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Cannabidiol attenuates behavioral changes in a rodent model of schizophrenia through 5-HT1A, but not CB1 and CB2 receptors

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ABSTRACT

Preclinical and clinical data indicate that cannabidiol (CBD), a non-psychotomimetic compound from the *Cannabis sativa* plant, can induce antipsychotic-like effects. In an animal model of schizophrenia based on the antagonism of NMDA receptors, the behavioral and molecular changes induced by repeated treatment with the NMDA receptor antagonist MK-801 were prevented when CBD was co-administered with MK-801. It is unknown, however, if CBD would reverse these changes once they have been established. Thus, in the present study we used male C57BL/6J mice, 6 weeks old, to evaluate whether daily CBD injection for seven days, starting after the end of the repeated treatment with MK-801 for 14 days, would reverse MK-801-induced deficits in the social interaction (SI) and novel object recognition (NOR) tests, which have been used to investigate the negative and cognitive symptoms of schizophrenia, respectively. We also assessed whether CBD effects would be blocked by pretreatment with AM251, a CB1 receptor antagonist, AM630, a CB2 receptor antagonist, or WAY100635, a 5-HT1A receptor antagonist. CBD and the second-generation antipsychotic clozapine, used as a positive control, attenuated the impairments in the SI and NOR tests induced by repeated administered MK-801. CBD effects were blocked by WAY100635, but not by AM251 or AM630. These data suggest that CBD induces antipsychotic-like effects by activating 5-HT1A receptors and indicate that this compound could be an interesting alternative for the treatment of negative and cognitive symptoms of schizophrenia.

1. Introduction

Schizophrenia is a complex, chronic, and disabling disorder characterized by a variety of manifestations that include positive (e.g., delusions and hallucinations), negative (deficits in emotional experience), and cognitive symptoms (impairments in several domains such as verbal learning, executive function, and working memory) [1–3]. Antipsychotic drugs, the mainstay treatment for schizophrenia, are effective for the treatment of the positive symptoms. However, they have limited efficacy against negative and cognitive symptoms [4,5]. In addition, these drugs are frequently associated with low tolerability and a high rate of adverse effects [5–8], indicating a need for new antipsychotic medications [9].

Dopamine and glutamate are the main neurotransmitters that have been involved in the pathophysiology of schizophrenia. Drugs that interact with these neurotransmitters can cause manifestations similar to those found in schizophrenia patients [10,11]. For example, while drugs that potentiate dopaminergic neurotransmission, such as amphetamine, induce changes resembling the positive symptoms, antagonists of the glutamate N-methyl-D-aspartate (NMDA) receptor, such as ketamine, phencyclidine (PCP) and MK-801, induce changes resembling positive, negative and cognitive schizophrenia manifestations in healthy humans. These latter drugs also and worsen these symptoms in patients [11–13]. In rodents, NMDA receptor antagonists produce hyperlocomotion and stereotyped behavior, disruption of cognitive function, including those evaluated by the novel object recognition (NOR) test, and impairments in social interaction (SI). These behavioral changes have been associated with the positive, cognitive, and negative symptoms of schizophrenia [14–16].

Some of the behavioral deficits induced by repeated treatment with NMDA receptor antagonists, including MK-801, can last for up to 6 weeks [17]. Also, these drugs cause neurochemical and neuroanatomical changes related to schizophrenia [17]. In conclusion, both the acute and chronic administration of NMDA receptor antagonists have been used as models to study the neurobiology of schizophrenia [16].

Cannabidiol (CBD), the major non-psychotomimetic compound

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from *Cannabis sativa,* showed antipsychotic-like properties in preclinical and clinical studies, with a pharmacological profile similar to second-generation antipsychotics [18]. Most of these studies, however, have focused on the positive symptoms of schizophrenia. We have recently reported that repeated CBD treatment prevented the impairments in the SI, NOR, and prepulse inhibition (PPI) tests in a mouse model of schizophrenia based on the chronic antagonism of NMDA receptors with MK-801 [15,19,20]. In these studies, CBD was co-administered with MK-801. It is unknown, however, if CBD could reverse the long-term behavioral deficits induced by the repeated treatment with NMDA receptor antagonists once they have been established. Similarly, the mechanisms responsible for the antipsychotic-like effects of CBD are still poorly understood.

Multiple mechanisms have been associated with the effects of CBD [18]. Regarding psychopathologies, it has been proposed that the activation of cannabinoid receptors (CB1 and CB2) and/or serotonin 5-HT1A receptors mediate CBD behavioral effects [18]. For example, anxiolytic and antidepressant-like effects induced by CBD were blocked by a 5-HT1A receptor antagonist [21,22]. However, the involvement of the 5-HT1A receptor in the antipsychotic-like effects of CBD is unknown.

Besides 5-HT1A receptors, other mechanisms could also be involved in CBD antipsychotic effects [18,21]. CBD anti-compulsive-like effects depend on the activation of CB1 receptors [23]. Although CBD presents a low affinity for the cannabinoid receptor subtypes CB1 and CB2, it inhibits the fatty acid amide hydrolase (FAAH) enzyme, which is responsible for the metabolism of the endocannabinoid anandamide (AEA) [24,25]. This mechanism leads to an increase in AEA levels, which in turn would increase the activation of cannabinoid receptors. Hence, CBD could act through an indirect mechanism to activate cannabinoid receptors [24,25]. In fact, the clinical improvement observed in schizophrenia patients after CBD treatment correlates with increases in AEA plasma levels [26]. It is still controversial, however, if the activation of cannabinoid receptors would produce antipsychotic-like effects.

Thus, we tested if the repeated treatment with CBD reverses the behavioral deficits in the SI and NOR tests induced by repeated MK-801. We also verified if CBD effects would involve the activation of CB1, CB2, or 5-HT1A receptors. Given that CBD induced antipsychotic-like effects with a pharmacological profile similar to that of second-generation antipsychotics [15,19,27], CBD effects were compared to those produced by the second-generation antipsychotic clozapine.

2. Materials and methods

2.1. Animals

Male C57BL/6J mice, 6 weeks old, drug and test naïve, obtained from the animal farm of the University of Sao Paulo at Ribeirao Preto, Brazil, were used in the experiments. They were housed in groups of five per cage (41 × 33 × 17 cm) in a temperature-controlled room (24 ± 1 °C) under standard laboratory conditions with free access to food and water and a 12 h light/dark cycle (lights on at 6:00 AM). A total of 465 male C57BL/6J mice were used in this study and the number of animals per group was calculated based on previous studies involving the same model and tests [15,19]. Procedures were conducted in conformity with the Brazilian Society of Neuroscience and Behavior guidelines for the care and use of laboratory animals, which comply with international laws and politics. The Animal Ethics Committee of the institution approved the housing conditions and experimental procedures (process number: 145/2015). We made all efforts to reduce the suffering and number of animals used in this study.

2.2. Drugs

The following drugs were used: CBD (THC Pharm, Germany), dissolved in 2% Tween 80 in saline, clozapine (Sigma-Aldrich, USA), dissolved in saline supplemented with 30 µl of 0.1 M hydrochloric acid (the pH was adjusted to values close to neutrality when necessary), MK-801 (Sigma-Aldrich, USA), dissolved in saline, AM630 (a CB2 receptor antagonist, Tocris, USA), diluted in 2% Tween 80 in saline, AM251 (a CB1 receptor antagonist, Tocris, USA), dissolved in 2% Tween 80 in saline, and WAY100635 (a 5-HT1A receptor antagonist, Abcam Biochemicals, USA), dissolved in saline. The drugs were injected intraperitoneally (i.p.) in a 10 mL/kg volume.

2.3. Experimental design

2.3.1. Experiment 1

Behavioral deficits induced by repeated MK-801 treatment.

Three protocols were tested. In the first protocol, animals received intraperitoneal injections (i.p.) of saline or MK-801 (0.25, 0.5, or 1 mg/kg) twice a day (11:30 AM and 5:30 PM) for 7 days. In the second protocol, animals received i.p. injections of saline or MK-801 (0.5, or 1 mg/kg) twice a day (11:30 AM and 5:30 PM) for 14 days. In both protocols, 8 days after the last MK-801 injection, animals were submitted to social interaction (SI) test. On the same day, after the SI test, animals were habituated for 15 min to the arena used for novel object recognition (NOR) test. The acquisition and retention trials of the NOR test were performed 24 h later (see details below). In a third protocol, we evaluated if the treatment with MK-801 (0.5 mg/kg), twice a day, for 14 days induces changes in the SI and NOR tests, which were carried out one and two days after the MK-801 treatment, respectively. The doses of MK-801 were similar to those previously used by our group to induce schizophrenia-like changes in mice [15,19].

2.3.2. Experiment 2

CBD effects on the behavioral deficits induced by repeated MK-801

Based on the results of experiment 1, we investigated whether repeated treatment with CBD (15, 30, and 60 mg/kg, i.p.) or clozapine (1

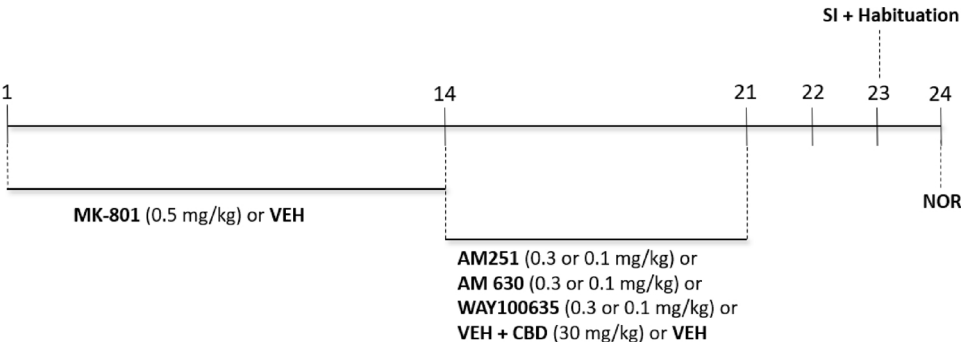

Fig. 1. Experimental design. The animals received i.p. injections of saline (SAL) or MK-801 (0.5 mg/kg), twice a day, for 14 days. CBD (30 mg/kg, i.p.) or vehicle VEH was administered daily from the 15th to the 21st day. In the experiments with the receptor antagonists, AM251 (0.3 or 0.1 mg/kg), AM630 (0.3 or 0.1 mg/kg), WAY100635 (0.3 or 0.1 mg/kg) or VEH injections were administered 10 min before each injection of CBD (30 mg/kg) or VEH. Two days after the end of the treatments, animals were submitted to the social interaction (SI) test and to the habituation session of the novel object recognition (NOR) test. Acquisition and retention trials of the NOR test were performed 24 h later.

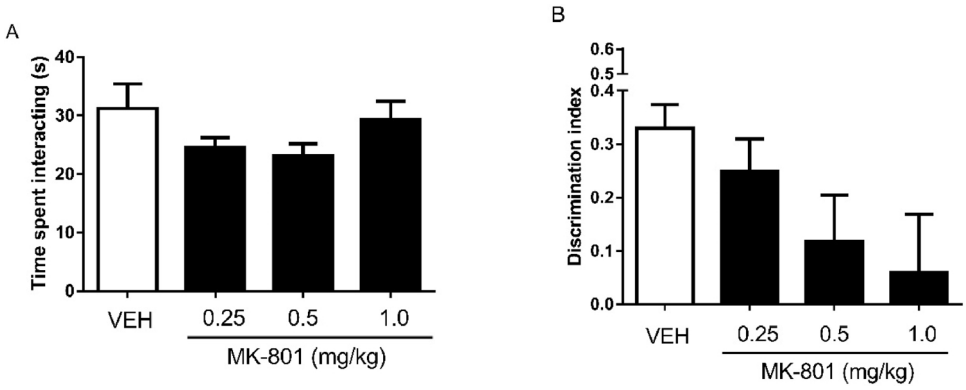

Fig. 2. Effects of MK-801 (0.25; 0.5 or 1 mg/kg), twice a day, for 7 days in the (A) SI and (B) NOR test performed 8 days after the end of the MK-801 treatment (n = 12–13/group). Data are presented as the mean ± SEM.

mg/kg, i.p.) would reverse SI and NOR impairments induced by repeated treatment with MK-801 (0.5 mg/kg,) twice a day, for 14 days (Fig. 1). The doses of CBD and clozapine were the same used by our group in studies in which these drugs prevented MK-801-induced changes when they were co-administered with MK-801 [15,19]. The treatment with CBD or clozapine, given once a day, started 24 h after the end of the MK-801 treatment and lasted for 7 days, resulting in the following groups: saline + vehicle, saline + CBD 60 mg/kg, saline + clozapine, MK-801 + vehicle, MK-801 + CBD 15 mg/kg, MK-801 + CBD 30 mg/kg, MK-801 + CBD 60 mg/kg, and MK-801 + clozapine. Two days after the end of the treatment with CBD or clozapine, animals were submitted to the SI test and to the habituation session of the NOR test. The acquisition and retention trials of the NOR test were performed 24 h later.

2.3.3. Experiment 3

Involvement of CB1, CB2, and 5-HT1A receptors in the CBD effects

To explore the possible mechanisms of action involved in the antipsychotic-like effects of CBD, a protocol similar to that described in experiment 2 was used. In this case, independent groups of animals received i.p. injections of AM251 (0.1 or 0.3 mg/kg), AM630 (0.1 or 0.3 mg/kg) or WAY100635 (0.1 or 0.3 mg/kg) 10 min before each CBD or vehicle injection. The doses of these antagonists were chosen based on studies showing that they can block behavioral effects induced by CBD [22,28]. In all protocols and tests made, the experimental groups were alternate to avoid temporal variation in results.

2.4. Social interaction (SI) test

The SI test was performed according to a protocol previously described by our group [19]. Briefly, two animals (an experimental mouse and an unfamiliar conspecific mouse with the same age) were placed in the opposite sides of a box (41 × 33 × 17 cm) that they could freely explore for 10 min. The time of active social behavior showed by the experimental mice, such as sniffing, following, grooming, and climbing on or under the other mice, was recorded. The experimental animals had not been previously exposed to the box used in the test or to the unfamiliar mouse.

2.5. Novel object recognition (NOR) test

The NOR was carried out right after SI test. It began with a habituation session at a Plexiglas circular arena (40 cm diameter and 40 cm height) for 15 min. Twenty-four hours later, each animal was submitted to two trials: acquisition (T1) and retention trial (T2). At the acquisition trial, each mouse was placed in the arena containing two identical objects for 10 min. One hour later, animals were placed back in the arena for 5 min for the retention trial (T2). In this trial, one of the objects presented in T1 was replaced by a novel, unfamiliar object. The behavior was recorded on video, and the time the animal spent directing its face to the object, up to 2 cm away from it, while watching, licking, sniffing, or touching it with the forepaws, was measured manually using two stopwatches. The arena and the objects were cleaned between each trial using alcohol 70 % to avoid odor trails. The familiar and novel objects were 16 cm high, being too heavy to be displaced by the animals and having a different shape, color, and texture. The discrimination index (discrimination index = (novel − familiar/novel + familiar)) was used to assess the recognition memory as indicated in previous studies [19,29]. To evaluate possible changes in locomotor activity, we also measured the distance traveled by the animals during the habituation session of the NOR test.

2.6. Statistical analysis

The data were analyzed by one-, two-, or three-way ANOVA as appropriated. *Post-hoc* comparisons were performed using the Dunnett's test. For the acquisition and retention trial of the NOR test, Student t-tests were performed for each treatment group. Data are presented as mean ± SEM. Results of statistical tests with $p < 0.05$ were considered significant.

3. Results

3.1. Treatment with MK-801, an NMDA receptor antagonist, for 14, but not 7 days, induced deficits in the SI and NOR tests

Repeated treatment for 7 days with MK-801 did not impair SI ($F_{3,46} = 1.68$, $p > 0.05$; n = 12–13/group, Fig. 2a) nor did it have any effect in the NOR test ($F_{3,46} = 2.30$, $p > 0.05$; n = 12–13/group, Fig. 2b). However, the repeated treatment with MK-801 (0.5 mg/kg) for 14 days impaired both the SI ($F_{2,25} = 3.88$, $p < 0,05$; n = 9–10/group, Fig. 3a) and NOR tests performed 8 days after the end of the treatment ($F_{2,25} = 3.71$, $p < 0.05$; n = 9–10/group, Fig. 3b). Similar changes were found 24 h after the end of a 14-day treatment with MK-801 (SI, $t_{(10)} = 2,03$, $p = 0.06$; n = 5–7/group, Fig. 4a; NOR, $t_{(10)} = 4,17$, $p = 0.002$; n = 5–7/group, Fig. 4b). In all experiments, there was no significant difference among groups in the time spent exploring the two identical objects in the acquisition trial of the NOR test (Supplementary Fig. 1). On the other hand, the time exploring the novel versus the familiar object in the retention trial was significantly different for all animals, except for those treated for 14 days with MK-801 (0.5 mg/kg), or for 7 days with MK-801 (0.25 mg/kg) (Supplementary Fig. 2).

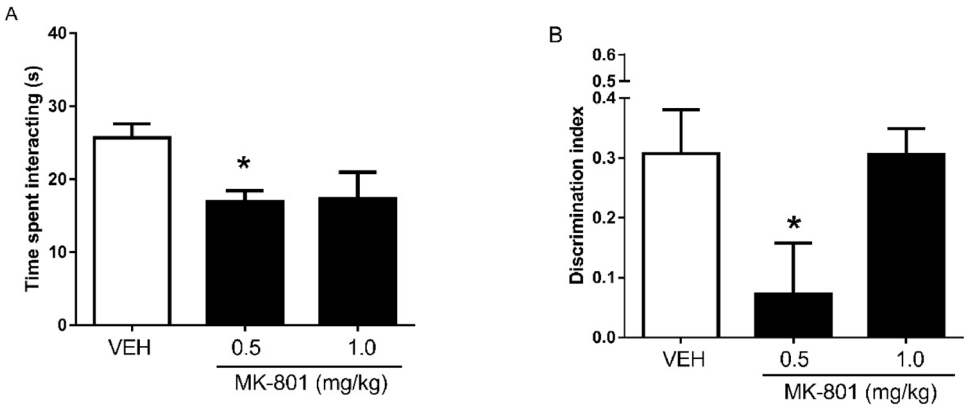

Fig. 3. Effects of MK-801 (0.5 or 1 mg/kg), twice a day, for 14 days in the (A) SI and (B) NOR test performed 8 days after the end of the MK-801 treatment (n = 9-10/group). Data are presented as means ± SEM. *P < 0.05 compared to VEH + SAL group.

3.2. CBD attenuated the impairments induced by MK-801 in the SI and NOR tests

Similar to the second-generation antipsychotic clozapine, CBD attenuated the behavioral deficits in the SI and NOR test induced by a 14-day treatment with MK-801 ($F_{2,64}$ = 9.44, p < 0.001; n = 8–10/group, Fig. 5a). In the SI test, the decrease in the time that MK-801-treated mice spent exploring a conspecific animal was attenuated by the repeated treatment with CBD (15, 30, and 60 mg/kg) or clozapine (1 mg/kg). Also, CBD 60 mg/kg, *per se*, increased social interaction ($F_{7,64}$ = 6.57, p < 0.05, n = 8–10/group, Fig. 5b).

In the NOR test, there were no significant differences in time spent exploring the two identical objects in the acquisition trial among the groups (Supplementary Fig. 3). In the retention trial, animals that received MK-801 + vehicle did not have any preference for the novel or familiar object, while MK-801-treated animals that received CBD (15 and 30 mg/kg) and clozapine (1 mg/kg) spent more time exploring the novel object compared to the familiar object ($F_{7,64}$ = 3.63, p < 0.05, Supplementary Fig. 4). The impairment induced by MK-801 was also expressed as a decrease in the discrimination index. The impairment induced y MK-801 was attenuated by CBD (15 and 30 mg/kg) and clozapine (1 mg/kg) ($F_{7,64}$ = 3.02, p < 0.05; n = 8–10/group, Fig. 5b). Interestingly, CBD at 60 mg/kg was not effective in attenuating MK-801-induced deficits in the NOR test (Fig. 5b). Finally, CBD and clozapine did not induce any effect in the NOR test *per se* (p > 0.05) and did not change locomotor activity and body weight (data not shown).

3.3. A 5-HT1A receptor antagonist, but neither a CB1 nor a CB2 receptor antagonist, blocked CBD effects on MK-801-induced behavioral deficits

Confirming our previous results, repeated CBD administration attenuated the deficit in the SI test induced by MK-801. Pretreatment with the 5-HT1A receptor antagonist WAY100635 (0.1 mg/kg) blocked this effect ($F_{1,43}$ = 5.86, p = 0.02). The Dunnett's *post-hoc* test indicated a difference among MK-801 + Veh + Veh, MK-801 + WAY100635 + Veh, and MK-801 + WAY100635 + CBD groups compared to Sal + Veh + Veh group (p < 0.05; n = 6–9/group, Fig. 6a), which indicates a behavioral impairment these groups. Similar findings were observed in the NOR test ($F_{1,43}$ = 11.29, p = 0.002; 6–9/group) where the CBD effect was also blocked by WAY100635 (0.1 mg/kg) (Fig. 6b).

On the other hand, the pretreatment with either the CB1 receptor antagonist AM251 (0.1 mg/kg) or the CB2 receptor antagonist AM630 (0.1 mg/kg) did not change the effects of CBD in attenuating MK-801-induced deficits in the SI test. *Post-hoc* analysis indicated a difference only between MK + Veh + Veh and MK + AM251 + Veh compared to Sal + Veh + Veh ($F_{1,62}$ = 10.84, p = 0.002; n = 8–9/group, Fig. 7a). There was also a difference between MK + Veh + Veh and MK + AM630 + Veh compared to Sal + Veh + Veh ($F_{6,36}$ = 8.37, p < 0.05, n = 5–7/group, Fig. 8a). In the NOR test, there was only a difference for MK + Veh + Veh and MK + AM251 + Veh compared to controls (Sal + Veh + Veh; $F_{1,62}$ = 18.85, p < 0.001; n = 8–9/group Fig. 7b).

Similar findings were observed when animals were pre-treated with AM630 (n = 5–7/group, Fig. 8b). Thus, these results indicate that CB1 or CB2 receptor antagonists were not able to attenuate the beneficial effects of CBD on MK-801 induced behavioral deficits in the SI and NOR tests.

Higher doses (threefold) of all antagonists were also tested. Interestingly, these doses attenuated the MK-801-induced behavioral deficits by themselves ($F_{1,39}$ = 9.92, p = 0.003). There were significant differences between MK + Veh + Veh and MK + WAY100635 + CBD compared to Sal + Veh + Veh group, suggesting that the pretreatment

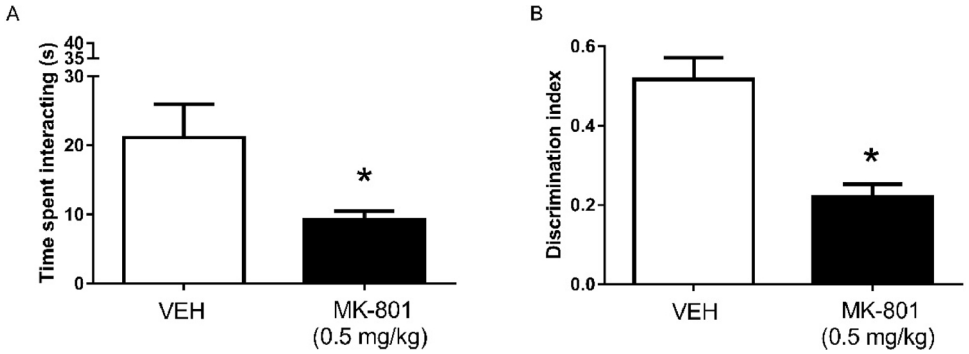

Fig. 4. Effects of MK-801 (0.5 mg/kg), twice a day, for 14 days in the (A) SI and (B) NOR test performed 24 h after the end of the MK-801 treatment (n = 5-7/group). Data are presented as means ± SEM. *P < 0.05.

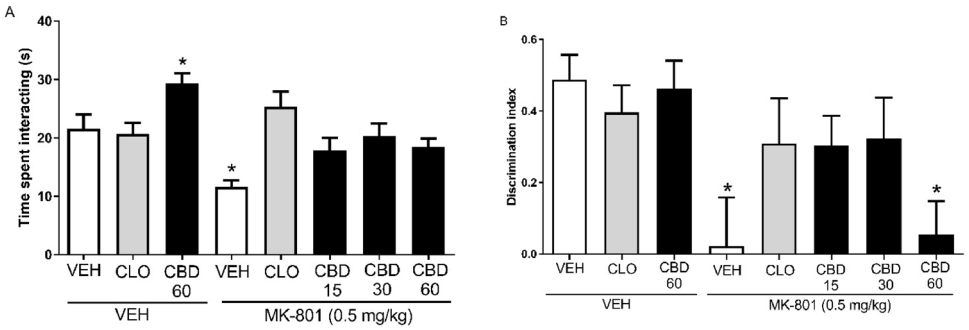

Fig. 5. Effects of repeated CBD and clozapine (CLO) treatment after pretreatment with MK-801 (0.5 mg/kg), twice a day, for 14 days in the (A) SI and (B) NOR test (n = 8-10/group). Data are presented as the mean ± SEM. *P < 0.05 compared to VEH + SAL group.

with WAY100635 (0.3 mg/kg) blocked CBD effects in the NOR test ($p < 0.05$; n = 5–8/group, Supplementary Fig. 5b). WAY100635 (0.3 mg/kg) *per se* also attenuated the impairments induced by MK-801 ($p < 0.05$; n = 5–8/group, Supplementary Fig. 5b). In the SI test, there were significant differences between MK + Veh + Veh, MK + WAY100635 + Veh, and MK + WAY100635 + CBD compared to Sal + Veh + Veh group ($F_{1,39} = 9.43$, $p < 0.001$; n = 5–8/group, Supplementary Fig. 5a). Thus, WAY100635 (0.3 mg/kg) also blocked CBD effect but, contrary to the NOR, WAY100635, at this dose, did not attenuate MK-801-induced changes in the SI test. In addition, repeated treatment with AM251 (0.3 mg/kg) or AM630 (0.3 mg/kg) did not block CBD effects. However, each of these drugs, at this dose, attenuated the behavioral deficits induced by MK-801 in the SI and NOR tests *per se* (Supplementary Figs. 6a, b, 7a, and b).

4. Discussion

Our findings show that the administration of MK-801, twice a day, for 14 days, but not for 7 days, induces impairments in the SI and NOR tests 24 h and 8 days after the end of the MK-801 treatment. These findings corroborate the proposal that repeated administration of NMDA receptor antagonists induces long-lasting behavioral changes resembling schizophrenia. For example, repeated administration of PCP (10 mg/kg/day for 10 days) caused long-lasting cognitive deficits that were observed up to 6 weeks after the end of the treatment [13,15]. No study, however, had yet investigated if MK-801 induces long-lasting changes.

Despite the development of antipsychotics with fewer extrapyramidal effects, these drugs are still poorly effective for treating negative and cognitive symptoms [4,6,7]. In this context, CBD inhibits apomorphine-induced stereotypies and inhibits amphetamine-induced hyperlocomotion, suggesting a possible therapeutic effect on the positive symptoms of schizophrenia [30,31]. Besides, even at high doses, CBD does not cause catalepsy, indicating a pharmacological profile similar to second-generation antipsychotics [30]. Acute treatment with CBD also reversed MK-801-induced impairment in the SI test [20]. Moreover, repeated treatment with CBD prevented the MK-801-induced deficits in the PPI, SI, and NOR tests [15,19]. In this study, CBD was co-administered with MK-801. We are now showing that a 7-day treatment with CBD started 24 h after the end of repeated MK-801 treatment attenuated the deficits in the SI and NOR tests. These findings indicate that CBD can reverse the behavioral impairments caused by the MK-801 treatment once they have been established, suggesting a potential therapeutic effect of CBD in a disorder already in course.

While CBD, at all doses tested (15, 30, and 60 mg/kg), was effective in attenuating the MK-801-induced deficits in the SI, the highest dose of CBD tested (60 mg/kg) did not attenuate the deficits in the NOR test. This discrepancy may be associated with the different neurobiological processes involved in these behavioral tests and with the documented bell-shaped dose-response curve induced by CBD in several animal models of psychiatry disorders [32,33].

Corroborating previous studies, CBD effects were similar to those induced by the second-generation antipsychotic clozapine [15,19,34]. Positive effects of CBD in SI and cognitive function have also been observed in other animal models of schizophrenia, including those based on neurodevelopmental disruption, such as the MAM model and the maternal immune activation model [35–38].

Although several studies have suggested that CBD may induce antipsychotic-like effects, very few have investigated the potential mechanisms involved. In a clinical study, the antipsychotic effect of CBD was associated with an increase in the plasmatic levels of AEA [26]. CBD is not a direct agonist of cannabinoid receptors, however, by inhibiting the FAAH enzyme, CBD could increase AEA levels [24,25]. Thus, the antipsychotic-like effects of CBD could involve the endocannabinoid system. Interestingly, in rodents, the blockade of AEA degradation attenuated both PCP and amphetamine-induced schizophrenia-like behaviors [39,40]. However, in the present study, the pharmacological antagonism of either CB1 or CB2 receptors did not

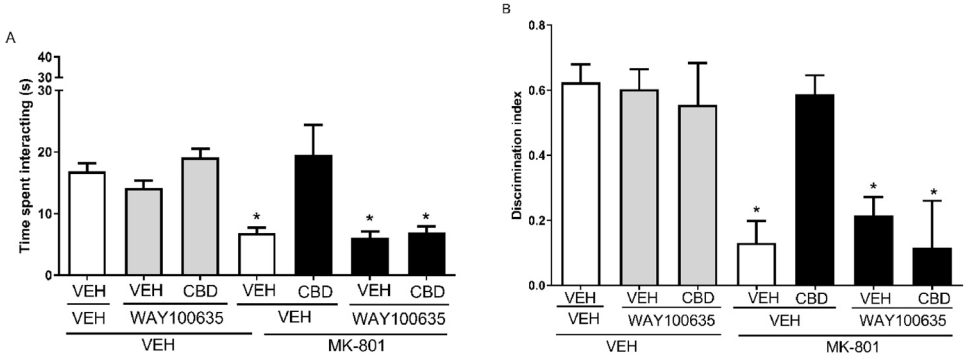

Fig. 6. Effects of repeated WAY100635 (0.1 mg/kg) and CBD treatment after pretreatment with MK-801 (0.5 mg/kg), twice a day, for 14 days in the (A) SI and (B) NOR test (n = 6–9/group). Data are presented as the mean ± SEM. *P < 0.05 compared to VEH + VEH + SAL group.

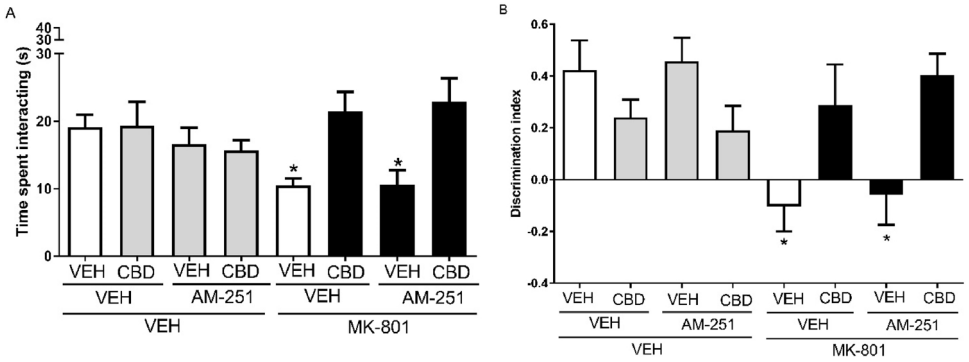

Fig. 7. Effects of repeated AM251 (0.1 mg/kg) and CBD treatment after pretreatment with MK-801 (0.5 mg/kg), twice a day, for 14 days in the (A) SI and (B) NOR test (n = 8-9/group). Data are presented as the mean ± SEM. *P < 0.05 compared to VEH + VEH + SAL group.

block the effects of CBD. These findings suggest that CBD does not engage CB1 and CB2 receptors to reverse MK-801-induced impairments in the SI and NOR tests. In contrast, the CB1 receptor antagonist AM251, at 0.3 mg/kg, attenuated the MK-801-induced behavioral deficits by itself. These findings are in accordance with studies showing that repeated treatment with AM251 reversed impairments in the SI and NOR tests in a model of schizophrenia based on social isolation and attenuated PCP-induced disruption in the PPI test [41,42].

Similar to CB1, CB2 receptors may be involved in some deficits observed in schizophrenia. Decreased expression of CB2 receptors was reported in first-episode psychosis as well as in antipsychotic-treated schizophrenia patients [43,44]. Moreover, whereas the depletion of CB2 receptors or the administration of the CB2 receptor antagonist AM630 induced schizophrenia-related behaviors in mice, the activation of these receptors reversed MK-801-induced disruptions of PPI in mice [45–47]. Although there is evidence indicating that some CBD effects could be mediated by the activation of CB2 receptors [48,49], AM630 did not block CBD effects on MK-801-induced behavioral impairments. Curiously, similar to the CB1 receptor antagonist AM251, AM630, at the dose of 0.3 mg/kg, also attenuated the MK-801-induced deficits in the SI and NOR test by itself.

Several effects of CBD in rodent models have been associated with the activation of 5-HT1A receptors (for review see [21]). These receptors seem to play a key role in psychosis, cognitive function, mood, and in schizophrenia treatment response (for review see [50]). Lurasidone (a potent 5-HT1A receptor partial agonist) and tandospirone (a selective 5-HT1A receptor agonist), but not the first-generation antipsychotic haloperidol, prevented NOR deficits induced by sub-chronic PCP in rats. These effects were blocked by the pretreatment with WAY100635, a selective 5-HT1A receptor antagonist [51]. In addition, 5-HT1A receptors have been related to the behavioral changes associated with the negative and cognitive symptoms of schizophrenia [52]. In animal models, the positive effects of perospirone, aripiprazole, lurasidone, and tandospirone on cognitive impairments were prevented by WAY100635. Moreover, the positive impact of aripiprazole on social function impairment was also blocked by WAY100635 [53–57]. Corroborating these findings, tandospirone (a 5-HT1A receptor agonist), either alone or in addition to perospirone, improved verbal memory in patients with schizophrenia [58,59]. In the present study, the beneficial effects of CBD on the behavioral deficits induced by MK-801 seem to involve the activation of these receptors, since WAY100635 blocked them. However, it is still unknown if 5-HT1A receptors would also mediate the effects of CBD on behaviors associated with the positive symptoms of schizophrenia.

It is thought that the ability of some antipsychotic drugs such as clozapine and olanzapine to improve negative/cognitive symptoms is attributed to their effect increasing dopaminergic transmission in the medial prefrontal cortex and hippocampus such as suggested by preclinical studies [60–62]. This effect seems to depend on the activation of 5-HT1A receptors since they are absent in 5-HT1A receptor knockout mice [63]. At the moment, however, it is still unknown if CBD could also increase dopamine in this brain region and if this effect would depend on the activation of 5-HT1A receptors [63].

Other mechanisms could also be involved in CBD antipsychotic effects. For example, there is evidence indicating that CBD can act as a partial agonist at dopamine D2-high affinity receptors [64]. Besides, similar to second-generation antipsychotics, repeated administration of CBD can induce several neuroplastic changes [65]. CBD attenuated some neuroplastic effects induced by chronic stress, such as the decrease in hippocampal neurogenesis and dendrite spines density [28]. Similar effects regarding neurogenesis and chronic stress have been recently reported for clozapine [66]. Also, similar to clozapine, CBD co-administered with MK-801 prevented both the increased microglia activation and the decreased number of parvalbumin-positive GABA interneurons in the prefrontal cortex induced by repeated MK-801 [15,19]. However, despite this evidence and the findings described here, further studies using refined approaches and different animal modes of schizophrenia are required to improve our understanding of the mechanisms and neurobiological processes involved in the antipsychotic properties of CBD. In addition, studies employing females are

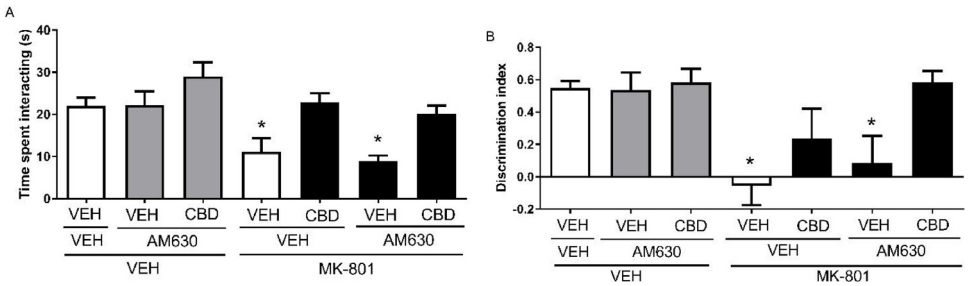

Fig. 8. Effects of repeated AM630 (0.1 mg/kg) and CBD treatment after pretreatment with MK-801 (0.5 mg/kg), twice a day, for 14 days in the (A) SI and (B) NOR test (n = 5-7/group). Data are presented as the mean ± SEM. *P < 0.05 compared to VEH + VEH + SAL group.

needed since sex differences are noted in several psychiatry disorders, including schizophrenia [67], and in response to antipsychotic drugs [68,69].

In conclusion, the present results indicate that CBD treatment reverses the impairments in social behavior and cognitive function in a model of schizophrenia induced by the treatment with an NMDA receptor antagonist. Our findings are in accordance with prior work indicating that CBD has antipsychotic properties and extend these observations by showing that the antipsychotic-like effects induced by CBD may involve the facilitation of the 5-HT1A receptor-mediated neurotransmission. Considering that it is usually well tolerated by patients [70], CBD could be a therapeutic medication for treating negative and cognitive symptoms of schizophrenia. However, the true therapeutic potential of CBD on these symptoms still need to be extensively validated in larger randomized-controlled trials.

Funding and disclosure

FSG is a co-inventor (Mechoulam R, JC, Guimaraes FS, AZ, JH, Breuer A) of the patent “Fluorinated CBD compounds, compositions and uses thereof. Pub. No.: WO/2014/108899. International Application No.: PCT/IL2014/050023” Def. US no. Reg. 62193296; 29/07/2015; INPI on 19/08/2015 (BR1120150164927). The University of São Paulo has licensed the patent to Phytecs Pharm (USP Resolution No. 15.1.130002.1.1). The University of São Paulo has an agreement with Prati-Donaduzzi (Toledo, Brazil) to “develop a pharmaceutical product containing synthetic cannabidiol and prove its safety and therapeutic efficacy in the treatment of epilepsy, schizophrenia, Parkinson’s disease, and anxiety disorders”.

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Declaration of Competing Interest

None.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.phrs.2020.104749.

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