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Activational role of cannabinoids on movement

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Abstract

Cannabinoid's major effect on movement is hypoactivity. Nevertheless, a biphasic excitatory/inhibitory effect of cannabinoids on movement has been repeatedly acknowledged. However, the literature is lacking a detailed description of such an effect. In this study, we performed a dose–response study of the effects of Δ^9-tetrahydrocannabinol on movement. Immediately after the administration of vehicle or a dose of Δ^9-tetrahydrocannabinol (0.2, 0.5, 1, 1.5, 2, 2.5, 3, 4, or 5 mg/kg), the animal was placed in an activity monitor and observed for 1 h. Several parameters were recorded. The horizontal and vertical activities were measured as the number of photobeams broken between the photocells on the walls of an activity monitor. The number of wet dog shakes, scratches with hindpaw, mouth movements, forepaw flutters were also recorded, as was the amount of time in minutes that each subject spent grooming. The number of fecal boluses was recorded as an index of autonomic activity. Each animal was subsequently tested for catalepsy in the bar test. A triphasic effect was observed: low doses of the cannabinoid receptor agonist Δ^9-tetrahydrocannabinol (0.2 mg/kg) decreased locomotor activity while higher doses (1–2 mg/kg) dose-dependently stimulated movement until catalepsy emerged (2.5 mg/kg) accompanied by decreases in activity.

Keywords: Δ^9-Tetrahydrocannabinol; Activity; Cannabinoid; Biphasic effect; Movement

1. Introduction

Cannabinoids are a family of compounds which receive their name after the principle active constituent of the marihuana plant (*Cannabis sativa*). The active principle in this plant was identified as Δ^9-tetrahydrocannabinol (Mechoulam et al., 1970). The cloning and subsequent mapping of a G-protein-coupled (Matsuda et al., 1990; Munro et al., 1993) receptor for cannabinoids and the high levels of these receptors expressed in the nervous system (Herkenham et al., 1991a,b; Mailleux and Vanderhaegen, 1992; Tsou et al., 1998a) led to an explosion in basic research that has attempted to integrate this putative novel neurotransmitter system in the current knowledge of central nervous system physiology. These efforts uncovered the cellular mechanisms of action of cannabinoids (Mackie and Hille, 1992; Deadwyler et al., 1993; Mackie et al., 1995; Howlett, 1995) and started to unveil the endogenous cannabinergic system (Devane and Axelrod, 1994; Devane et al., 1992; Piomelli et al., 1998; Tsou et al., 1998b). Two cannabinoid receptors have been identified: CB_1 (with its isoform CB_{1a} resulting from alternative splicing) and CB_2. The cannabinoid CB_1 receptor is mainly associated with the nervous system, although is also expressed in other organs (Rinaldi-Carmona et al., 1994; Facci et al., 1995; Shire et al., 1995; Pertwee and Fernando, 1996, Pertwee et al., 1996a,b; Tsou et al., 1998a). The CB_2 receptor is mainly associated with the immune system and is not expressed in neurons (Facci et al., 1995; Galiegue et al., 1995; Schatz et al., 1997). Currently, numerous agonists with different affinities for the receptor subtypes as well as specific antagonists for each receptor subtype are available (Martin et al., 1994; Rinaldi-Carmona et al., 1994,1998; Howlett, 1995).

Cannabinoids are classically known to induce a myriad of physiological actions among which are potent effects on movement. The neuronal localization of the receptor is consistent with these well-known motor effects of

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cannabinergic compounds. The brain has a distinct pattern of expression of cannabinoid CB_1 receptors that are highly concentrated in areas controlling motor behavior such as the basal ganglia and cerebellum. In contrast, the levels of cannabinoid CB_1 receptors are low in brainstem which may explain the low toxicity of cannabinoid receptor agonists, an attractive quality for putative therapeutic uses (Herkenham et al., 1991a,b; Mailleux and Vanderhaegen, 1992; Tsou et al., 1998a). Numerous recent reports suggest that the basal ganglia is involved in the motor effects of cannabinoids (Pertwee and Wickens, 1991; Romero et al., 1995, 1996; Garcia et al., 1996; Miller et al., 1998; Sañudo-Peña and Walker,1998a,b, 1999; Sañudo-Peña et al., 1996, 1998a,b; Corchero et al., 1999; Ferrari et al., 1999). Motor effects induced by cannabinoids seem to be mediated by the cannabinoid CB_1 receptor (Rinaldi-Carmona et al., 1994; Compton et al., 1996). In general, activation of cannabinoid CB_1 receptors by cannabinoid receptor agonists inhibit neurotransmission (Mackie and Hille, 1992; Mackie et al., 1995; Deadwyler et al., 1993; Howlett, 1995).

Cannabinoids major effect in movement is hypoactivity and catalepsy (Dewey, 1986; Hollister, 1986; Romero et al., 1996; Ferrari et al., 1999). Nevertheless, cannabinoid receptor agonists also induce biphasic effects on movement that are time- and dose-dependent. An increase in motor activity has been associated with relatively low doses or immediately after administration of higher doses of cannabinoid receptor agonists. Later after administration, high doses of cannabinoid receptor agonists inhibit movement and produce catalepsy (Carlini et al., 1970; Davis et al., 1972; Dewey, 1986; Hollister, 1986). A biphasic effect on movement has also been reported for the endogenous ligand of the cannabinoid receptor anandamide (Sulcova et al., 1998). This biphasic effect of cannabinoids on movement occurs in parallel with other parameters. Different doses of cannabinoid receptor agonists induce opposite effects on brain metabolism. Very low doses increased cerebral metabolism studied by 2-deoxyglucose uptake, while higher doses of cannabinoid receptor agonists decreased cerebral metabolism (Margulies and Hammer, 1991). Studies conducted with the cannabinoid CB_1 antagonist *N*-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-3-pyrazole-carboxamide (SR141716A) failed to show motor effects but an increase in arouse/awake states in the electroencephalogram was observed (Santucci et al., 1996). However, the pharmacology of this cannabinoid receptor antagonist is complicated by potential inverse agonist actions (Walker et al., 1999). A more recent study of knockout mice for the cannabinoid CB_1 receptor reported a decrease in the activity of these animals suggesting an activational role of CB_1 receptors on movement (Zimmer et al., 1999). However, another study with knockout animals for the CB_1 receptors failed to observe any basal effects on motor behavior (Ledent et al., 1999).

Although the biphasic excitatory/inhibitory effect of cannabinoids on movement has been repeatedly acknowledged, the literature is lacking a detailed description of such an effect. Many references are anecdotal (see Hollister, 1986; Howlett, 1995 for review). The single study showing a biphasic dose-dependent effect of Δ^9-tetrahydrocannabinol on locomotion in rats lacks detailed time and dose resolution (Davis et al., 1972). The aim of this study was to study the dose boundaries at which the natural cannabinoid agonist Δ^9-tetrahydrocannabinol induces opposite effects on movement.

2. Materials and methods

Male Sprague–Dawley rats (220–320 g, Charles River, $n = 65$) served as subjects. They were housed in groups in a temperature-regulated (22–23°C) room with food and water freely available. Artificial lighting was provided from 07:00 to 19:00 h.

On the test day, animals were weighed previous to intraperitoneal injection of the vehicle (propylene glycol, Sigma, St. Louis, MI, USA) or a dose of 0.2, 0.5, 1, 1.5, 2, 2.5, 3, 4, or 5 mg/kg of the cannabinoid agonist Δ^9-tetrahydrocannabinol (generously provided by the National Institute on Drug Abuse, Rockville, MD, USA). Immediately after the injection, each animal was placed in an activity

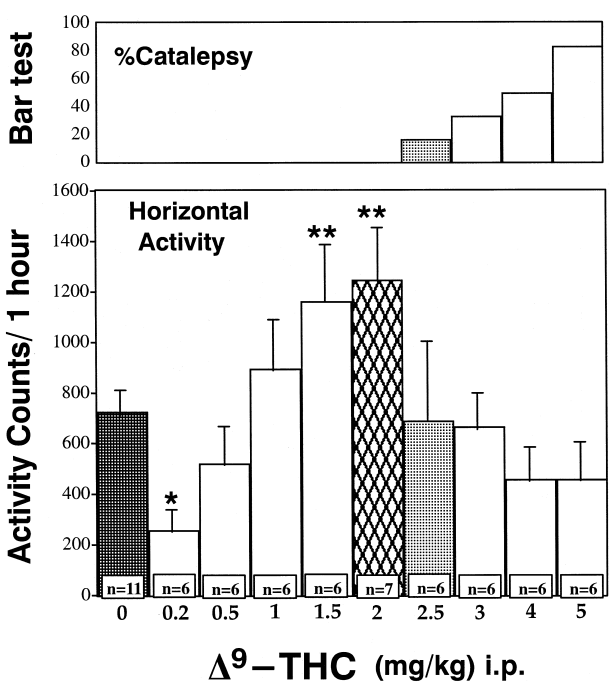

Fig. 1. Dose-curve of systemic administration of Δ^9-tetrahydrocannabinol effects on horizontal activity in rats. There is an increase in activity with relatively low doses (1–2 mg/kg) of the cannabinoid receptor agonist. (* significantly different from the rest of the groups except the ones receiving 4 or 5 mg/kg of Δ^9-tetrahydrocannabinol, $p < 0.05$; ** significantly different from the rest of the groups except the one receiving 1 mg/kg of Δ^9-tetrahydrocannabinol, $p < 0.05$).

chamber and observed for 1 h (Digiscan activity monitor, Columbus Instruments, Columbus, OH).

The horizontal and vertical activity was measured by the activity monitor as the number of photobeams broken between the photocells on the walls of the apparatus. The number of wet dog shakes, scratches with hindpaw, mouth movements, forepaw flutters were also recorded as was the amount of time in minutes that each subject spent grooming. The number of fecal boluses left in the activity monitor was recorded as an index of autonomic activity.

After 60 min in the activity cage, each animal was tested for catalepsy in the bar test. Briefly, each animal was placed over a 10-cm high bar and the descent latency was recorded. Only descent latencies of 1 min and over were recorded as catalepsy. The percentage of animals within each dose group that exhibit catalepsy is expressed as percent catalepsy in Fig. 1 (upper part).

A one-way analysis of variance (ANOVA) was employed to study differences between the nine drug doses and vehicle animal in activity parameters. Post-hoc comparisons were made using the Fisher's least significant difference test. The data on catalepsy was compared using a non-parametric ANOVA followed by a Mann–Whitney test.

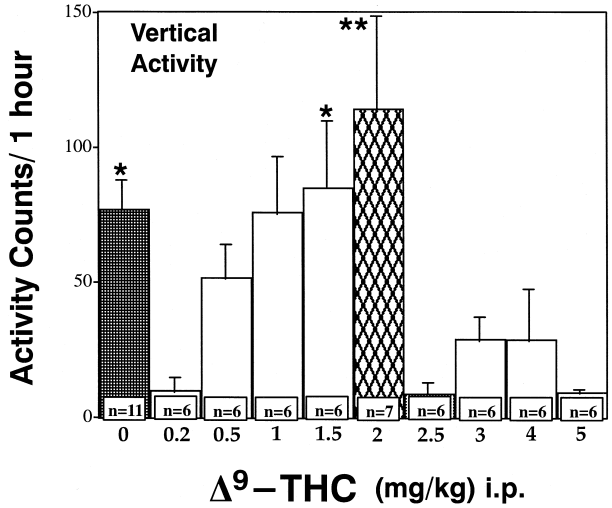

Fig. 3. Dose-curve of systemic administration of Δ^9-tetrahydrocannabinol effects on vertical activity in rats. There is an increase in activity with relatively low doses (1.5–2 mg/kg) of the cannabinoid receptor agonist. (* significantly different from the rest of the groups except the ones receiving 1 or 0.5 mg/kg of Δ^9-tetrahydrocannabinol, $p < 0.05$; ** significantly different from the rest of the groups except the one receiving 1 mg/kg of Δ^9-tetrahydrocannabinol, $p < 0.05$).

3. Results

An overall ANOVA revealed that the various doses of Δ^9-tetrahydrocannabinol administered produced markedly different effects on locomotor activity as showed by the horizontal activity ratings ($F(9,55) = 4.930$, $p \leq 0.0001$). Rats injected with vehicle showed significantly higher levels of activity than animals treated with 0.2 mg/kg of Δ^9-tetrahydrocannabinol but lower levels of activity than those exhibited by animals injected with either 1.5 or 2 mg/kg of Δ^9-tetrahydrocannabinol ($p \leq 0.01$, Fig. 1, lower part). On the contrary, the groups injected with the dose of 1.5 or 2 mg/kg of Δ^9-tetrahydrocannabinol showed higher levels of locomotion than the rest of the groups except for those injected with 1 mg/kg of Δ^9-tetrahydrocannabinol ($p \leq 0.05$, Fig. 1, lower part). Fig. 2 shows a 60-min time course of systemic administration of vehicle, the dose of Δ^9-tetrahydrocannabinol that induced the highest inhibition of movement (0.2 mg/kg), and the dose of Δ^9-tetrahydrocannabinol which induced the highest activation of movement (2 mg/kg).

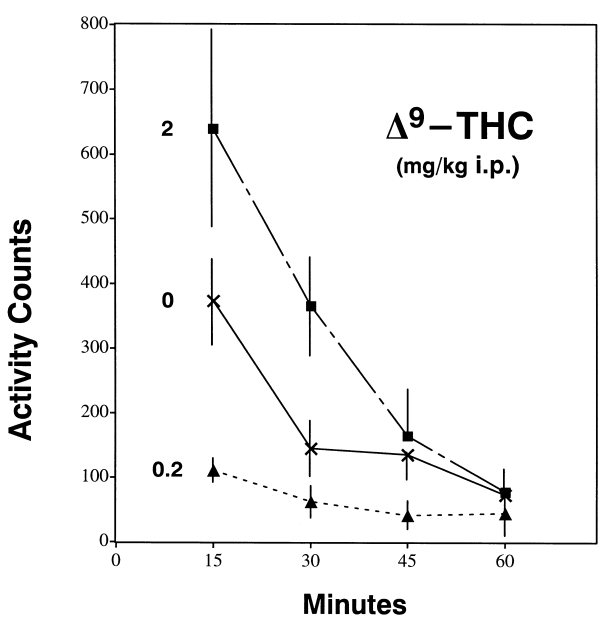

Fig. 2. Time-curve of systemic administration of vehicle, the dose of Δ^9-tetrahydrocannabinol which induced the highest inhibition of movement (0.2 mg/kg), and the dose of Δ^9-tetrahydrocannabinol which induced the highest activation of movement (2 mg/kg).

The vertical activity counts parallel the horizontal activity counts described above ($F(9,55) = 4.277$, $p \leq 0.0003$, Fig. 3). The control group and those that received 1.5 or 2 mg/kg of Δ^9-tetrahydrocannabinol showed higher levels of activity than the rest of the groups except for those receiving 0.5 and 1 mg/kg of Δ^9-tetrahydrocannabinol. Only the group receiving 2 mg/kg showed higher activity than that receiving 0.5 mg/kg of Δ^9-tetrahydrocannabinol ($p \leq 0.05$).

The 2.5-mg/kg dose of Δ^9-tetrahydrocannabinol is when catalepsy is first observed in 16.6% of the animals and dose-dependently increases its incidence to 33.3% with 3 mg/kg, 50% with 4 mg/kg, and to 83.3% with 5 mg/kg of Δ^9-tetrahydrocannabinol (Fig. 1, upper part). The various doses of Δ^9-tetrahydrocannabinol administered

produced different percentage of cataleptic animals ($H = 33.1$, $p \leq 0.0001$). The group that received 5 mg/kg of Δ^9-tetrahydrocannabinol showed significantly higher percentage of cataleptic animals than the groups receiving 0.2–2 mg/kg of Δ^9-tetrahydrocannabinol and the group receiving vehicle ($p \leq 0.003$).

No dose-dependent or major effects were observed in mouth movements ($F(9,55) = 2.130$, $p \leq 0.04$) or grooming ($F(9,55) = 2.033$, $p \leq 0.05$) where only the higher doses of Δ^9-tetrahydrocannabinol (4 and 5 mg/kg) produced lower levels in both parameters than controls ($p \leq 0.03$). No effects were observed in wet dog shakes ($F(9,55) = 1.109$, n.s.), scratches with hindpaw ($F(9,55) = 1.110$, n.s.), and forepaw flutters ($F(9,55) = 0.833$, n.s.), the last three parameters being almost non-existent in all groups equally. No differences in autonomic function between the groups were observed either ($F(9,55) = 1.768$, n.s.).

4. Discussion

The present work showed that very low doses of the cannabinoid receptor agonist Δ^9-tetrahydrocannabinol decrease locomotor activity while higher doses dose-dependently stimulate movement until catalepsy emerges accompanied by decreases in activity.

These findings suggest that cannabinoids seem to have mainly an activational role in movement. The initial inhibition of movement observed with the very low dose of the compound may result from an autoreceptor mechanism. Autoreceptors normally show a much higher affinity for ligands and act to inhibit the endogenous system (Mao et al., 1996; Disko et al., 1998). In accordance with this, the same low dose (0.2 mg/kg) of Δ^9-tetrahydrocannabinol increased 2-deoxyglucose uptake in a general manner all over the brain (Margulies and Hammer, 1991). Since cerebral metabolism as measured by 2-deoxyglucose uptake reflects activation of terminals (as opposite to cell bodies; Schwartz et al., 1979; Kadakaro et al., 1987) and cannabinoid receptor agonists inhibit neurotransmitter release which is the opposite effect observed in the 2-deoxyglucose study, it supports an autoreceptor effect at this dose.

The dose-dependency of the increase in movement by higher doses confirms the stimulatory role of the cannabinoid receptor agonist in movement which is interrupted by the appearance of catalepsy. The dose that induced the higher levels of activity in this study reduced 2-deoxyglucose uptake in a general manner (Margulies and Hammer, 1991), this time indicating the inhibitory action of cannabinoid receptor agonists on neurotransmitter release. The doses inducing hyperactivity coincide with doses reported effective in reducing the threshold for brain stimulation (Gardner et al., 1988) and do not produce aversion in the place preference paradigm (Sañudo-Peña et al., 1997). When administered into the brain, cannabinoids induce movement when microinjected along the direct pathway of the basal ganglia (striatonigral) (Sañudo-Peña and Walker, 1998a, 1999; Sañudo-Peña et al., 1996, 1998a,b) and have the opposite effect along the indirect pathway (pallidosubthalamic) (Miller et al., 1998; Sañudo-Peña and Walker, 1998b; Sañudo-Peña et al., 1998a,b,1999). Furthermore, cannabinoids act in opposite systems in the basal ganglia, blocking glutamate or GABA transmission within the same nucleus (Miller and Walker, 1995, 1996; Sañudo-Peña and Walker, 1997, 1998a,b, 1999; Sañudo-Peña et al., 1996). It appears that the cannabinergic system plays a major regulatory role in the basal ganglia, but the opposite effects complicate any attempt to predict the total systemic actions of a cannabinoid receptor agonist. A recent study by our group found a cannabinergic link between feeding and the production of movement associated with the procurement of food (Sañudo-Peña et al., 2000). A cannabinoid agonist induced motor activation in this system similar to the highest levels of movement observed with dopaminergic receptor agonists in the basal ganglia. Accordingly, a decrease in locomotor activity was observed in a study of knockout animals for the neural cannabinoid receptor that supports the activational role of the endogenous system on movement (Zimmer et al., 1999). The observed hypoactivity maybe mediated by changes detected in the basal ganglia (Steiner et al., 1999).

Catalepsy is an active phenomenon which may or may not be accompanied by inhibition of movement (Klemm, 1989). The dissociation between activity and catalepsy was reported for the noradrenergic (Sukul et al., 1988) and dopaminergic systems (Sañudo-Peña and Walker, 1998a). We recently reported the induction of catalepsy by unilateral administration of a dopamine D_1 receptor agonist in the globus pallidus accompanied by high levels of turning behavior. In that experiment, the animals exhibited a profound decrease in muscle tone that expressed itself as catalepsy but did not interfere with locomotion. The catalepsy observed with Δ^9-tetrahydrocannabinol in the present study is characterized by enhanced muscle tone and rigidity. It resembles the rigidity observed after lesions of the dopaminergic innervation of the basal ganglia (Sañudo-Peña et al., 1998b). Such a lesion is characterized by a diminished striatal inhibitory tone to basal ganglia output nuclei and is associated with decreases in locomotion (Albin et al., 1989). Similarly, catatonia characterized by muscular rigidity and accompanied by intense fear is reported after benzodiazepine withdrawal in humans (Rosebush and Mazurek, 1995). Again, inferring a lack of GABAergic inhibition as the cause of the rigidity and immobility accompanied by anxiety and fear. Animals rendered cataleptic by cannabinoid agonist express distress manifested by vocalizations and aggressiveness towards handling. Cataleptic doses of cannabinoids have also proven to induce aversion (Sañudo-Peña et al., 1997). All these data point to a diminished GABAergic function in

the cataleptic state induced by cannabinoids. A similar state of anxiety and fear to that induced in humans by a diminished GABAergic function might be associated and responsible for the drastic drop in locomotor measures observed in our study at the first onset of catalepsy.

Cannabinoids inhibit GABA release from striatal terminals at the output nuclei of the basal ganglia (Miller and Walker, 1995, 1996; Sañudo-Peña et al., 1996). However, as mentioned above, they also inhibit glutamate release from subthalamic terminals at the output nuclei of the basal ganglia, and this action would resemble an effect opposite (GABA-like) to the former one (Sañudo-Peña et al., 1997). We propose that the increase in movement could be related to the inhibitory effect of cannabinoids on glutamatergic transmission. In the basal ganglia the subthalamic input is tonically active and thus would be the primary determinant of the action of a cannabinoid receptor agonist. The secondary effect of cannabinoid could be on the phasically active striatal input. As the dose of the cannabinoid is increased the secondary action of cannabinoids blocking the GABAergic transmission (striatal) in the basal ganglia, would produce an opposite inhibitory effect on movement. The simultaneous increase and decrease in motor output to movement may result as rigidity and catalepsy. Further studies using different cannabinoid receptor agonists and antagonists should be conducted to test these possibilities.

In summary, this study describes the systemic actions of Δ^9-tetrahydrocannabinol on motor behavior. With an autoreceptor like effect the cannabinoid receptor agonist decreased movement at very low doses followed by a dose-dependent stimulating effect on activity that is interrupted by the appearance of rigidity and catalepsy. We propose that cannabinoids have an activational role in movement that is overridden at higher doses by the major modulatory actions of these compounds counteracting opposite systems.

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