed in the MBT. Whereas a higher dose of mCPP decreased the number of buried marbles, lower doses increased this parameter, an effect interpreted as pro-compulsive [19]. The low dose of mCPP did not change the total distance traveled or the percent of time spent in central and peripheral zones in open field, suggesting that the increase in the number of buried marbles is not due to alterations in locomotion or anxiety-related behavior.

The neurobiology of OCD is still poorly understood but, as mentioned before, 5HT is proposed to play a central role, not only in OCD-symptoms but also in drug therapy response (for review see [4]). However, the non-selective 5-HT agonist mCPP has produced contrasting results regarding OCD in patients and particularly preclinical models. Acute mCPP administration

Table I Effect of fluoxetine (FLX) and cannabidiol (CBD) injection in total distance traveled and anxiety-related parameters in animals submitted to the open field.

	Total distance (m)	% time in periphery	% time in center
Vehicle (n = 6)	18.48 ± 1.23	86.37 ± 3.59	14.97 ± 3.87
FLX 3 mg/kg (n = 6)	17.50 ± 1.72	91.64 ± 1.70	9.56 ± 1.97
FLX 10 mg/kg (n = 6)	17.87 ± 0.94	90.01 ± 1.75	11.73 ± 2.07
CBD 15 mg/kg (n = 6)	15.25 ± 1.26	88.11 ± 3.73	13.21 ± 3.93
CBD 30 mg/kg (n = 6)	16.51 ± 1.63	89.24 ± 3.99	11.74 ± 4.27
CBD 15 mg + FLX 3 mg (n = 6)	15.43 ± 1.52	92.29 ± 2.02	8.58 ± 2.05

reduced the number of buried marbles in mice tested in the MBT at a 1–20 mg/kg dose range [18] while increasing anxiety-associated behaviors [9] and repetitive movements [12,21] at 0.1–4 mg/kg dose in rats. Also in rats, using the reinforced spatial alternation model, Tsaltas and colleagues [11] observed that mCPP at a 20 mg/kg dose acutely increased persistent behavior, an effect attenuated by fluoxetine but not by desipramine or diazepam. In patients, chronic treatment with fluoxetine [22] and clomipramine [23] can prevent mCPP-induced exacerbation of obsessive-compulsive (OC) symptoms. Erzegovesi and colleagues [6] showed that a 0.25 mg/kg dose of mCPP induces a more prominent exacerbation of OCD-symptoms than 0.5 mg/kg. This higher dose also induced anxiety feelings that were not observed with the lower dose. These authors explain such dual dose-dependent effect based on mCPP lack of specificity on 5HT receptors. Our present results, showing a facilitation of repetitive behavior at low doses, agree with this possibility. Other studies, using more selective drugs, have suggested that 5HT1D receptors are responsible for OCD exacerbation while 5HT2C could be involved in the anxiogenic effects of mCPP [7,24]. However, controversial data are also found regarding the role of 5HT1D receptor in OCD-symptoms. Sumatriptan, a more selective 5HT1D agonist, exacerbated OCD-symptoms in one study [24] but failed to do so in another [25]. As the same dose was used in these two studies, the distinct outcome could depend on methodological differences. Whereas Pian et al. [25] administered a single dose of sumatriptan in a cross-over design, Koran and colleagues [24] used a 5-day repeated protocol administration. In addition, case studies have also found an anti-OCD effect of repeated sumatriptan treatment [26].

Fluoxetine and CBD reduced the number of buried marbles as observed in experiments 2 and 3. The combination of subeffective doses of these drugs also produced the same effect. In accordance with this finding, we recently demonstrated that CBD exhibited an anticompulsive-like effect in MBT [16]. Contrary to the effects observed in other anxiety-related models, the anticompulsive-like properties of CBD was not blocked by 5HT1A. On the other hand, a 5HT1A-dependent mechanism was found for the positive control paroxetine. The CBD effects on MBT were prevented by previous treatment with the CB1 receptor antagonist AM251 [16]. This finding corroborates later data showing that drugs which facilitate CB1-mediated neurotransmission, that is, direct agonists or endocannabinoid uptake and degradation enzymes inhibitors are also effective in the MBT [27,28]. The anticompulsive-like effect of FLX in this model was also blocked by the CB1 antagonist AM251 [20]. Taken together, these results suggest that the serotonergic and cannabinoid systems interact to control repetitive behaviors, although the precise nature of this interaction is not clear.

The MBT is based in the animal's natural behavior (for review see [29–32]) and pharmacologically induced increase in such behavior could be complementary to data from previously observed drug effects on natural burying. To investigate whether CBD and FLX could also prevent the exacerbation of burying behavior, in experiments 4 and 5 we verified if FLX and CBD were able to counteract the mCPP-induced increase in the number of buried marbles. The results showed that subeffective doses of FLX or CBD were effective in blocking this effect. Similar, to our data, SRIs were also able to reduce mCPP-induced repetitive behaviors such as increased reinforced alternation [11] or chewing behavior [12].

A possible limitation of the MBT is its response to acute drug treatment [16], while only chronic administration is effective in other animal models [11,12] or patients [22,23]. However, a similar temporal mismatch has been observed in other animal models, for example, antidepressant-like effects in the forced swimming [33]. Similar to the later model, the MBT appears to be a useful tool for screening compounds with anticompulsive properties, but particular attention should be paid to possible drug effects on locomotion. To control for this possible effect, the animals were submitted to the open field test and the total distance traveled and anxiety-related parameters (percent time spent in center and periphery of the apparatus) were determined. As shown in *Figure* 1 and *Table* I, no drug effect in these parameters was

observed. Therefore, it is plausible to assume that none of the changes observed in MBT are due to impaired locomotion.

Concluding, the present data indicate that mCPP has a dose-dependent dual effect in burying behavior. The observed increase in burying following the lower dose of mCPP was counteracted by a clinically effective SRI, fluoxetine, and CBD. The results, in addition to reinforcing a possible anticompulsive effect of CBD, also suggest that mCPP-induced repetitive burying could be a useful additional test for the screening of compounds with presumed anticompulsive properties.

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ABBREVIATIONS LIST

CBD – cannabidiol
FLX – fluoxetine
MBT – marble-burying test
mCPP – meta-chloro-phenyl-pyperazine
OCD – obsessive-compulsive disorder

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