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Pharmacology, Biochemistry and Behavior 81 (2005) 71–77

PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR

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Acute Δ^9-tetrahydrocannabinol exposure facilitates quinpirole-induced hyperlocomotion

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Received 22 October 2004; received in revised form 29 January 2005; accepted 24 February 2005
Available online 21 April 2005

Abstract

The endogenous cannabinoid system works as a feedback signal controlling dopamine-induced facilitation of motor behaviors. The present study explored whether a single acute stimulation of CB1 cannabinoid receptors with (-)-Δ^9-tetrahydrocannabinol (THC, 5 mg kg^{-1} i.p.) results in modifications in the sensitivity to the acute behavioral effects of the dopamine D_2/D_3 receptor agonist quinpirole (0.025, 0.25 and 1 mg kg^{-1}, s.c.) 24 h after THC administration. Cannabinoid pretreatment increased the sensitivity to quinpirole-induced hyperlocomotion 24 h after its administration. The data indicated that THC induced a desensitization of cannabinoid receptors, as revealed by a reduction in CB1 receptor-agonist induced GTP-γ-S incorporation in striatal membranes. These results might be relevant for understanding the effect of cannabinoid exposure in dopamine-related neuropsychiatric disorders.

Keywords: Behavior; Cannabinoids; CB1 receptors; Dopamine receptors; Locomotion; Quinpirole; THC; Sensitization

1. Introduction

The endogenous cannabinoid system is composed of the brain cannabinoid receptor–CB1–and several lipid transmitters, such as anandamide and 2-arachidoylglycerol (Piomelli, 2003; Herkenham et al., 1991; Mechoulam et al., 1995; Devane et al., 1992). The CB1 receptor is the target for cannabinoids, the psychoactive constituents of *Cannabis sativa*, whose preparations (hashish, marijuana) are still the most widely used illicit drugs (Gardner and Vorel, 1998). Several physiological functions are regulated by anandamide-induced activation of CB1 receptors (Piomelli, 2003). The endogenous cannabinoid system has been found to modulate dopamine signaling in mesotelencephalic circuits involved in motor control, emotional responses or cognitive processes (Gardner and Vorel, 1998; Ng Cheong Ton et al., 1988; Chen et al., 1990; Gueudet et al., 1995; Giuffrida et al., 1999; Rodriguez de Fonseca et al., 1998). As an example, in the dorsal striatum anandamide release stimulated by activation of dopamine D_2/D_3 receptors acts as a negative feedback signal that limits behavioral activation elicited by dopamine (Giuffrida et al., 1999). The interactions observed appear to be of a bidirectional nature because dopaminergic activity regulates the expression of the cannabinoid CB1 receptor gene (Mailleux and Vanderhaeghen, 1993) and cannabinoid CB1 receptor-mediated responses (Gardner and Vorel, 1998).

However, many gaps remain in our knowledge of the physiological role of dopamine–cannabinoid interactions. The analysis of these relationships may help to understand the contribution of the endogenous cannabinoid system to

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doi:10.1016/j.pbb.2005.02.004

the pathogenesis of dopamine-related neuropsychiatric disorders such as Parkinson's disease, Tourette's syndrome, drug addiction or psychosis (Piomelli et al., 2000; Piomelli, 2003). It is therefore important to clarify what effect the exogenous administration of CB1 cannabinoid receptor agonists may have on the physiological functions regulated by dopamine, as suggested by recent reports (Gardner and Vorel, 1998; Gueudet et al., 1995; Rodriguez de Fonseca et al., 1998; Mailleux and Vanderhaeghen, 1993; Piomelli et al., 2000; Sanudo-Pena et al., 1998; Sanudo-Pena and Walker, 1998). This is relevant not only to explain the effects of acute marijuana smoking but also from the viewpoint of the therapeutic utility of drugs acting on the endogenous cannabinoid system (Piomelli et al., 2000). Previous clinical research has shown that the acute and chronic consumption of cannabis is associated with an increased risk for the onset of psychotic syndromes (Andreasson et al., 1987) and with a decrease of the therapeutic effectiveness of dopamine antagonists (Knudsen and Vilmar, 1984). Furthermore, administration of a CB1 receptor agonist is able to attenuate the dyskinesias induced by dopaminergic agonists in Parkinson's disease (Ferrer et al., 2003).

We investigated whether acute stimulation with a cannabinoid receptor agonist, THC (given at a dose close to that taken by persons smoking hashish (Rosenkrantz et al., 1975), results in an adaptive modification of the behavioral responses to the dopamine D_2/D_3 receptor agonist quinpirole. We selected the hyperlocomotion induced by quinpirole because this response has been found to be a good index of the status of the modulatory capacity of the endogenous cannabinoid system on dopamine signaling (Giuffrida et al., 1999). The study was performed over short periods of time (24 h) to avoid the well-known neuroadaptive changes observed after prolonged treatment with this natural cannabinoid receptor agonist (Sim et al., 1996; Rodriguez de Fonseca et al., 1997). Moreover, recent reports indicate that a single exposure to THC is able to produce long-lasting changes in the physiological contribution of the endogenous cannabinoid system to plasticity events in the ventral striatum and hippocampus (Mato et al., 2004). The findings suggest that acute exposure to psychoactive cannabinoids may alter the sensitivity of basal ganglia neurons, facilitating the induction of abnormal responses in which endocannabinoid-regulated striatal transmitters (including dopamine) may have a relevant contribution.

2. Material and methods

2.1. Animals

Male Wistar rats (Panlab, Barcelona, Spain) weighing 350 ± 35 g at the start of the experiment were housed individually and maintained in a temperature- and light-controlled environment on a 12-h light/dark cycle (lights on: 08:00–20:00 hours) with free access to food and water. Animals were allowed at least a 2-week period for acclimatization to the animal room. They were subsequently handled daily for a week before the beginning of the experimental sessions. All the procedures were carried out according to the European Communities Directive of 24 November 1986 (86/609/EEC) regulating animal research. All the experiments took place between 10:00–13:00 hours.

2.2. Drugs

THC [(-)-Δ9-tetrahydrocannabinol, 5 mg kg^{-1}] was obtained through NIDA (Project 4886-OB). It was suspended in saline/propylenglycol/Tween 80 (90:5:5 v/v) as vehicle and made up to the appropriate concentrations to be administered i.p. in a volume of 1 ml/kg. Quinpirole hydrochloride (1 mg kg^{-1}) was provided by Research Biochemicals International as part of the Chemical Synthesis Program of the US National Institute of Mental Health, contract N01MH30003. It was dissolved in saline and injected s.c. in a final volume of 0.5 ml kg^{-1}.

2.3. Behavioral testing

Open field testing was conducted as previously described (Giuffrida et al., 1999). The apparatus consisted of an opaque open field ($100 \times 100 \times 40$ cm), the floor of which was marked with 20×20 cm squares. The open field was illuminated using a 500 W ceiling halogen light which was regulated to yield 350 lx at the center of the open field. Animals were habituated to the open field for 10 min 24 h before the test session. The rats were placed in the open field and the following behaviors were scored by trained observers, who were blind to experimental conditions: the total time spent in immobility, locomotor activity, defined as the total number of lines on the floor of the open field crossed (crossings), the number of rearings performed, the time spent grooming and the time spent sniffing. The duration of the test was 5 min and it was repeated 5, 30, 60 and 120 min after the injection of quinpirole. After testing each animal, the apparatus was cleaned with a weak acid solution (1% acetic acid) to prevent olfactory cues from affecting the behavior of subsequently tested rats.

2.4. Experimental designs

Animals were randomly divided into two groups. The first group received an i.p. injection of vehicle, whereas the second group received 5 mg kg^{-1} THC i.p. They were then returned to their home cages. Twenty-four hours after the injection the animals received a single subcutaneous injection of either vehicle (sterile saline) or quinpirole (0.025, 0.25 or 1 mg kg^{-1}). Five minutes after this administration the animals were placed in the open field and their behavior videotaped on a video-cassette recorder for 5 min. This procedure was repeated 5, 30, 60 and 120

min after the administration of quinpirole or vehicle. When the behavioral test was complete, those animals which had received the acute dose of vehicle were sacrificed by decapitation, their brains removed and the dorsal striatum dissected.

2.5. Membrane preparation

Tissues were homogenized in 50 mM Tris buffer, pH 8, containing 0.32 M sucrose. Homogenates were centrifuged first at 1000 $\times g$ (5 min), the pellet discarded and the supernatant centrifuged at 45,000 $\times g$ (30 min). The pellets obtained were solubilized at 0–4 °C in Tris buffer. Protein content in the membrane fraction was measured with the Bradford method. All tissue samples and membrane fractions were stored at −70 °C until used.

2.6. Agonist-stimulated [35S]-GTP-γ-S binding in membranes

Cannabinoid-stimulated [35S]-GTP-γ-S binding was determined as described previously (Sim et al., 1996) using 20 μg protein from membrane fractions. Membranes were incubated at 30 °C for 1 h in assay buffer (50 mM Tris–HCl, 3 mM MgCl2, 0.2 mM EGTA, 100 mM NaCl, 0.1 mg/ml BSA, pH 7.4), with 10 μM of WIN 55212-2 in the presence of 20 μM GDP and 0.05 nM [35S]-GTP-γ-S in 1 ml total volume. Basal binding was measured in the absence of agonist, and nonspecific binding was measured with 10 μM guanidyl imidodiphosphate. The reaction was terminated by rapid centrifugation (20,000 $\times g$) at 4 °C, followed by two washes with cold Tris buffer. Bound radioactivity was determined by liquid scintillation spectrophotometry, at 95% efficiency for [35S], after overnight extraction in 5 ml Ecolite scintillation fluid. Data are reported as the mean ± SE of percentage stimulation over basal levels.

2.7. Fatty acid amidohydrolase activity

We assayed membrane-bound FAAH activity using arachidonoyl-[1-3H]-ethanolamide as a substrate, and measuring metabolized [3H]anandamide (as [3H]ethanolamine) in the aqueous phase after chloroform extraction, as described (Rodriguez de Fonseca et al., 2001). Enzymatic assays were run under conditions that were linear in time and protein concentration.

2.8. Statistics

Data were assessed by multifactorial analysis of variance (ANOVA). Factors included were pretreatment (vehicle versus THC), treatment doses of quinpirole (0, 0.025, 0.23 and 1 mg kg^{-1}) and time interval (5, 30, 60 and 120 min after quinpirole injection). Following a significant F value, post hoc analysis (Newman–Keuls) was performed to assess specific group comparisons. Calculations were performed using the statistical package SPSS.

3. Results

Fig. 1A hows how pretreatment with THC resulted in increased sensitivity to the locomotor effects of quinpirole: a dose of 0.25 mg kg^{-1} resulted in a similar number of crossings to that induced by the 1 mg kg^{-1} dose of the dopamine D_2 agonists (pretreatment × treatment interaction, $F(1,98)=8.46$, $P<0.005$). However, animals pretreated with vehicle displayed a differential response to each dose of quinpirole (0.25 or 1 mg kg^{-1}). In THC-pretreated animals the administration of 1 mg kg^{-1} dose of quinpirole elicited a maximal behavioral response that precluded the observation of differences with vehicle-pretreated animals ($F(1,99)=0.59$, $P=0.45$, n.s.). Time analysis showed that animals pretreated with THC 24 h before quinpirole at 0.25

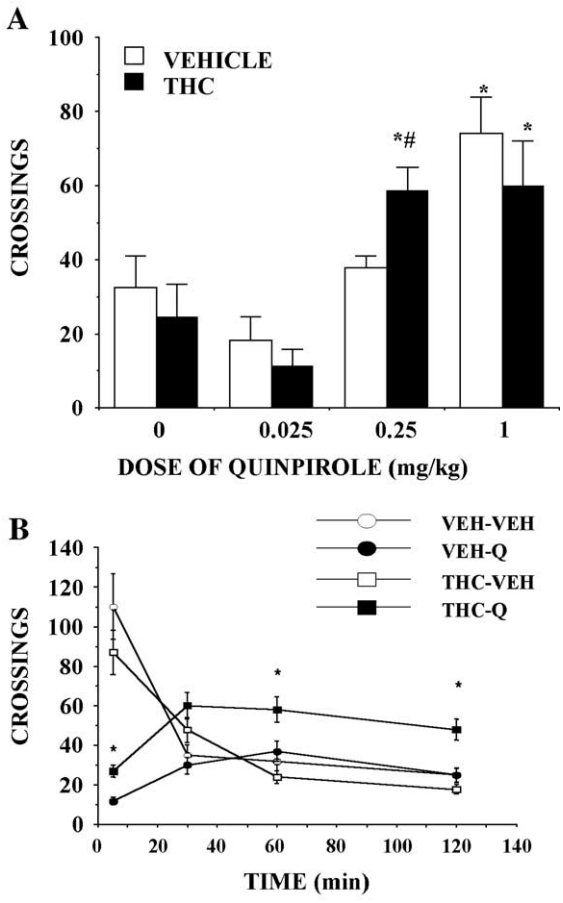

Fig. 1. (A) Effects of acute s.c. administration of the dopamine D_2/D_3 receptor agonist quinpirole on locomotor activity displayed 60 min after injection in animals pretreated with either vehicle or THC 24 h before the test. (B) Time course of the effects of quinpirole (0.25 mg kg^{-1} s.c.) on locomotion. Animals exposed to THC 24 h before quinpirole always displayed greater locomotor activity than those exposed to vehicle. Values are means ± SEM of 7–8 animals per group. (*) $P<0.05$, Newman–Keuls, versus saline-treated animals.

Table 1
Cumulative time spent in the center of the open field in animals receiving different doses of the dopamine D_2 receptor agonist quinpirole after pretreatment with either vehicle or THC 5 mg kg^{-1} 24 h before the test

	Dose of quinpirole (mg kg^{-1})			
	0	0.025	0.25	1
Vehicle	18.8 ± 6	46.1 ± 10.5*	11.6 ± 2.1	9.8 ± 2.8
THC 5 mg/kg	17.3 ± 4.9	25.8 ± 4.6	20.3 ± 5.6	5.6 ± 1.1*

Values are means ± SEM of 7–8 animals per group. *$P<0.05$, Newman–Keuls, versus saline-treated animals.

mg kg^{-1} always exhibited higher locomotor activity than those exposed to vehicle (Fig. 1B). Interestingly, see Table 1, analysis of the activity of the animals in the center of the open field, a known index of anxiolysis, indicates that the lower dose of quinpirole (0.025 mg kg^{-1}) results in increased exploration of the center area. In animals exposed to THC 24 h before quinpirole, this sedative effect disappears, whereas a significative decrease in exploration was observed with the highest dose of quinpirole tested (1 mg kg^{-1}).

A similar pattern was observed when time spent sniffing was analyzed (Fig. 2A, B): a clear increase in time spent sniffing was observed in animals pretreated with THC and receiving quinpirole 0.25 mg kg^{-1} ($F(3,99)=5.5$, $P<0.01$). Although pretreatment with THC did not affect the overall immobility induced by any of the three doses of quinpirole (data not shown), time analysis revealed that the 0.025 mg kg^{-1}-induced immobility was increased in animals exposed to THC, whereas this effect was abolished in animals receiving the 0.25 mg kg^{-1} dose (Fig. 3A), that resulted in lower

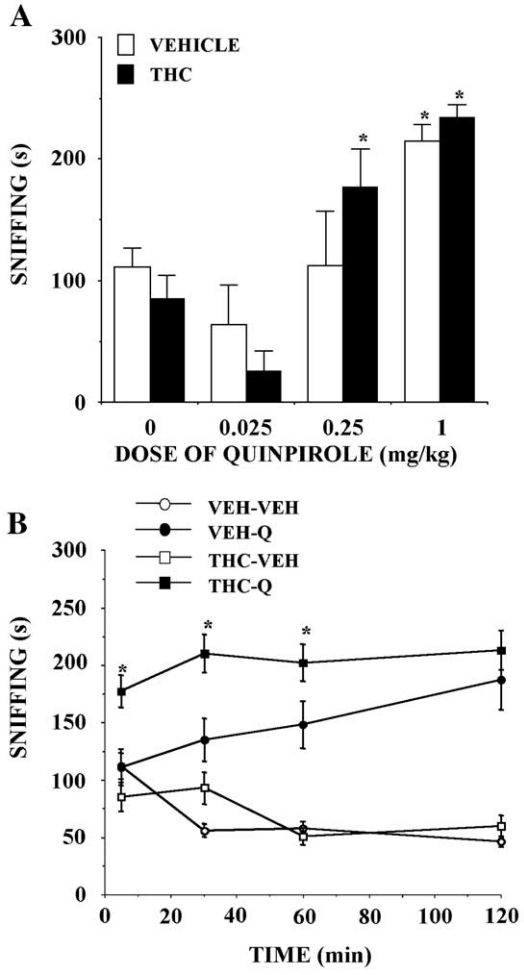

Fig. 2. (A) Effects of acute s.c. administration of the dopamine D_2/D_3 receptor agonist quinpirole on the time spent sniffing displayed 60 min after injection in animals pretreated with either vehicle or THC 24 h before the test. (B) Time course of the effects of quinpirole (0.25 mg kg^{-1} s.c.) on the time spent sniffing. Animals exposed to THC 24 h before quinpirole displayed greater sniffing activity than those exposed to vehicle. Values are means ± SEM of 7–8 animals per group. (*) $P<0.05$, Newman–Keuls, versus saline-treated animals.

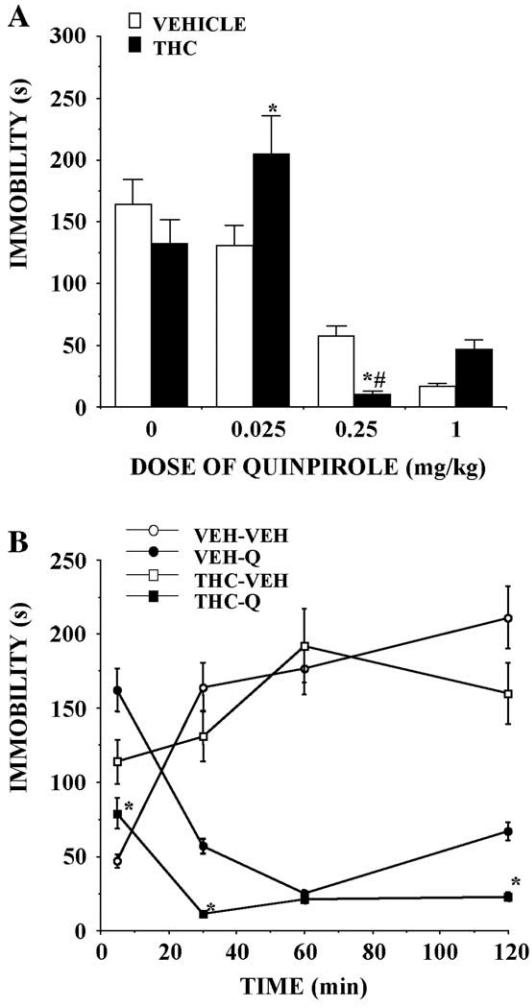

Fig. 3. (A) Effects of acute s.c. administration of the dopamine D_2/D_3 receptor agonist quinpirole on the time in immobility displayed 30 min after injection in animals pretreated with either vehicle or THC 24 h before the test. (B) Time course of the effects of quinpirole (0.25 mg kg^{-1} s.c.) on the time spent in immobility. Values are means ± SEM of 7–8 animals per group. (*) $P<0.05$, Newman–Keuls, versus saline-treated animals.

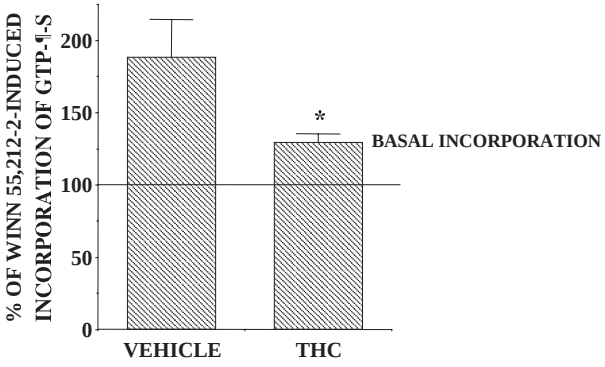

Fig. 4. Effects of acute i.p. administration of THC 24 h before sacrifice on cannabinoid CB1 receptor agonist WIN 55,212-2 induced incorporation of [35S]-GTP-γ-S to striatal membranes. Values are means ± SEM of 7–8 animals per group. (*) $P<0.05$, Newman–Keuls, versus saline-treated animals.

immobility scores at 5 and 30 min after quinpirole injection (Fig. 3B; $F(3,104)=5.7$, $P<0.01$). This finding suggests that global motor activity induced by the dopamine D_2/D_3 receptor agonist quinpirole was exacerbated as results of pre-exposure to THC. Neither time spent grooming nor rearing activity were differentially affected by quinpirole in vehicle or in THC-pretreated animals (data not shown).

Since the findings suggest that acute cannabinoid exposure results in an apparent loss of efficacy of the inhibitory endocannabinoid feedback response to dopamine D_2/D_3 receptor stimulation (Giuffrida et al., 1999), we investigated whether THC administration might be inducing changes in cannabinoid receptor coupling by using cannabinoid-stimulated [35S]-GTP-γ-S incorporation to striatal membranes. The data indicated that THC exposure results in a decrease in coupling efficacy of more than 50%, suggesting receptor desensitization (Fig. 3). Analysis of FAAH activity indicated that THC exposure also produced a 60% decrease in the endocannabinoid degradatory activity of striatal membranes (Figs. 4 and 5).

4. Discussion

The present results further support the previously proposed role for the endogenous cannabinoid system as a feed-back signal controlling dopamine D_2/D_3 receptor-mediated neurobiological responses, including locomotion (Giuffrida et al., 1999), rotational behavior (Sanudo-Pena et al., 1998; Sanudo-Pena and Walker, 1998), alleviation of akinesia in the reserpine-treated rat model of Parkinson's disease (Maneuf et al., 1997) or the control of prolactin release (Rodriguez de Fonseca et al., 1995). The shift to the left of the quinpirole dose–response curve for locomotion resembles that observed when animals pretreated with the CB1 cannabinoid receptor antagonist SR141716A were injected with this dopamine D_2/D_3 receptor agonist (Giuffrida et al., 1999). Moreover, it is also similar to the behavioral sensitization to the locomotor effects of amphetamine found 24 h after the end of subchronic (14 days) treatment with THC (6.4 mg kg^{-1} i.p.) (Gorriti et al., 1999). This quick sensitization indicates the establishment of rapid changes in dopamine D_2/D_3 receptor-mediated signaling after acute THC administration, reflected in the quinpirole-induced hyperlocomotion. One explanation for this enhanced response to quinpirole might lie in the induction by THC of a rapid desensitization of the CB1 receptors in the dorsal striatum. This desensitization would prevent the negative feedback signaling carried out by quinpirole-activated anandamide release, which limits dopamine-mediated hyperactivity in normal conditions (Giuffrida et al., 1999). Although THC has been reported to be a partial agonist, it can induce a profound desensitization of the CB1 receptor (Rodriguez de Fonseca et al., 1997) even after short-term (7 days) treatment. In vitro receptor coupling testing using CB1 agonists confirms this hypothesis (Fig. 3). The fact that CB1 receptor desensitization is associated with a marked decrease in FAAH activity suggests the induction of a physiological counter-regulatory response aimed at increasing anandamide bioavailability to overcome the deficit in endocannabinoid signaling derived from CB1 receptor desensitization. Alternatively, it has been reported that the CB1 receptor is able to shift its coupling from the Gi to the Gs pathway depending on the concurrent stimulation of the D_2/D_3 receptor in striatal neurons (Glass and Felder, 1997). The equilibrium between the positive and the negative coupling of the CB1 receptor to cAMP production in striatal neurons may be altered after acute THC treatment, leading to decreased effectiveness of the CB1 receptor in the modulation of dopamine signaling.

The abolition of quinpirole-induced anxiolytic/sedative effect (see Table 1) after acute THC exposure further

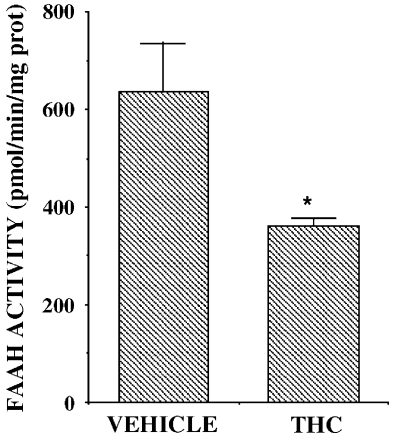

Fig. 5. Effects of acute i.p. administration of THC 24 h before sacrifice on fatty acid amidohydrolase activity in striatal membranes. Values are means ± SEM of 7–8 animals per group. (*) $P<0.05$, Newman–Keuls, versus saline-treated animals.

support the notion of a discoupling of the negative feedback signaling carried out by quinpirole-activated anandamide release. Cannabinoid receptor agonists potentiate dopamine D_2/D_3 receptor agonist-induced sedation (Meschler et al., 2000). In this context, the observed desensitization of cannabinoid CB1 receptor in THC-exposed animals is consistent with the shift to decreased exploratory behavior after acute quinpirole exposure.

The results of this study may help understand two well-described clinical effects of acute cannabinoid exposure. One is the association of acute cannabis exposure and the onset of a psychotic episode (Andreasson et al., 1987), and the other is the decreased efficacy of neuroleptics found in schizophrenics smoking marijuana. If THC is able to induce a rapid desensitization of the CB1 receptor-mediated brake to dopamine signaling, the acute exposure to cannabis preparations may result in enhanced sensitivity of dopamine D_2 receptors to dopamine. Ultimately, this situation may result in either the manifestation of positive psychotic symptoms or in an abatement of the antipsychotic efficacy of neuroleptics (Knudsen and Vilmar, 1984), which act as dopamine D_2 receptor antagonists. Acute exposure to CB1 agonists may then be considered a factor promoting psychotic episodes, as suggested by the extensive study of Andreasson et al. (1987). In support of a role for the endogenous cannabinoid system in the pathogenesis of psychosis, two recent reports have shown elevated anandamide levels in the CSF of schizophrenic patients (Giuffrida et al., 2004; Leweke et al., 1999). This finding may reflect the existence of an increased synthesis and release of endogenous cannabinoids as a neuroadaptive response aimed at counteracting either a hyperdopaminergic state or the presence of desensitized CB1 receptors in these patients. Nevertheless, this hypothesis needs to be confirmed in future studies since the contribution of cannabis consumption to the incidence of schizophrenia has been questioned in recent epidemiological studies (Arseneault et al., 2004) and the association of CB1 receptor gene polymorphisms and schizophrenia has not been replicated in all the populations studied (Tsai et al., 2000).

5. Conclusion

Acute exposure to a single moderate dose of (-)-Δ^9-tetrahydrocannabinol, the main psychoactive constituent of marijuana, is able to induce a behavioral sensitization to the locomotor effects of dopamine D_2 receptor agonists in rats. The enhanced quinpirole-induced hyperlocomotion found 24 h after exogenous THC administration suggests the existence of rapid adaptive changes in endocannabinoid/dopamine signaling mechanisms, compensating for the excess THC-induced activation of CB1 receptors present in these circuits. This finding may help to understand the psychopathology associated with acute cannabis exposure and may limit the potential usefulness of direct cannabinoid receptor agonists as therapeutic agents for the treatment of neuropsychiatric disorders.

Acknowledgments

This work was supported by the Fondo de Investigación Sanitaria (REDES CIEN C03/06, RTA G03/05 and G03/184) and Delegación del Gobierno para el Plan Nacional Sobre Drogas. The authors are indebted to NIDA for providing THC. They thank Dr. Francisco Barceló for critical reading of the manuscript.

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