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Intrastriatal Injection of Cannabinoid Receptor Agonists Induced Turning Behavior in Mice

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SOUILHAC, J., M. PONCELET, M. RINALDI-CARMONA, G. LE FUR AND P. SOUBRIÉ. *Intrastriatal injection of cannabinoid receptor agonists induced turning behavior in mice.* PHARMACOL BIOCHEM BEHAV **51**(1) 3–7, 1995.— When injected unilaterally into the mouse striatum, cannabinoid agonists such as Win 55212-2 (1–100 ng/mouse), CP 55940 (0.1–50 ng/mouse), and anandamide (0.5–50 ng/mouse), the putative endogenous ligand of CB_1 receptor, dose-dependently induced turning behavior. SR 141716A [*N*-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide hydrochloride], the selective antagonist of CB_1 receptor, antagonized the three cannabinoid receptor agonists-induced turning with similar ED_{50}s (0.13–0.15 mg/kg, IP). Spiroperidol (a D_2 receptor blocker), (+)-SCH 23390 (a D_1 receptor blocker), or prior 6-OHDA lesions of the striatum blocked Win 55212-2- and CP 55940-induced turning, thus suggesting the involvement of DA transmission in cannabinoid-induced turning. Taken together, these findings reinforce the notion of a cannabinoid receptor-mediated control of nigrostriatal function.

Cannabinoid receptor agonists Anandamide SR 141716A Striatum Turning Dopamine 6-OHDA lesions Mouse

THE MAJOR psychoactive constituent of cannabis, Δ^9-tetrahydrocannabinol (Δ^9-THC), as well as synthetic cannabinoids bind to a specific G-protein-coupled receptor in the brain, the CB_1 receptor (6). This receptor, which has been cloned in both rat and human (22,11), reveals a unique and conserved brain distribution, with binding being most dense in the cerebellum, hippocampus, and outflow nuclei of the basal ganglia, including the substantia nigra (pars reticulata), the striatum, and the globus pallidus. Sparse densities were observed in lower brain stem areas (13,15). Such a regional distribution is consistent with the characteristic cognitive, analgesic, and motor effects of cannabinoids (16,26), even though the cellular events and physiological regulations triggered by CB_1 receptor activation remain largely to be discerned (9).

To further explore the role of cannabinoid receptor in the control of basal ganglia function, we examined whether, when injected unilaterally into one striatum, cannabinoid agonists such as Win 55212-2, CP 55940, and anandamide (arachidonylethanolamide), the putative endogenous ligand of CB_1 receptors (7,4), may produce circling behavior. Furthermore, we explored whether such a rotational response was blocked by SR 141716A [*N*-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide hydrochloride], the selective antagonist of CB_1 receptor (29) and whether it may involve nigrostriatal dopamine (DA) neurons and SP efferent striatal neurons.

METHOD

Animals

Female Swiss mice (CD_1 strain, Charles River, France) weighing 25–30 g were used. One week before experiments, mice were caged in groups of 10 and housed in a room at constant temperature (21 ± 1°C) on an automatic dark : light schedule (light 0700–1900 h) with food and tap water freely available.

Drugs

SR 141716A, SR 140333 (the NK_1 receptor antagonist), and SR 140603 [its *(R)*-antipode (17)] and the NK_2 receptor antagonist SR 48968 (27) (Sanofi Recherche, Montpellier, France) were suspended with Tween 80 in distilled water. Win 55212-2 (RBI, Natick, MA) (1 mg/ml) was solubilized in 50% dimethyl sulfoxide (DMSO), CP 55940 (Pfizer) (0.5 μg/μl) was solubilized in 80% DMSO, and anandamide (Sanofi Re-

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cherche) (0.5 μg/μl) was solubilized in 40% ethanol then diluted in 0.9% NaCl for the studied concentrations. Lesion of DA neurons was performed using 2,4,5-trihydroxyphenethylamine hydrobromide (6-OHDA) dissolved in sterile 0.9% NaCl (see below). Spiroperidol (Sigma, St. Louis, MO) was dissolved in tartaric acid (0.1%) and distilled water, (+)-SCH 23390 (RBI) was solubilized in distilled water.

For systemic administrations, intraperitoneal route (IP), or oral route (PO), the injection volume was 0.4 ml/20 g body weight. Groups of 10–20 mice (8 for 6-OHDA lesions) were used.

Statistical analysis was performed using ANOVA followed by Dunnett's *t*-test.

Turning Behavior

Intrastriatal injection was performed according to Worms et al. (34). The microinjection was made free-hand in a volume of 1 μl, in the right striatum of conscious, nonrestrained mice by means of a 5-μl Hamilton microsyringe and a 10-mm calibrated needle (final length below the skin: 3.5 mm). The descending point of the needle was slightly internal and caudal to the right orbitus. The duration of injection was 2–3 s. Control mice received 1 μl of vehicle. After injection, the animals were placed individually in Plexiglas cages (10 × 10 × 15 cm). The number of complete contralateral rotations (e.g., away from the injected side) was visually recorded and cumulated over three periods of 2 min (2–4, 5–7, 8–10 min) postintrastriatal injection of Win 55212-2 (1–100 ng/mouse), CP 55940 (0.1–50 ng), or anandamide (0.1–50 ng). For further studies, the doses of Win 55212-2, CP 55940, and anandamide were fixed at 50, 10, and 25 ng/mouse, respectively. Vehicle, SR 141716A, spiroperidol, (+)-SCH 23390, SR 140333, SR 140603, and SR 48968 were given IP 30 min before intrastriatal injection.

6-OHDA Lesions of the Striatum

Mice were lesioned according to the method described by Von Voigtlander and Moore (31). After pentobarbitone anaesthesia (60 mg/kg, IP), 1 μl of 6-OHDA solution (10 mg/ml of saline containing 1 mg/ml of ascorbic acid) was infused slowly (5 min) into the right striatum (coordinates: 0 anterior to bregma; 2 mm lateral on the sagittal suture; 3.5 mm ventral to the pial surface). Two weeks later, mice were tested for turning behavior as described above.

For biochemical controls, mice were killed by decapitation; their striatum was removed and the DA levels were measured with HPLC (Waters instruments, 715 Ultra Wisp, 510 solvent delivery system, and 460 electrochemical detector). A μBondapack phenyl column (Waters Assoc.) was used for the separation. The mobile phase consisted of a 3% methanol in 0.1 M Na-phosphate buffer, pH 2.5, and 1 mM 1-octan sulphonic acid (PIC B-8, Waters). Frozen samples were homogenized in 0.1 N $HClO_4$ containing 4 mM Na-metabisulfite and 1 mM EDTA.

RESULTS

The unilateral application of Win 55212-2 (1, 5, 10, 50, 100 ng), CP 55940 (0.1, 0.5, 1, 5, 10, 50 ng), or anandamide (0.5, 1, 5, 10, 25, 50 ng) (Fig. 1A–C, left panels, respectively) produced contralateral circling behavior with a similar inverted U-shaped dose-effect relationship. The respective calculated ED_{50}s (ng/mouse) were 0.6 ng for CP 55940, 2.6 ng for anandamide, and 3.5 ng for Win 55212-2 when the highest

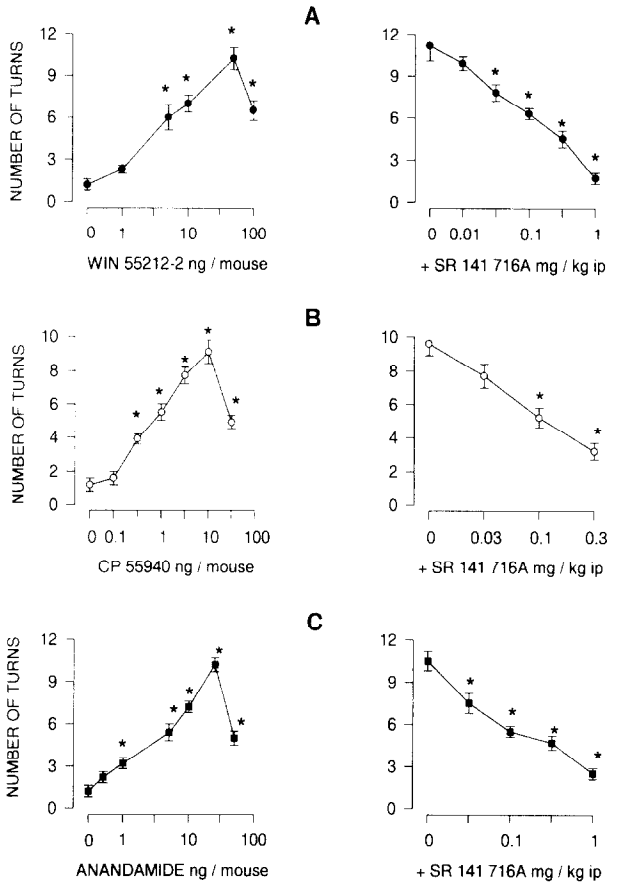

FIG. 1. Turning behavior elicited by intrastriatal injection (1 μl/right striatum/mouse) of Win 55212-2 (A), CP 55940 (B), or anandamide (C); dose-effect relationship (left panels) and antagonism by SR 141716A (right panels). For these latter studies SR 14176A was injected IP and the amounts injected per striatum were (ng/mouse): Win 55212-2, 50 ng; CP 55940, 10 ng; and anandamide, 25 ng. Data are the mean ± SEM of contralateral turns in 6 min (Dunnett's *t*-test: $^*p \leq 0.05$).

dose was not taken into account. The doses producing the maximal effect that were chosen for further studies for Win 55212-2, CP 55940, and anandamide were 50, 10, and 25 ng, respectively.

SR 141716A, given IP 30 min before test, significantly antagonized the three cannabinoid receptor agonists-induced turning (Fig. 1A–C, right panels) with similar ED_{50}s. SR 141716A dose-dependently reduced Win 55212-2-induced turning (Fig. 1A, right panel) [linear regression, $F(1, 54) = 139.7$, $p < 0.001$] with an ED_{50} of 0.13 mg/kg (0.09–0.17, 95% confidence limits). SR 141716A given PO 60 min before test (not shown) dose-dependently reduced Win 55212-2-induced turning [linear regression, $F(1, 63) = 160.96$, $p < 0.001$, and $ED_{50} = 0.24$ mg/kg].

SR 141716A dose-dependently reduced CP 55940-induced turning (Fig. 1B, right panel) [linear regression, $F(1, 36) = 60.67$, $p < 0.001$] with an $ED_{50} = 0.13$ mg/kg (0.09–0.18, 95% confidence limits).

SR 141716A dose-dependently reduced anandamide-induced turning (Fig. 1C, right panel) [linear regression, $F(1, 50) = 106.6$, $p < 0.001$] with an $ED_{50} = 0.15$ mg/kg (0.098–0.22, 95% confidence limits).

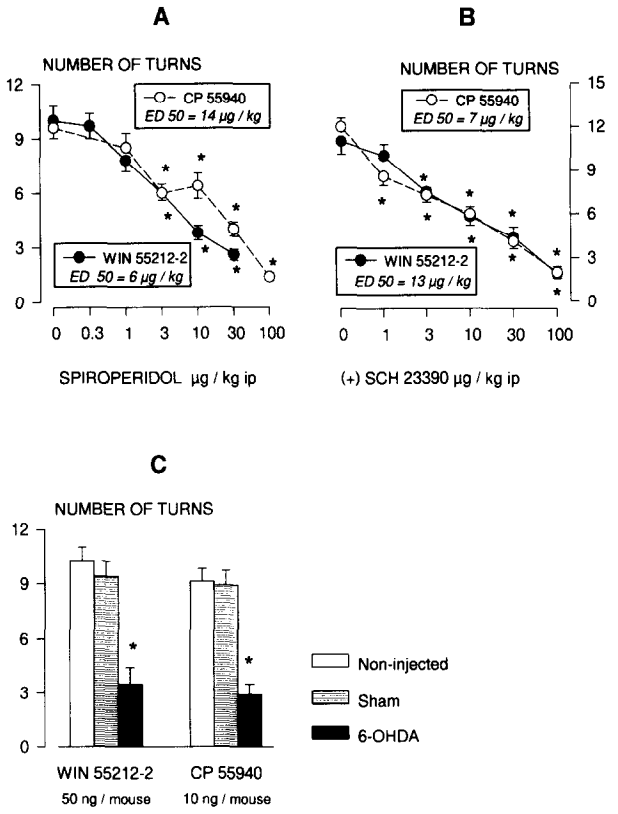

FIG. 2. Effect of spiroperidol (IP) (A), (+)-SCH 23390 (IP) (B), and 6-OHDA lesions (C) on turning behavior elicited by intrastriatal injection of Win 55212-2 (50 ng/mouse) or CP 55940 (10 ng/mouse). In lesioned mice striatal DA levels were reduced by 72 ± 5%. Data are the mean ± SEM of contralateral turns in 6 min (Dunnett's *t*-test: $*p < 0.001$).

Spiroperidol (Fig. 2A), given IP 30 min before test, dose-dependently reduced Win 55212-2-induced turning [linear regression, $F(1, 54) = 154.2$, $p < 0.001$] with an ED_{50} of 0.006 mg/kg (0.005–0.008, 95% confidence limits); likewise, this DA blocker dose-dependently reduced CP 55940-induced turning [linear regression, $F(1, 54) = 78.8$, $p < 0.001$] with an ED_{50} = 0.014 mg/kg (0.003–0.084, 95% confidence limits).

(+)-SCH 23390 (Fig. 2B), given IP 30 min before test, dose-dependently attenuated Win 55212-2- and CP 55940-induced turning [linear regression, $F(1, 54) = 145.3$, $p < 0.001$ and $F(1, 54) = 222.8$, $p < 0.001$, respectively]. The respective calculated ED_{50}s were 0.013 mg/kg (0.010–0.017, 95% confidence limits) and 0.007 mg/kg (0.005–0.010, 95% confidence limits).

In 6-OHDA-lesioned mice, the DA levels measured with HPLC were decreased by 72 ± 5% (19.3 ± 3.4 vs. 68.6 ± 3.3 ng/mg proteins). In these lesioned mice, the number of turns induced by 50 ng of Win 55212-2 was significantly decreased (63%, $p < 0.001$) vs. sham mice (3.5 ± 0.9 vs. 9.4 ± 0.8). Likewise, the number of turns induced by 10 ng of CP 55940 was significantly reduced (67%, $p < 0.001$) vs. sham mice (2.9 ± 0.6 vs. 8.9 ± 0.8) (Fig. 2C).

SR 140333, given IP 30 min before test, reduced significantly Win 55212-2-induced turning [linear regression, $F(1, 66) = 55.1$, $p < 0.01$] with 43% inhibition at 3 mg/kg, the maximal dose possible. Neither SR 140603 (3 mg/kg, IP), the (*R*)-antipode of SR 140333 with no affinity for NK_1 receptors, nor SR 48968 (1 mg/kg, IP), the NK_2 receptor antagonist altered the number of turns induced by Win 55212-2 (Table 1). In binding assays using [^{3}H]CP55940 as ligand, spiroperidol, (+)-SCH 23390, and SR 140333 (up to 10^{-5} M) were found to have no affinity for CB_1 receptors (unpublished observations).

DISCUSSION

Using a well-defined rotational model in mice (34,28), this study shows that cannabinoid receptor agonists such as Win 55212-2, CP 55940 and anandamide produce circling behavior with a rank order of potency compatible with their respective affinity for CB_1 receptors (4,6,7,20). Furthermore, all three rotational responses were blocked by SR 141716A, a selective CB_1 receptor antagonist with similar ED_{50}s. Together these findings support the CB_1 receptor mediation of these behavioral responses and reinforce the notion of a modulatory role of CB_1 receptors upon basal ganglia function. Such a notion is substantiated by the enrichment of basal ganglia structures, including the striatum in CB_1 receptors, as revealed by autoradiographic studies (13,15) and by functional biochemical studies showing that cannabinoid agonists may regulate striatal cAMP accumulation induced by various agents, including selective DA D_1 agonists (1). Furthermore, previous behavioral experiments have revealed that cannabinoid agonists produce or potentiate motor disturbances suggestive of an altered nigrostriatal function (12,24,33).

The second important aspect of this study is that 6-OHDA lesions, as well as DA D_1 and D_2 receptor blockade with spiroperidol and (+)-SCH 23390, indicate that the induction of turning behavior by cannabinoid agonists involves DA nigrostriatal systems. That both DA D_1 and D_2 receptors might be implicated in cannabinoid-induced turning is consonant with two sets of data. The intrastriatal injection of DA D_1 and D_2 agonists is known to elicit turning responses (34), and DA D_1 and D_2 receptor activation reportedly exerts synergistic effects upon behavior (32).

That DA D_1 receptor blockade suppresses cannabinoid-induced turning is reminiscent of the notion of a close anatomico-functional association between CB_1 and DA D_1 receptors (1,14). Interestingly, whereas CB_1 and DA D_1 receptors are negatively coupled to control adenylyl cyclase activity (1), activation of these same receptors similarly reverses firing sup-

TABLE 1

EFFECTS OF SR 140333, A NK_1 RECEPTOR ANTAGONIST, SR 140603, ITS *R*-ANTIPODE, AND SR 48968, A NK_2 RECEPTOR ANTAGONIST, ON WIN 55212-2 (50 ng/MOUSE)-INDUCED TURNING

Compounds	Dose (mg/kg, IP)	Number of Turns	Inhibition (%)
Saline		10.8 ± 0.5	–
SR 140333	0.3	9.7 ± 0.6	10
	1	8.2 ± 0.4*	24
	3	6.2 ± 0.4*	43
SR 140603	3	10.1 ± 0.8	6
SR 48968	1	10.0 ± 0.6	7

Data are the mean ± SEM of contralateral turns in 6 min.
*Dunnett's *t*-test, * = $p < 0.001$.

pression of nigral cells following electrical stimulation of the ipsilateral striatum (21,23).

These data, together with the contralateral direction of the rotations, could indicate that the intrastriatal application of cannabinoid agonists enhances DA transmission. Such a mechanism of action would appear surprising in light of the catalepsygenic activity of cannabinoid agonists, not only after systemic but also after intrastriatal injection (12). In this latter condition, however, the dose of cannabinoid agonists (namely, Δ^9-THC) was 40–80 μg (i.e., in a range 1000-fold higher than that used in the present study in mice). This might have some relevance in light of the often-described biphasic effect of cannabinoid agonists. As an example, it has been frequently observed that locomotor activity in rats is increased by low doses of Δ^9-THC but decreased by large doses (5,12). In fact, the notion that cannabinoid-induced turning after intrastriatal injection could be associated with enhanced DA function is reminiscent of converging biochemical and behavioral observations.

Ng Cheong-Ton et al. (25) reported that Δ^9-THC may facilitate in vivo striatal DA release as revealed by electrochemical and microdialysis techniques. Similar data have been obtained at the level of the mesolimbic and mesocortical DA systems (2,3). Furthermore, Sakurai-Yamashita et al. (30) found that, given systematically, Δ^9-THC induced amphetamine-like (ipsiversive) circling behavior in rats with unilateral nigrostriatal denervation. This rotational behavior was abolished by haloperidol. Finally, Δ^9-THC reportedly augments electrical brain stimulation, an effect generally associated with the activation of DA mesotelencephalic reward systems (10).

However, binding experiments dealing with the fine neuronal localization of CB_1 receptors in the rat basal ganglia clearly indicate—in agreement with in situ hybridization studies—that these receptors are not localized on DA nigrostriatal cell bodies or terminals (15,18). This implies that the facilitatory consequences of CB_1 receptor activation upon nigrostriatal DA function involve indirect, local, and/or distal neuronal circuits. Although some DA release studies might favor the role of local circuitery (3), the role of distal, polysynaptic circuits in increasing DA synthesis and/or terminal release would be consonant with the abundance of CB_1 receptors on striato-pallidal and striato-nigral neurons (15,18). Finally, that SR 140333, an antagonist of NK_1 receptor with no affinity for calcium channels (8), antagonized the rotational behavior obtained after Win 55212-2 is consonant with the notion that substance P is one of the main neuropeptidergic component of these striatal neurons (19).

In summary, the present findings appear to further support the nigrostriatal impact of cannabinoid agonists, and these agents may act to facilitate DA transmission. In addition, this study confirms that SR 141716A penetrates the brain after intraperitoneal or oral administration and could be a valuable tool for studying the physiological roles of CB_1 receptors.

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