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Effects of cannabinoid receptor stimulation and blockade on catalepsy produced by dopamine receptor antagonists

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Abstract

The ability of cannabinoid receptor stimulation or blockade to alter catalepsy produced by dopamine D_1 and D_2 receptor antagonists was studied in rats. The cannabinoid receptor antagonist SR 141716A (*N*-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamidehydrochloride) (0.5 and 2.5 mg/kg) reduced catalepsy elicited by the cannabinoid receptor agonist CP 55,940 (1α,2-(*R*)-5-(1,1-dimethylheptyl)-2-[5-hydroxy-2-(3-hydroxypropyl)cyclohexyl-phenol) (0.5 mg/kg). However, SR 141716A (0.5 and 2.5 mg/kg) did not decrease catalepsy produced by the dopamine D_1 receptor antagonist SCH 23390 (*R*-(+)-7chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1-*H*-3-benzazepine) (0.5 mg/kg) or the dopamine D_2 receptor antagonist raclopride (*S*(−)-3,5-dichloro-*N*-(1-ethyl-2-pyrrolidinyl)-methyl-6-methoxysalicylamide) (2.5 mg/kg), suggesting that, under these conditions, endogenous cannabinoid ligands do not modulate the cataleptic effects of dopamine D_1 or D_2 receptor antagonists. In contrast, CP 55,940 (0.025 and 0.1 mg/kg), at doses which do not produce catalepsy when administered alone, enhanced catalepsy produced by SCH 23390 and raclopride. These results suggest that stimulation, but not blockade, of brain cannabinoid receptors modifies catalepsy behavior produced by selective dopamine D_1 and D_2 receptor blockade.

Keywords: Marijuana; SR 141716A; CP 55,940; Basal ganglion; Antipsychotic

1. Introduction

Compounds which stimulate brain cannabinoid receptors elicit catalepsy and reduce locomotor activity in rodents. The alterations in motor behavior may be mediated by the basal ganglia since these brain areas have important functions in regulating the motor system and also contain a high density of cannabinoid receptors. Indeed, cannabinoid receptor binding is dense in many nuclei of the basal ganglia including the striatum, entopeduncular nucleus, substantia nigra pars reticulata, and globus pallidus (Herkenham et al., 1990, 1991; Thomas et al., 1992). Cannabinoid receptors are synthesized by striatal projection neurons and are localized on cell bodies and terminals of these neurons (Herkenham et al., 1991; Mailleux and Vanderhaeghen, 1992). The naturally occurring cannabinoid receptor agonist, Δ^9-tetrahydrocannabinol, causes catalepsy when injected directly into the striatum (Gough and Olley, 1978). Hence, the striatum may be a neural substrate underlying the cataleptic effect of systemically administered cannabinoid receptor agonists.

Dopamine within the basal ganglia plays an important role in regulating normal motor function since degeneration of dopaminergic nigrostriatal neurons results in the motor abnormalities of Parkinson's disease. Interactions between cannabinoids and dopamine have been demonstrated. For example, Δ^9-tetrahydrocannabinol potentiates catalepsy induced by depletion of brain amines by reserpine or blockade of dopamine

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receptors by nonselective dopamine antagonists (Moss et al., 1981, 1984). It is unclear whether cannabinoid receptor agonists potentiate catalepsy produced by selective dopamine D_1 and D_2 receptor antagonists. Dopamine D_1 and D_2 receptors may be differentially segregated on striatonigral and striatopallidal neurons, respectively (Gerfen et al., 1990) and antagonists of D_1 and D_2 receptors may produce catalepsy by selective effects on the striatonigral and striatopallidal pathways, respectively (Ögren and Fuxe, 1988). Cannabinoid receptor agonists have been shown to reduce contralateral rotation induced by a dopamine D_1 but not a D_2 receptor agonist in rats with 6-hydroxydopamine lesions of the nigrostriatal pathway (Anderson et al., 1995). Therefore, cannabinoid receptor stimulation may selectively modify dopaminergic effects on striatonigral activity.

In addition to the pharmacological characterization (Devane et al., 1988) and cloning (Matsuda et al., 1990) of the brain cannabinoid receptor, an endogenous ligand for the cannabinoid receptor has been isolated and identified as anandamide (arachidonylethanolamide) (Devane et al., 1992). Anandamide binds with high affinity to brain cannabinoid receptors (Felder et al., 1993; Vogel et al., 1993) and mimics the behavioral effects of naturally occurring and synthetic cannabinoid receptor agonists (Crawley et al., 1993; Fride and Mechoulam, 1993; Smith et al., 1994). Since Δ^9-tetrahydrocannabinol potentiates the cataleptic effect of dopamine antagonists, the question arises as to whether endogenous anandamide or other putative endogenous ligands for the cannabinoid receptor (Evans et al., 1994), plays a role in the production of catalepsy produced by dopamine receptor antagonists. The recent development of a selective antagonist of the brain cannabinoid receptor, SR 141716A (*N*-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide-hydrochloride) (Rinaldi-Carmona et al., 1994), allows for the testing of this hypothesis.

The purpose of the present study was to examine the effect of cannabinoid receptor stimulation and blockade on catalepsy produced by selective dopamine D_1 and D_2 receptor antagonists. The ability of the cannabinoid receptor antagonist SR 141716A to reduce catalepsy produced by the dopamine D_1 receptor antagonist SCH 23390 (*R*-(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1-*H*-3-benzazepine) and the dopamine D_2 receptor antagonist raclopride (*S*(−)-3,5-dichloro-*N*-(1-ethyl-2-pyrrolidinyl)-methyl-6-methoxysalicylamide) was investigated. In addition, the ability of the synthetic cannabinoid receptor agonist CP 55,940 (1α,2-(*R*)-5-(1,1-dimethylheptyl)-2-[5-hydroxy-2-(3-hydroxypropyl)cyclohexyl-phenol) to potentiate catalepsy elicited by SCH 23390 and raclopride was also tested.

2. Materials and methods

2.1. Animals

All procedures were performed in accordance with the NIH Guide for the Care and Use of Laboratory Animals. Male Sprague-Dawley rats weighing 280–300 g (Taconic Farms, Germantown, NY, USA) were housed two per cage on a 12 h light/dark cycle with free access to food and water.

2.2. Catalepsy

Catalepsy testing was performed between 11:00–4:00 h. Catalepsy was assessed utilizing the grid test by an observer unaware of the treatment conditions. The grid test consisted of placing the animal on a grid (stainless steel cage cover) with a 60° inclination to the counter top. Time was recorded until the rat removed one hindpaw from the grid, with a maximum cut-off of 60 or 300 s depending on the experiment. Vehicle controls were tested in the same sessions as drug-treated animals.

2.3. Drugs

CP 55,940 was donated by Pfizer (Groton, CT, USA) and dissolved in 60% dimethyl sulfoxide (Sigma Chemical Co., St. Louis, MO, USA). SR 141716A was provided by Sanofi Recherche (Montpellier, France) and dissolved in 100% dimethyl sulfoxide. SCH 23390 was purchased from Research Biochemicals International (Natick, MA, USA) and dissolved in deionized water. Raclopride was donated by Astra Arcus (Södertalje, Sweden) and dissolved in saline.

2.4. Statistical analysis

Catalepsy data was analyzed by Kruskal-Wallis nonparametric analysis of variance followed by Mann-Whitney *U*-tests when justified. For the sake of clarity, standard error bars are not included on the line graphs; however, representative means ± S.E.M. for each treatment are provided in the corresponding bar graphs.

3. Results

3.1. Effect of SR 141716A on catalepsy produced by CP 55,940

The cannabinoid receptor agonist CP 55,940 (0.5 mg/kg i.p.) produced catalepsy within 25 min of injection in vehicle-treated control rats (Fig. 1A). Pretreatment with the cannabinoid receptor antagonist SR

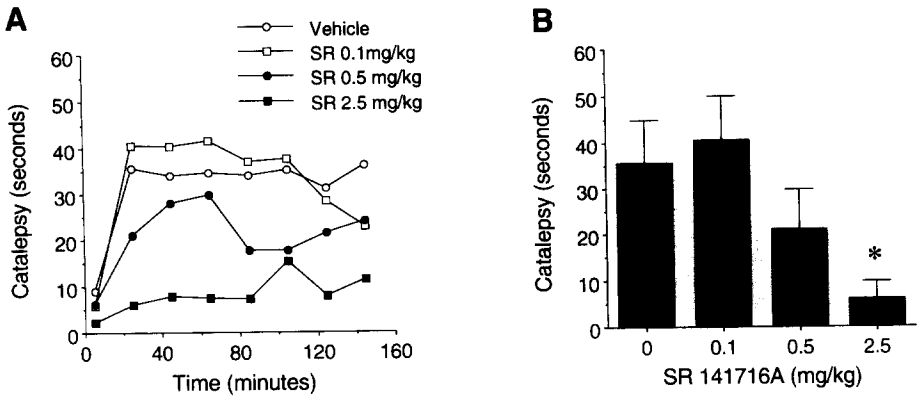

Fig. 1. Effect of the brain cannabinoid receptor antagonist SR 141716A on catalepsy produced by the cannabinoid receptor agonist CP 55,940. SR 141716A (0.1, 0.5, or 2.5 mg/kg i.p.) or vehicle (100% dimethyl sulfoxide) was injected 5 min before administration of CP 55,940 (0.5 mg/kg i.p.). Five minutes later, the animals were tested for catalepsy behavior, using the grid test with a 60 s maximum cut-off, at 20 min intervals for 140 min. Line graphs (A) represent the time course of the effect of SR 141716A on CP 55,940-induced catalepsy (each point represents the mean duration of catalepsy). Bar graphs (B) represent the mean (±S.E.M.) effect of SR 141716A on CP 55,940-induced catalepsy 25 min after injection. $^{*}P < 0.05$ versus vehicle-treated controls by Kruskal-Wallis analysis of variance and Mann-Whitney U-tests ($n = 8$ rats/group).

141716A dose-dependently decreased catalepsy elicited by CP 55,940 (Fig. 1A and B). At 25 min after injection, SR 141716A (0.5 and 2.5 mg/kg i.p.) reduced catalepsy by 40 and 83%, respectively, although the effect at 0.5 mg/kg was not statistically significant. SR 141716A (2.5 mg/kg) effectively blocked the cataleptic

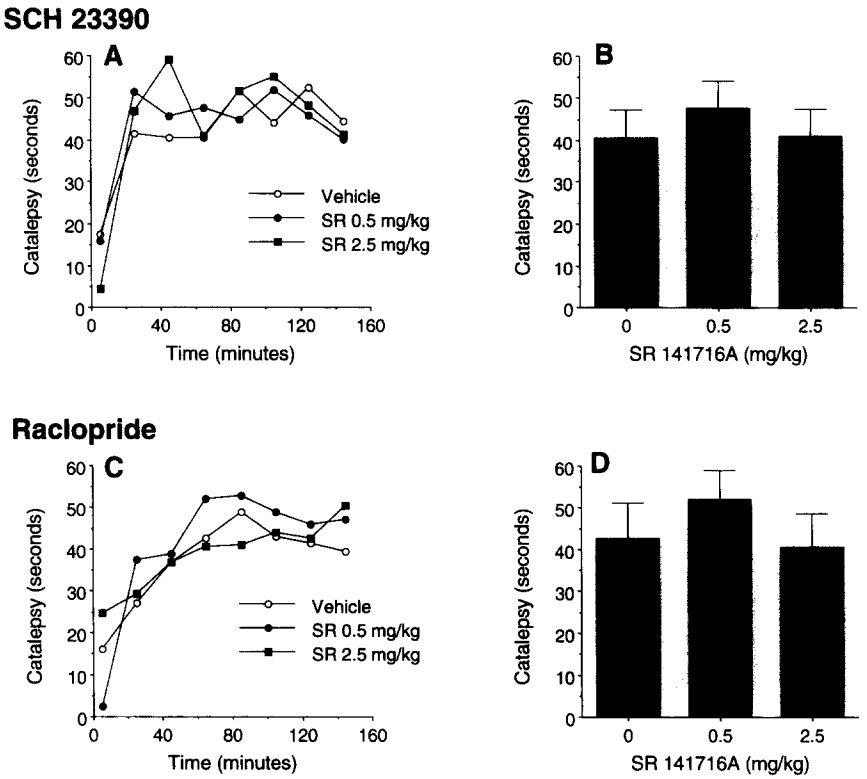

Fig. 2. Effect of the brain cannabinoid receptor antagonist SR 141716A on catalepsy produced by the dopamine D_1 receptor antagonist SCH 23390 or the dopamine D_2 receptor antagonist raclopride. SR 141716A (0.5 or 2.5 mg/kg i.p.) or vehicle (100% dimethyl sulfoxide) was injected 15 min prior to injection of SCH 23390 (0.5 mg/kg s.c.) or raclopride (2.5 mg/kg i.p.). Five minutes later, the animals were tested for catalepsy behavior, using the grid test with a 60 s maximum cut-off, at 20 min intervals for 140 min. Line graphs represent the time course of the effect of SR 141716A on SCH 23390-induced (A) or raclopride-induced (C) catalepsy (each point represents the mean duration of catalepsy). Bar graphs represent the mean (±S.E.M.) effect of SR 141716A on SCH 23390-induced (B) or raclopride-induced (D) catalepsy 65 min after injection ($n = 8$ rats/group).

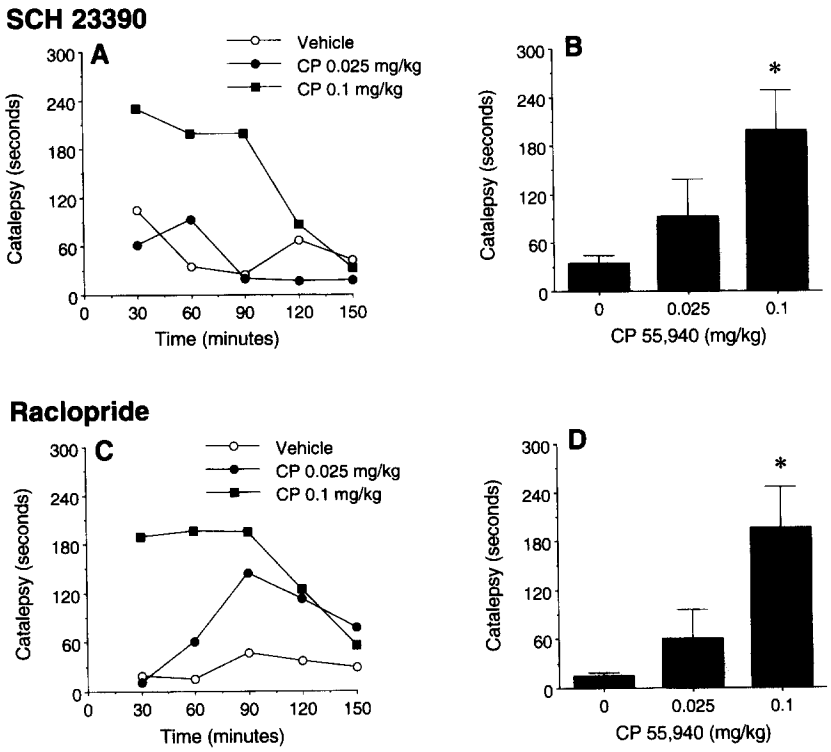

Fig. 3. Effect of the cannabinoid receptor agonist CP 55,940 on catalepsy produced by the dopamine D_1 receptor antagonist SCH 23390 or the dopamine D_2 receptor antagonist raclopride. CP 55,940 (0.025 or 0.1 mg/kg i.p.) or vehicle (60% dimethyl sulfoxide) was injected 15 min before injection of SCH 23390 (0.5 mg/kg s.c.) or raclopride (2.5 mg/kg i.p.). Thirty minutes later, the animals were tested for catalepsy behavior, using the grid test with a 300 s maximum cut-off, at 30 min intervals for 120 min. Line graphs represent the time course of the effect of CP 55,940 on SCH 23390-induced (A) or raclopride-induced (C) catalepsy (each point represents the mean duration of catalepsy). Bar graphs represent the mean (±S.E.M.) effect of CP 55,940 on SCH 23390-induced (B) or raclopride-induced (D) catalepsy 60 min after injection. $^*P < 0.05$ versus vehicle-treated controls by Kruskal-Wallis analysis of variance and Mann-Whitney U-tests ($n = 8$ rats/group).

effect of CP 55,940 throughout the duration of the experiment. By itself, SR 141716A had no effect on catalepsy at any of the doses tested (data not shown).

3.2. Effect of SR 141716A on catalepsy produced by SCH 23390 and raclopride

The dopamine D_1 receptor antagonist SCH 23390 (0.5 mg/kg s.c.) elicited catalepsy within 25 min of injection in vehicle-treated control animals (Fig. 2A). Pretreatment with SR 141716A (0.5 and 2.5 mg/kg i.p.) did not decrease catalepsy produced by SCH 23390 (Fig. 2A and B).

The dopamine D_2 receptor antagonist raclopride (2.5 mg/kg i.p.) also elicited catalepsy within 25 min of injection in vehicle-treated control rats (Fig. 2C). Pretreatment with SR 141716A (0.5 and 2.5 mg/kg i.p.) did not reduce catalepsy elicited by raclopride (Fig. 2C and D).

3.3. Effect of CP 55,940 on catalepsy produced by SCH 23390 and raclopride

Since we were interested in examining the ability of CP 55,940 to potentiate SCH 23390 and raclopride-induced catalepsy, the maximum cut-off time for catalepsy testing was increased to 300 s in these experiments. In addition, doses of CP 55,940 (0.025 and 0.1 mg/kg i.p.) were used which do not produce catalepsy (Anderson et al., 1995). CP 55,940 at the 0.1 mg/kg dose, but not the 0.025 mg/kg dose, enhanced catalepsy elicited by SCH 23390 by 568% (Fig. 3A and B). Likewise, CP 55,940 (0.1 mg/kg) potentiated catalepsy produced by raclopride by 1306% (Fig. 3C and D).

4. Discussion

The present results suggest that stimulation, but not blockade, of brain cannabinoid receptors modifies catalepsy behavior produced by selective dopamine receptor antagonists. The brain cannabinoid receptor antagonist SR 141716A, at doses which blocked the cataleptic effects of the cannabinoid receptor agonist CP 55,940, did not reduce catalepsy elicited by the dopamine D_1 receptor antagonist SCH 23390 or the dopamine D_2 receptor antagonist raclopride. Conversely, stimulation of cannabinoid receptors by CP 55,940 potentiated the cataleptic effects of both dopamine D_1 and D_2 receptor blockade.

The demonstration that SR 141716A antagonized catalepsy elicited by a cannabinoid receptor agonist

confirms the results of Rinaldi-Carmona et al. (1994) in which intraperitoneal injection of SR 141716A blocked catalepsy produced by the cannabinoid receptor agonist WIN 55,212-2 in mice. These investigators also reported that SR 141716A reduced hypothermia and antinociception elicited by WIN 55,212-2 (Rinaldi-Carmona et al., 1994). In addition, intraperitoneal administration of SR 141716A decreased the contralateral rotation induced by unilateral intrastriatal injection of WIN 55,212-2 and CP 55,940 in mice (Souilhac et al., 1995). Hence, a growing body of in vivo evidence, coupled to in vitro binding data (Rinaldi-Carmona et al., 1994), indicates that SR 141716A is a potent and selective antagonist of brain cannabinoid receptors.

Although catalepsy produced by dopamine D_1 and D_2 receptor antagonists is thought to result from blockade of dopaminergic transmission, other neurotransmitter systems may mediate the sequence of events from dopamine receptor blockade to the appearance of catalepsy. For example, antagonists of muscarinic receptors (Setler et al., 1976; Arnt and Christensen, 1981; Arnt et al., 1986) reduce catalepsy produced by dopamine receptor antagonists. Acetylcholine, therefore, may play an important role in the production of catalepsy elicited by dopamine receptor antagonism, since blockade of muscarinic receptors reduces catalepsy. In the present study, however, blockade of cannabinoid receptors did not reduce dopamine antagonist-induced catalepsy. This finding implies that, under the present circumstances, endogenously released cannabinoid ligands do not participate in the cataleptic effects of the dopamine receptor antagonists. However, further studies are needed with anandamide and with higher doses of SR 141716A to clarify this point. Interestingly, low doses of anandamide have recently been shown to reduce the biochemical and behavioral effects of Δ^9-tetrahydrocannabinol, possibly a result of the partial agonist activity of anandamide (Fride et al., 1995). Nevertheless, cannabinoid receptors involved in motor control may have little tonic activity since SR 141716A did not alter a number motor behavioral measures when administered alone (Rinaldi-Carmona et al., 1994).

The ability of the synthetic cannabinoid receptor agonist CP 55,940 to potentiate catalepsy induced by selective dopamine D_1 and D_2 receptor antagonists is consistent with previous reports demonstrating that Δ^9-tetrahydrocannabinol enhances catalepsy produced by nonselective dopamine receptor antagonists and by monoamine depletion with reserpine (Moss et al., 1981, 1984). Although we report that sub-cataleptic doses of CP 55,940 enhance the cataleptic effects of dopamine antagonists, it is unknown if cataleptic doses of CP 55,940 have additive effects on catalepsy produced by the dopamine antagonists.

Even though the compounds employed in this study were administered systemically, the basal ganglia, and striatum in particular, may be possible sites of action. The striatum is thought to be an important neural substrate underlying the cataleptic effects of dopamine receptor antagonists (Costall et al., 1972; Fletcher and Starr, 1988; Calderon et al., 1988). In addition, the striatum as well as its targets including the entopeduncular nucleus, substantia nigra pars reticulata, and globus pallidus, contain high densities of cannabinoid receptor binding sites (Herkenham et al., 1990, 1991; Thomas et al., 1992). It has been hypothesized that dopamine D_1 and D_2 receptor antagonists produce catalepsy by selective effects on striatonigral and striatopallidal pathways, respectively (Ögren and Fuxe, 1988). Since cannabinoid receptor stimulation potentiates both dopamine D_1 and D_2 receptor antagonist-induced catalepsy, cannabinoids may influence changes in activity of both striatonigral and striatopallidal pathways. In other paradigms, however, cannabinoid receptor agonists preferentially alter effects mediated by dopamine D_1 receptor-selective drugs. For instance, cannabinoid receptor agonists attenuate contralateral rotation induced by a dopamine D_1 but not a D_2 receptor agonist in rats with unilateral 6-hydroxydopamine-induced lesions of the nigrostriatal pathway (Anderson et al., 1995). In addition, chronic treatment with a dopamine D_1, but not a D_2 receptor agonist enhanced catalepsy produced by the cannabinoid receptor agonist HU-210 (Rodriguez de Fonseca et al., 1994). Furthermore, chronic dopamine D_1 receptor antagonist treatment increased striatal cannabinoid receptor mRNA levels to a greater degree than dopamine D_2 receptor antagonist treatment (Mailleux and Vanderhaeghen, 1993). Nevertheless, stimulation of cannabinoid receptors has the potential to influence both dopamine D_1 and D_2 receptor-mediated processes, since cannabinoid receptors co-localize with dopamine D_1 receptors on striatonigral neurons and dopamine D_2 receptors on striatopallidal neurons. Whether or not cannabinoid agonists preferentially alter dopamine D_1 or D_2 receptor-mediated effects may depend upon the experimental conditions as well as the behavioral or biochemical outcome measured.

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