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Cannabidiol inhibits the hyperlocomotion induced by psychotomimetic drugs in mice

Fabrício A. Moreira*, Francisco S. Guimarães

Department of Pharmacology, FMRP, University of São Paulo, 14049-900, Ribeirão Preto, SP, Brazil

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Abstract

Cannabidiol is a non-psychotomimetic compound from *Cannabis sativa*. It is proposed as a possible antipsychotic drug, since it can prevent some psychotomimetic-like effects of Δ^9-tetrahydrocannabinol or apomorphine. Therefore, the aim of this work was to test the hypothesis that cannabidiol would inhibit the hyperlocomotion induced by two psychotomimetic drugs, D-amphetamine or ketamine. Male Swiss mice received i.p. injections of haloperidol (0.15–0.6 mg/kg), clozapine (1.25–5 mg/kg) or cannabidiol (15–60 mg/kg) followed by D-amphetamine (5 mg/kg) or ketamine (60 mg/kg). Thirty minutes after the first injection, the distance moved in circular arena was measured during 10 min. In another group of experiments, catalepsy was measured 30 min after haloperidol, clozapine or cannabidiol injections. Cannabidiol, like clozapine but unlike haloperidol, inhibited hyperlocomotion without inducing catalepsy. Moreover, cannabidiol itself, unlike haloperidol and clozapine, did not decrease locomotion. In conclusion, cannabidiol exhibits an antipsychotic-like profile without inducing extrapyramidal-like effects.

Keywords: Cannabidiol; Cannabinoid; Antipsychotic; Psychotomimetic; Locomotion; Catalepsy

1. Introduction

Cannabidiol is a compound from *Cannabis sativa*, formerly proposed as a cannabinoid devoid of psychopharmacological activity, Δ^9-tetrahydrocannabinol (Δ^9-THC) being the main active compound (Mechoulam, 1970; Mechoulam and Shani, 1970). This latter cannabinoid exhibits a typical pharmacological profile, namely the induction of psychotic-like reactions, hypolocomotion, catalepsy, analgesia and hypothermia (Compton et al., 1992). These effects are mediated by cannabinoid CB-1 receptors, where anandamide and 2-aracdonylgycerol act as the main endogenous ligands (for a review, see Piomelli, 2003). Although not sharing this profile, behavioural studies revealed that cannabidiol does induce central effects such as anticonvulsive, hypnotic and anxiolytic effects (Carlini et al., 1973; Guimarães et al., 1990; Monti, 1977). In addition, cannabidiol can antagonize some behavioural effects of Δ^9-THC, such as catalepsy and impairment of variable-interval schedule performance (Formukong et al., 1988, Zuardi and Karniol, 1983). Moreover, cannabidiol blocks psychotomimetic and anxiogenic effects of Δ^9-THC in humans (Karniol et al., 1974; Zuardi et al., 1982), an effect that probably involves pharmacodynamic rather than pharmacokinetic interactions (Hunt et al., 1981).

These observations led to the hypothesis that cannabidiol could have antipsychotic activity. Its presence in the cannabis plant could protect the user from developing Δ^9-THC-induced psychosis (Rottanburg et al., 1982).

Supporting this idea, Zuardi et al. (1991) demonstrated that cannabidiol inhibited apomorphine-induced stereotyped behaviour in rats. In addition, antipsychotic effects comparable to haloperidol were observed in a single patient treated with the drug (Zuardi et al., 1995).

Schizophrenia is a complex disease characterized by the presence of psychotic or "positive symptoms", such as delusions and hallucinations, and by a core of "negative symptoms", for example social avoidance and impaired cognitive function (Egan and Weinberger, 1997; Freed-

* Corresponding author. Tel.: +55 16 6023209; fax: +55 16 6332301.
E-mail address: moreiraf@usp.br (F.A. Moreira).

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man, 2003). Many neurotransmitters are implicated in this syndrome, especially dopamine and glutamate, and some manifestations of schizophrenia may be induced by drugs acting in these systems (Carlsson et al., 2000; Freedman, 2003; Moghadam, 2003; Vollenweider and Geyer, 2001). Potentiation of the dopaminergic neurotransmission or antagonism of the *N*-methyl-D-aspartate (NMDA) glutamate-receptor subtype induces psychotic states in healthy individuals and worsens symptoms in schizophrenic patients (Harris and Batki, 2000; Lahti et al., 2001; Laruelle et al., 1996). In rodents, these drugs may induce stereotyped behaviour, hyperlocomotion, reduction of social interaction and disruption of the prepulse inhibition of the startle reflex. The antagonism of these effects is predictive for compounds with antipsychotic activity (Iversen, 1987; Kilts, 2001; Lipska and Weinberger, 2000).

The aim of this work was to test the hypothesis that cannabidiol would inhibit the hyperlocomotion induced by the indirect dopaminergic agonist D-amphetamine or by the non-competitive NMDA-receptor antagonist ketamine, thereby employing both dopamine-based and glutamate-based models predictive of antipsychotic activity in mice. The effect of cannabidiol was also evaluated in the catalepsy test, a model predictive of extrapyramidal side effects (Hoffman and Donovan, 1995; Sanberg et al., 1988). Haloperidol and clozapine were used as standard typical and atypical antipsychotic drugs, respectively.

2. Materials and methods

2.1. Animals

Male Swiss mice (20–30 g) were housed in groups in a temperature-controlled room (24 ± 1 °C) under standard laboratory conditions with free access to food and water and a 12 h light/12 h dark cycle (lights on at 06:30 a.m.). 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.

2.2. Drugs

Cannabidiol (kindly supplied by Dr. Raphael Mechoulam, Hebrew University, Jerusalem, Israel) was suspended in polyoxyethylenesorbitan monooleate (Tween 80) 2% saline. Clozapine (SIGMA) was dissolved in acetic acid 0.5% saline. Haloperidol (Haldol®, JANSSEN-CILAG), D-amphetamine (SIGMA) and ketamine (SIGMA) were dissolved in saline (0.9% NaCl). The solutions were prepared immediately before use and were protected from the light during the experimental session. Due to the low pH solution, clozapine was administered by subcutaneous injection. The other drugs were intraperitoneally injected in a volume of 10 ml/kg.

2.3. Behavioral measurements

The experiments were performed in a sound-attenuated, temperature-controlled (25 ± 1 °C) room, illuminated with three 40 W fluorescent bulbs placed 4 m above the apparatus. The experiments measuring locomotion were carried out in a circular arena (40 cm in diameter with a 50 cm high Plexiglas wall) and the mice were videotaped during 10 min. The behavior was analyzed with the help of the Ethovision software (version 1.9; Noldus, the Netherlands). This software detects the position of the animal in the open arena and calculates the distance moved.

For the catalepsy test, mice forepaws were placed over a horizontal glass bar (diameter: 0.5 cm) elevated 4.5 cm from the floor. The time in seconds during which the mice maintained both forepaws over the bar and both hindpaws

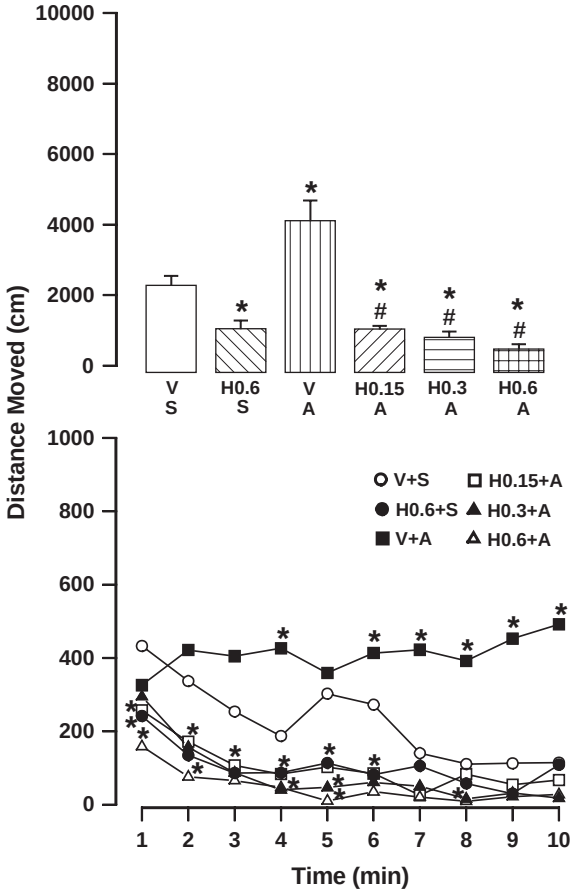

Fig. 1. Effects of haloperidol (H) on the hyperlocomotion induced by D-amphetamine (A, 5 mg/kg). The points in the lower panel represent the mean distance moved in each minute (S.E.M. were omitted for clarity). The total distance moved during 10 min (mean ± S.E.M.) is represented in the upper panel (n=7 per group). *P<0.05 compared to vehicle (V)+saline (S) group and $^{\#}P$<0.05 compared to vehicle+D-amphetamine group (ANOVA followed by Duncan).

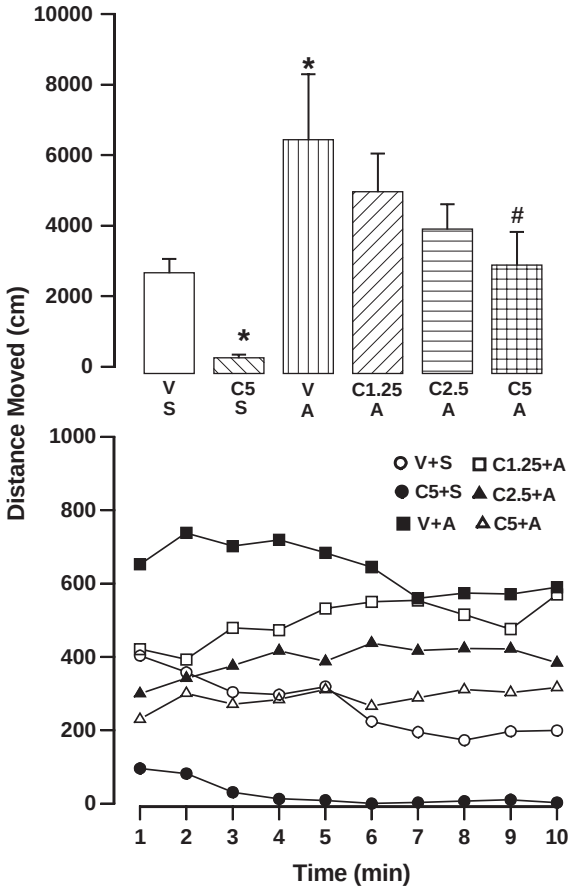

Fig. 2. Effects of clozapine (C) on the hyperlocomotion induced by D-amphetamine (A, 5 mg/kg). *$P<0.05$ compared to vehicle (V)+saline (S) group and $^{\#}P<0.05$ compared to vehicle+D-amphetamine group (ANOVA followed by Duncan). Further specifications as in Fig. 1.

on the ground was recorded (with a cut-off time of 300 s) by an experimenter who was blind to the treatments. Three immediate attempts to replace the animal in cataleptic position were allowed within the first 10 s.

2.4. Procedures

The animals were randomly assigned to one of the treatment groups (n=7 per group in all experiments). For locomotion measurement, the mice received a first injection of vehicle, haloperidol (0.15, 0.30 or 0.60 mg/kg), clozapine (1.25, 2.50 or 5.00 mg/kg) or cannabidiol (15, 30 or 60 mg/kg). In one group of experiments, D-amphetamine (5 mg/kg) or saline were administered 20 min after the first injection, while in the other series of experiments ketamine (60 mg/kg) or saline were administered 10 min after the first injection. Thirty minutes after the first injection, the animals were placed in the circular arena for behavior analysis. The doses of D-amphetamine and ketamine were based on dose–response curves for the induction of hyperlocomotion in mice (Irifune et al., 1991; Rifee and Wilcox, 1985). The catalepsy test was performed in independent groups 30 min after drug administration.

2.5. Statistical analysis

The distance moved was analyzed by repeated measures analysis of variance (rANOVA) with time (1 to 10 min) as the within-subjects factor and drug as the between-subjects factor. The degrees of freedom of the repeated factors were corrected by the Huynh-Feldt epsilon. In case of a significant interaction, post hoc comparisons were performed by one-way analysis of variance (ANOVA) followed by the Duncan test. Catalepsy time was analyzed by one-way ANOVA followed by the Duncan test. Differences were considered significant at $P<0.05$ level.

3. Results

In the first experiment (Fig. 1), an overall rANOVA revealed a significant drug effect [$F(5,36)=21.93$,

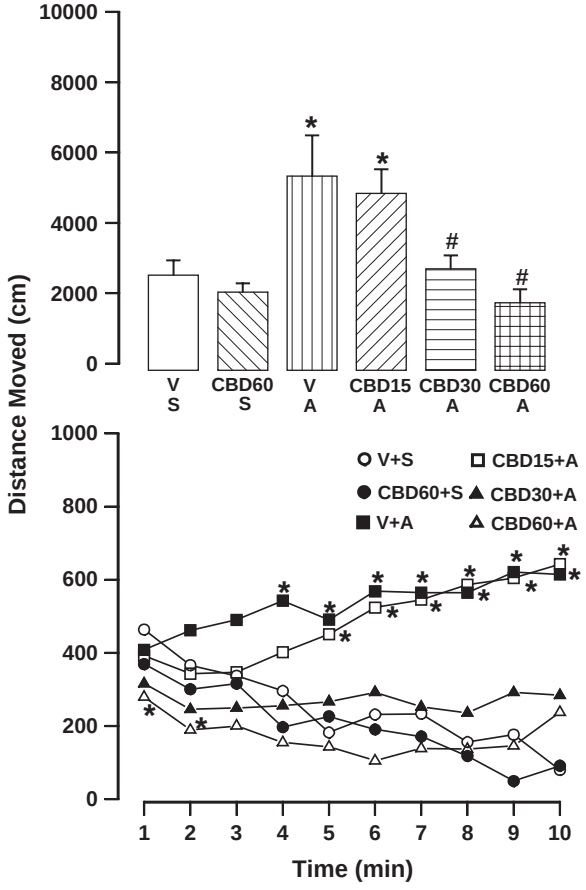

Fig. 3. Effects of cannabidiol (CBD) on the hyperlocomotion induced by D-amphetamine (A, 5 mg/kg). *$P<0.05$ compared to vehicle (V)+saline (S) group and $^{\#}P<0.05$ compared to vehicle+D-amphetamine group (ANOVA followed by Duncan). Further specifications as in Fig. 1.

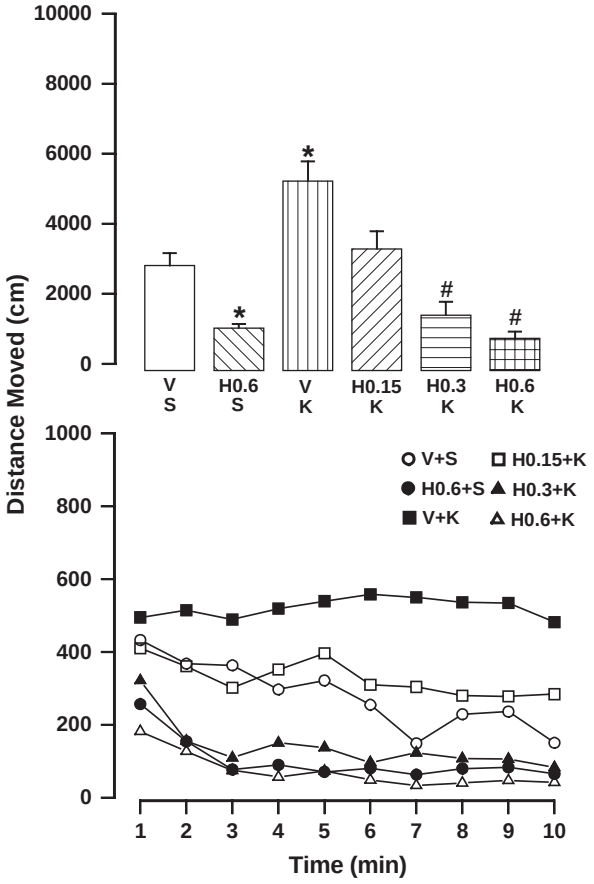

Fig. 4. Effects of haloperidol (H) on the hyperlocomotion induced by ketamine (K, 60 mg/kg). *$P<0.05$ compared to vehicle (V)+saline (S) group and #$P<0.05$ compared to vehicle+ketamine group (ANOVA followed by Duncan). Further specifications as in Fig. 1.

$P<0.0001$], drug×time interaction [$F(45,132)=1.75$, $P=0.008$)] and time effects [$F(9,28)=9.25$, $P<0.001$]. Amphetamine increased locomotion, as compared to control (vehicle+saline), at the 4th, 6th, 7th, 8th, 9th and 10th minutes. This effect was prevented by pre-treatment with haloperidol. The latter drug decreased locomotion at the 1st, 2nd, 3rd, 4th, 5th, 6th and 8th minutes. Analysis of the total distance moved showed that D-amphetamine induced a significant increase as compared to control. On the other hand, all the groups treated with haloperidol showed a decreased locomotion.

In the second experiment (Fig. 2), there was a significant drug effect [$F(5,36)=4.40$, $P=0.0031$], but neither a drug×time interaction [$F(45,132)=1.45$, $P=0.059$)] nor a time effect [$F(9,28)=0.66$, P=0.739]. D-Amphetamine induced a significant increase in the total distance moved compared to the control group. This effect was prevented by 5 mg/kg of clozapine. This treatment, however, induced a significant decrease in locomotion as compared to the control group.

In the third experiment (Fig. 3), there was a significant drug effect [$F(5,36)=5.86$, $P=0.0005$], drug×time interaction [$F(45,132)=1.49$, $P=0.044$)] and a time effect [$F(9,28)=3.43$, $P=0.006$]. D-Amphetamine induced a significant increase in locomotion from the 4th minute to the end of the experiment. This effect was prevented by cannabidiol 30 and 60 mg/kg, but not by 15 mg/kg. The higher dose of cannabidiol (60 mg/kg) decreased the distance moved, as compared to control, at the 1st and 2nd minutes. Analysis of the total distance moved showed that D-amphetamine induced a significant increase as compared to control. This effect was prevented by 30 or 60 mg/kg of cannabidiol.

In the fourth experiment (Fig. 4), an overall rANOVA revealed a significant drug effect [$F(5,36)=19.34$, $P<0.0001$], a lack of drug×time interaction [$F(14,132)=1.10$, $P=0.33$)], but a significant time effect [$F(9,28)=6.31$, $P<0.001$]. Ketamine induced a significant increase in the total distance moved. This effect was prevented by 0.3 and 0.6 mg/kg of haloperidol. By itself, haloperidol (0.6 mg/kg) decreased locomotion as compared to control group.

In the fifth experiment (Fig. 5), there was a significant drug effect [$F(5,36)=30.51$, $P<0.0001$], a lack of drug×time interaction [$F(14,132)=1.44$, $P=0.58$)], but a

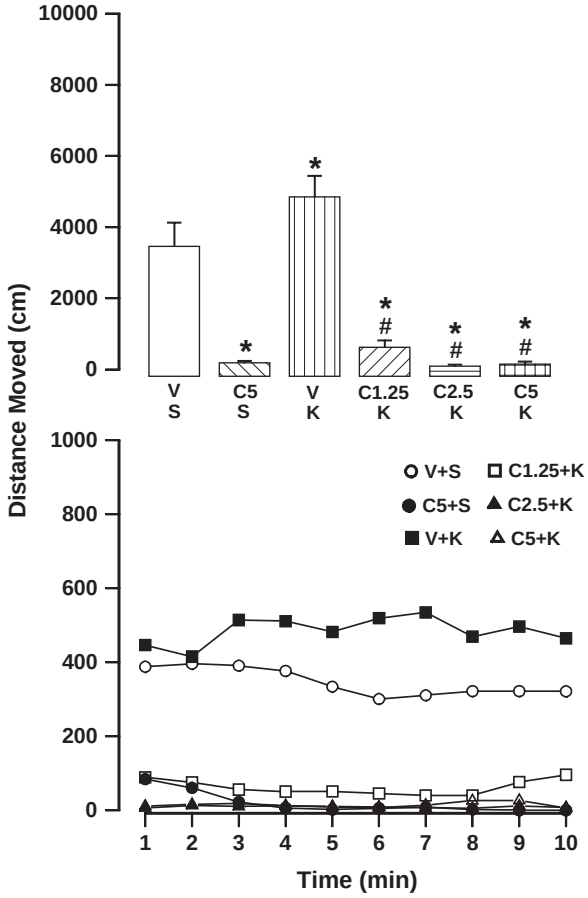

Fig. 5. Effects of clozapine (C) on the hyperlocomotion induced by ketamine (K, 60 mg/kg). *$P<0.05$ compared to vehicle (V)+saline (S) group and #$P<0.05$ compared to vehicle+ketamine group (ANOVA followed by Duncan). Further specifications as in Fig. 1.

significant time effect [$F(9,28)=3.02$, $P=0.012$]. Ketamine significantly increased locomotion, an effect that was prevented by clozapine. The latter drug, when administered alone, decreased the total distance moved as compared to the control group.

In the sixth experiment (Fig. 6), there was a significant drug effect [$F(5,36)=3.57$, $P=0.01$], a drug×time interaction [$F(45,132)=1.48$, $P=0.045$)], but no time effect [$F(9,28)=0.91$, $P=0.53$]. Ketamine increased locomotion from the 4th minute to the end of the trial. This effect was decreased by cannabidiol 30 mg/kg from the 4th to the 9th minutes. At the 4th, 5th, 6th and 8th minutes, the doses of 15 and 60 mg/kg of cannabidiol were also able to attenuate ketamine effect. Analysis of the total distance moved showed that ketamine induced a significant increase as compared to control. Cannabidiol 30 mg/kg tended ($P<0.1$) to decrease this effect.

For the catalepsy tests, ANOVA followed by the Duncan test revealed that, in three independent experiments, haloperidol significantly increased the descent latency. Neither clozapine nor cannabidiol produced any significant effect. [$F(3,24)=10.78$, $F(4,30)=25.00$, $F(4,30)=12.10$, respectively, $P<0.0001$; Fig. 7].

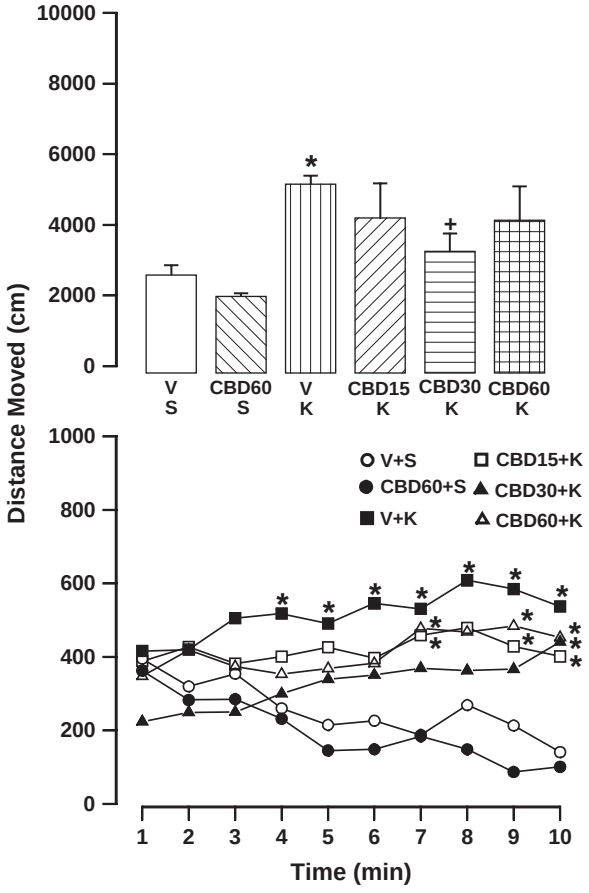

Fig. 6. Effects of cannabidiol (CBD) on the hyperlocomotion induced by ketamine (K, 60 mg/kg). *$P<0.05$ compared to vehicle (V)+saline (S) group and $^{+}P<0.1$ compared to vehicle+ketamine group (ANOVA followed by Duncan). Further specifications as in Fig. 1.

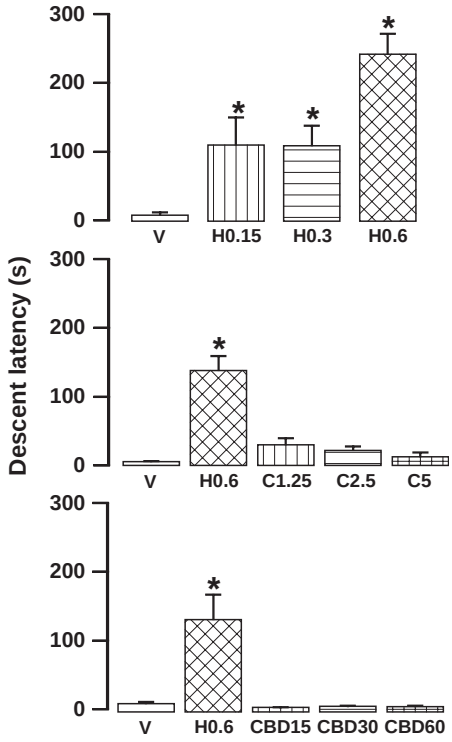

Fig. 7. Effects of haloperidol (H), clozapine (C) and cannabidiol (CBD) on the catalepsy test. Each bar represents the descent latency (mean ± S.E.M., $n=7$ per group). *$P<0.05$ compared to the vehicle group (ANOVA followed by Duncan).

4. Discussion

The present results show that cannabidiol inhibits the effects of psychotomimetic drugs in mice. Cannabidiol itself did not decreased locomotion, suggesting that its inhibitory effect on hyperlocomotion is not secondary to a motor impairment. The inhibition of D-amphetamine-induced hyperlocomotion is in accordance with previous results in which cannabidiol inhibited apomorphine-induced stereotyped behaviour, another dopamine-based model for the screening of antipsychotic drugs (Zuardi et al., 1991).

In addition to dopamine-related drugs, the use of NMDA-receptor antagonists in the screening for antipsychotic drugs has increased in the last years, reflecting the growing importance of the glutamatergic hypothesis of schizophrenia (Goof and Coyle, 2001; Moghadam, 2003). Therefore, the attenuation of ketamine effect by cannabidiol reinforces a possible antipsychotic profile of this compound.

In doses that inhibited the effect of psychotomimetic drugs, only haloperidol, but not cannabidiol or clozapine, induced catalepsy. The catalepsy test is a rodent model used for evaluation of extrapyramidal side effects-inducing potential (Hoffman and Donovan, 1995; Sanberg et al., 1988). A large difference between doses used to inhibit the

effects of psychotomimetic drugs and those needed to induce catalepsy is a characteristic profile of atypical antipsychotic drugs (Gerlach, 1991; Hoffman and Donovan, 1995; Casey, 1994). Therefore, the present results suggest that cannabidiol may share with clozapine an atypical antipsychotic profile. Moreover, haloperidol and clozapine, but not cannabidiol, induced a significant motor impairment in the arena, probably reflecting cataleptic and marked sedative effects, respectively, of these two drugs (Casey, 1994; Pretorius et al., 2001).

It is not entirely clear which brain structures are related to the effects of cannabidiol. The nucleus accumbens is a limbic structure proposed to mediate the effects of antipsychotic drugs on the positive symptoms of schizophrenia, while the dorsal striatum is involved on their motor side effects (for reviews, see Seeman, 2002; Strange, 2001). Employing Fos-protein immunoreactivity to detect functional neuronal activation (Morgan and Curran, 1991), Guimarães et al. (2004) showed that cannabidiol, like clozapine, activates the nucleus accumbens but not the dorsal striatum, while haloperidol activates both structures. The different Fos-expression pattern of clozapine and haloperidol are in accordance with other results in the literature (Robertson and Fibiger, 1992) and it is proposed to distinguish atypical from typical antipsychotic compounds in rats (Robertson et al., 1994). Therefore, the present behavioural data reinforces these findings, suggesting that cannabidiol possess an atypical antipsychotic profile.

While cannabidiol antagonized the effect of D-amphetamine in a dose-related fashion, it attenuated the effect of ketamine in a U-shaped profile. We have no explanation for these discrepancies, since its mechanisms of antipsychotic-like action are unknown. An endocannabinoid hypothesis of schizophrenia has been proposed (Emrich et al., 1997). However, it is not clear if a counteraction of the endocannabinoid system would properly explain the effects of cannabidiol, provided that this compound binds to the cannabinoid CB-1 receptor with very low affinity (Petitet et al., 1998; Thomas et al., 1998). Other possible mechanisms of action ascribed to cannabidiol involve agonism at the vanilloid-receptor and inhibition of the cellular uptake and enzymatic hydrolysis of anandamide (Bisogno et al., 2001).

In conclusion, cannabidiol was able to attenuate hyperlocomotion induced by D-amphetamine and ketamine. The results support the hypothesis that this compound may have antipsychotic-like effects.

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