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

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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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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