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Effects of Intrastriatal Cannabinoids on Rotational Behavior in Rats: Interactions With the Dopaminergic System

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ABSTRACT The effect of unilateral intrastriatal cannabinoid receptor stimulation on rotational behavior in rats was explored. The potent cannabinoid agonist CP 55,940 (5 μg/0.5 μl) induced contralateral turning when microinjected unilaterally into the striatum. The D_2 dopamine agonist quinpirole reversed this contralateral rotation but failed to affect motor behavior on its own. Finally, the D_1 dopamine agonist SKF 82958 inhibited movement when administered into the striatum and this inhibition was reversed by co-administration of the cannabinoid agonist. Surprisingly, microinjections of the cannabinoid agonist into the striatum induced movement through activation of the striatonigral pathway and/or inhibition of the striatopallidal pathway, while the D_1 dopamine agonist produced the opposite effect. **Synapse 30:221–226, 1998.**

INTRODUCTION

The basal ganglia constitutes one neural substrate for the well-known motor actions of cannabinoids (Anderson et al., 1995; Dewey, 1986; Gough and Olley, 1978; Hollister, 1986; Miller and Walker, 1995, 1996; Miller et al., 1998; Navarro et al., 1993; Pertwee and Wickens, 1991; Romero et al., 1995, 1996a,b; Sañudo-Peña et al., 1996, 1998a,b; Sañudo-Peña and Walker, 1997; Souilhac et al., 1995; Stark and Dews, 1980; Tsou et al., 1995, 1998; Wickens and Pertwee, 1993, 1995). The striatum, a major input structure for the basal ganglia, produces both cannabinoid receptors and their encoding mRNA (Herkenham et al., 1991b; Mailleux and Vanderhaegen, 1992). Its efferent projections are a major source of cannabinoid receptors for other nuclei of the basal ganglia (Herkenham et al., 1991a). Cannabinoid receptors are concentrated in the sensorimotor sector of the striatum, which in turn projects to the globus pallidus and substantia nigra reticulata, areas that contain some of the highest levels of cannabinoid receptors in the brain (Herkenham et al., 1991a,b; Mailleux and Vanderhaegen, 1992). Besides being present in striatal output neurons, cannabinoid receptors might be expressed in GABAergic interneurons (Kawaguchi et al., 1995; Mailleux and Vanderhaegen, 1992).

The striatum produces movement through two major output pathways, one to the substantia nigra pars reticulata and entopeduncular nucleus (direct pathway), and another to the globus pallidus (indirect pathway) (Kawaguchi et al., 1990). Both pathways utilize the inhibitory neurotransmitter GABA and express cannabinoid receptors, but these pathways contain markedly different levels of neuropeptides and dopamine receptor subtypes. Striatopallidal neurons contain mainly enkephalin and D_2 dopamine receptors, whereas striatonigral neurons contain mainly dynorphin, substance P, and D_1 dopamine receptors (Gerfen and Young, 1988; Herkenham et al., 1991a; LeMoine et al., 1991; LeMoine and Bloch, 1995).

Several lines of evidence suggest that the induction of movement by intrastriatal dopamine agonists occurs by inhibition of the striatopallidal pathway through D_2 receptors or activation of the striatonigral pathway through D_1 receptors (Cooper et al., 1995; Gerfen, 1995). Either action produces movement consistent with the different molecular actions of D_2 and D_1 dopamine receptor types on their respective output pathways (Costall et al., 1972; Cooper et al., 1995; Gerfen et al., 1990, 1991; Graybiel, 1990; Herrera-Marschitz et al., 1985a,b; Herrera-Marschitz and Ungerstedt, 1987; Keefe and Gerfen, 1995; Nissenbaum et al.,

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1994; Robertson et al., 1989, 1990). Surprisingly, intrastriatal cannabinoids induce dose-related contralateral rotation in mice, resembling dopamine agonists (Souilhac et al., 1995). Moreover, the rotation induced by intrastriatal cannabinoids is blocked by systemic administration of dopamine antagonists or intrastriatal 6-OHDA lesions (Souilhac et al., 1995). This suggests a complex interaction between the cannabinoid and dopamine receptor systems, as revealed in previous studies (Anderson et al., 1995, Sañudo-Peña et al., 1996, Sañudo-Peña and Walker, 1997b).

The goal of this work was to determine the effect of intrastriatal cannabinoid administration on motor behavior in rats and to further examine the interaction between the dopamine and cannabinoid receptor systems in the striatum. For this purpose, a dopamine D_1, dopamine D_2, or cannabinoid agonist was administered unilaterally into the striatum, and the effect on turning behavior was studied. The cannabinoid agonist was also co-administered with each of the dopaminergic agonists to test for a cannabinoid–dopamine interaction in the striatum.

MATERIALS AND METHODS

Male Sprague-Dawley rats (Charles River Laboratories, Raleigh, NC), 250–300 g at the time of surgery, served as subjects. From the beginning of the experiment they were individually housed in metal cages in a temperature-regulated (22–23°C) room with food and water freely available. Artificial lighting was provided from 07.00 h to 19.00 h.

On the day of surgery, each animal was anesthetized with sodium pentobarbital (50 mg/kg) and placed in a stereotaxic frame. A 24-gauge guide cannula constructed from stainless steel hypodermic tubing was implanted with its tip 4.0 mm above the center of the left striatum (0.4 mm anterior, 2.7 mm lateral, 6.5 mm ventral from bregma and the skull surface) The cannula was fixed to the skull with stainless steel screws and dental acrylic. Stainless steel stylets, the length of the cannulas, kept the cannulas sealed.

Following at least 3 days recovery, each animal was tested for turning behavior after an intrastriatal injection of a drug or combination of drugs. Drugs were injected (0.5 µl over a 2-min period); the injection cannula (31 gauge stainless steel tubing) was left in place for an additional 30 sec before removal. Following the injection, the stainless steel stylet was replaced in the guide cannula and each animal was placed in a rotometer. An adjustable elastic harness fitted around each animal was connected by a metal cable to an optical transducer that encoded the position of the rat as a binary signal. A computer calculated the number and direction of half turns per minute for each animal during a 30-min testing session. Each rat was tested once.

The potent cannabinoid agonist CP 55,940 was generously provided by Pfizer (Groton, CT). All microinjected drugs were dissolved in 60% dimethylsulfoxide (Sigma Chemical, St. Louis, MO). The D_1 dopamine receptor agonist SKF 82958 and the D_2 dopamine agonist quinpirole were obtained from Research Biochemicals Intl. (Natick, MA). All other drugs and chemicals were obtained from Sigma.

After behavioral testing, rats were anesthetized and perfused transcardially with a 10% formalin solution. Brains were fixed in a 30% sucrose-formalin solution, frozen, sectioned (40 µm), stained with cresyl violet and examined under a microscope to localize injection sites. For all studies, only the data from animals with correct cannula placements and minimal nonspecific damage were included (Fig. 1).

Rotation following intrastriatal injections of the cannabinoid agonist CP 55,940 (5 µg) was examined. CP 55,940 and the D_1 agonist SKF 82958 (10 µg) were co-administered to test their combined effect on the rotation induced by the administration of either single compound. Finally, we examined the effect of the D_2 agonist quinpirole (2.5 µg) on the turning induced by intrastriatal administration of CP 55,940. Each animal received a single injection and was tested only once.

Net contralateral half turns (contralateral minus ipsilateral) were used in all data analyses. Due to variance heterogeneity, data were analyzed using a nonparametric one-way Kruskal-Wallis test. Post-hoc comparisons were made using the Mann-Whitney test.

RESULTS

As shown in Figure 1, all injection sites were confined to the striatum. An overall analysis of variance revealed that various drug combinations administered into the striatum produced markedly different effects on rotational behavior: Kruskal-Wallis test ($H = 16{,}814$, $P \leq 0.004$). Rats that received 5 µg CP 55,940 showed significant contralateral rotation compared to the rest of the groups (Mann-Whitney test $P \leq 0.003$, Fig. 2).

Injections of SKF 82958 (10 µg) in the striatum induced significant ipsilateral rotational behavior (Mann-Whitney test $P \leq 0.04$, Fig. 2). Co-administration of the D_1 agonist with the cannabinoid agonist significantly reduced the turning produced by administration of any of the compounds alone ($P \leq 0.02$).

Unlike the D_1 agonist, the D_2 agonist quinpirole did not produce circling when microinjected in the striatum (Fig. 2). However, co-administration of quinpirole with the cannabinoid reversed the contralateral rotation induced by the administration of the cannabinoid agonist alone ($P \leq 0.003$).

DISCUSSION

This study showed that unilateral microinjection of the cannabinoid agonist CP 55,940 into the striatum of

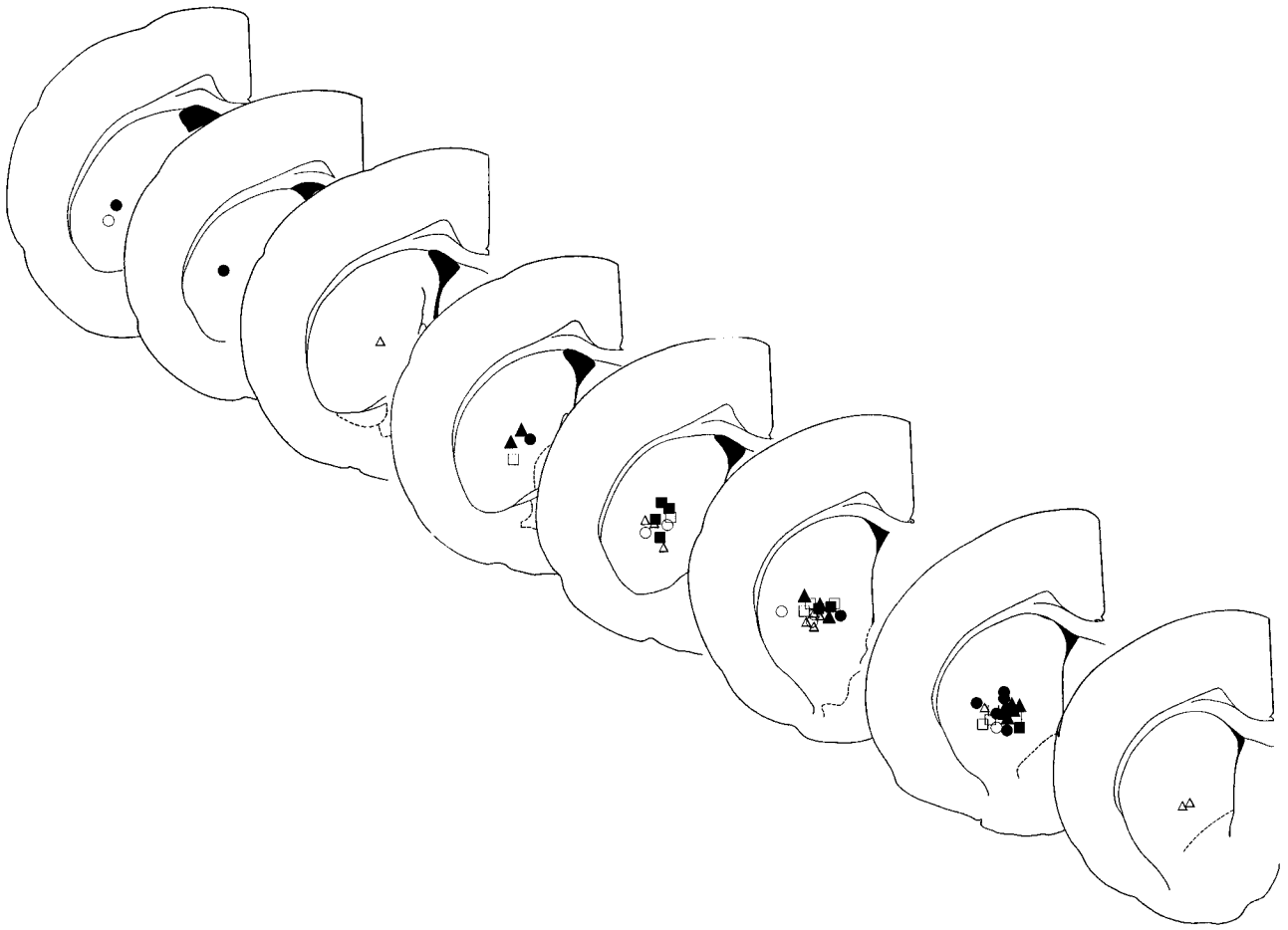

Fig. 1. Diagrammatic representation of the localization of cannulae tips for intrastriatal administration of (○) vehicle, (☒') the cannabinoid agonist CP 55,940, (□) the dopamine D_1 agonist SKF 82958, (■) SKF 82958 + CP 55,940, (&tri:)the dopamine D_2 agonist quinpirole, (&trif;) quinpirole + CP 55,940.

intact rats produced contralateral turning, an effect consistent with an overall increase in motor activity. These data add to our previous observations of contralateral rotation after intranigral (Sañudo-Peña et al., 1996, 1998a) and ipsilateral rotation after intrapallidal (Sañudo-Peña and Walker, 1998b) or intrasubthalamic (Miller et al., 1998) administration of CP 55,940. The induction of contralateral turning by intrastriatal administration of a cannabinoid agonist in rats agrees with a previous experiment on mice (Souilhac et al., 1995). However, it contrasts with the induction of ipsilateral turning by systemic cannabinoids in the 6-OHDA model (Sakurai et al., 1985), suggesting that in the latter case the major site of action of the cannabinoid was outside the striatum.

The observation of contralateral rotation suggests that the drug either activated the striatonigral pathway or inhibited the striatopallidal pathway (Cooper et al., 1995; Gerfen, 1995; Graybiel, 1990; Herrera-Marschitz et al., 1985a,b; Nissenbaum et al., 1994; Robertson et al., 1989, 1990; You et al., 1994). Cannabinoids presynaptically inhibit neurotransmitter release (Mackie and Hille, 1992; Mackie et al., 1995). Postsynaptically, cannabinoids have been reported to either inhibit (Deadwyler et al., 1993) or increase the excitability of neurons (Schweitzer et al., 1996). Therefore, a direct excitatory action of cannabinoids on striatonigral or an inhibitory action on striatopallidal neurons, or similar actions among striatal interneurons, could account for the observed motor effect.

Intrastriatal administration of the D_1 dopamine agonist in this study unexpectedly inhibited movement. The literature on the motor effects of intrastriatally administered dopaminergic agonists in intact animals is sparse; nevertheless, administration of a different D_1 dopamine agonist (SKF38393) into the striatum produced increased movement and consonant changes in nigral neurochemistry in intact animals (Worms et al., 1986; You et al., 1994). However, SKF 38393 is now known to be a partial agonist at the D_1 receptor (Arnt et al., 1992), and this study on motor function (Worms et al., 1986) used mice. Therefore, differences in the intrinsic activity of the drugs and/or species differences could account for the discrepancy between the expecta-

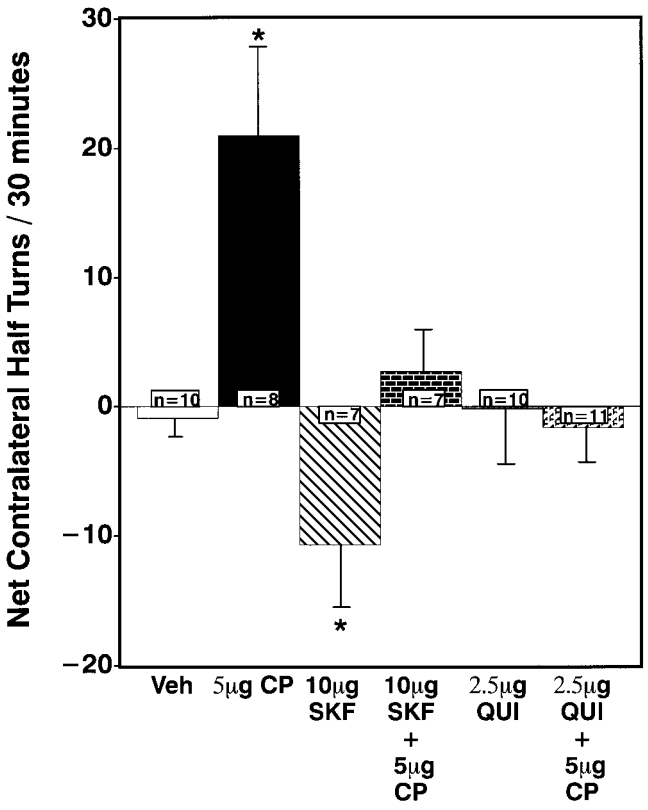

Fig. 2. Effect of unilateral microinjections of the cannabinoid agonist CP 55,940 alone or together with the D_1 dopamine receptor agonist SKF 82958 or the D_2 dopamine receptor agonist quinpirole into the striatum on turning behavior (* significantly different from the rest of the groups, $P \leq 0.05$). The cannabinoid agonist induced contralateral turning which was reversed by co-administration of a D_1 or a D_2 dopamine receptor agonist. The D_1 dopamine receptor agonist alone induced ipsilateral turning, while the D_2 dopamine receptor agonist had no effect.

tion of contralateral turning and the observation of ipsilateral turning.

The results with the D_1 agonist are in general agreement with the extremely low behavioral efficacy of SKF 82958 in the 6-OHDA turning model, which occurs despite its high efficacy (greater than that of dopamine) in stimulating adenylate cyclase (Gnanalingham et al., 1995). In line with its strong effect on adenylate cyclase, SKF 82958 induced robust expression of immediate early genes into the intact striatum, while the more commonly used SKF 38393 consistently failed to induce immediate early gene expression in the intact striatum (Wang and McGinty, 1996). Therefore, although their biochemical basis is unclear, significant differences between SKF 38393 and SKF 82958 have been observed.

Unlike the dopamine D_1 agonist, the dopamine D_2 agonist induced no behavioral effect in this study after intrastriatal administration. According to most current models of basal ganglia physiology, dopamine acts through D_2 receptors in the striatum to induce movement by inhibition of the striatopallidal pathway (Cooper et al., 1995; Costall et al., 1972; Gerfen, 1995; Graybiel, 1990; Herrera-Marschitz et al., 1985a,b, 1987; Keefe and Gerfen, 1995; You et al., 1994). Contralateral rotation after intrastriatal administration of a D_2 dopamine agonist in intact animals has been reported in studies that used mice (Worms et al., 1986). However, although intact mice showed contralateral rotation after intrastriatal apomorphine (Worms et al., 1987), rats did not (Costall et al., 1975), implying important species differences. In fact, we are not aware of any reports of contralateral turning produced in unlesioned rats by intrastriatal administration of selective D_2 agonists.

Finally, the contralateral turning induced by intrastriatal administration of the cannabinoid agonist was reversed by co-administration of either a D_1 or D_2 dopamine agonist with the cannabinoid. Previous work indicated that the contralateral turning induced by intrastriatal administration of cannabinoid agonists is reversed by systemic administration of D_1 or D_2 dopamine antagonists or 6-OHDA intrastriatal lesions (Souilhac et al., 1995). In another report, cannabinoid agonists blocked the contralateral turning induced by systemic administration of dopamine D_1 but not D_2 agonists in rats with 6-OHDA lesions (Anderson et al., 1995). However, in this study the site of action of the cannabinoid is unknown because the drugs were administered systemically.

The present study suggests important interactions between cannabinoid and dopamine receptors in the striatum. In this regard, it is interesting to note that both D_1 and D_2 antagonists increased the level of mRNA for the cannabinoid receptor in the striatum (Mailleux and Vanderhaegen, 1993). This suggests a negative control by dopaminergic projections over the cannabinoid system in the brain via D_1 and/or D_2 receptors, and agrees with our findings and those of Souilhac et al. (1995). It would be reasonable to assume that cannabinoid agonists and dopamine D_1 agonists blocked each other's effects when co-administered, due to their opposite effects on second messenger systems and neurotransmission (Graybiel, 1990; Howlett, 1995). However, the D_2 dopamine agonist also opposes cannabinoid effects despite its similar actions at the molecular level. It is, thus, notable that another report showed an opposite action of cannabinoids at the molecular level when co-administered with dopamine D_2 receptor agonists in the striatum (Glass and Felder, 1996).

In conclusion, cannabinoids stimulate movement when injected into the striatum of the rat. In contrast, activation of dopamine D_1 receptors inhibited movement. Intrastriatal co-administration of dopamine D_1 or D_2 agonists with the cannabinoid agonist failed to affect movement. Together with the extremely high density of cannabinoid receptors in basal ganglia and the powerful motor effects of cannabinoids observed

previously, these findings might be relevant to degenerative diseases such as Parkinson's disease (in which dopaminergic innervation to the striatum is damaged), since combined drug treatments have been more valuable than treatments focusing solely on the dopaminergic system.

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