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Cannabinoid and dopamine interaction in rodent brain: effects on locomotor activity

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Abstract

We investigated interactions between cannabinoid and dopamine receptor systems in ICR mice. Mice were treated with the cannabinoid agonist levonantradol, the D_1 dopamine agonist 6-Br-APB, or the D_2 dopamine agonist quinelorane, or with combinations of these drugs. In addition, the D_1 antagonist SCH23390 was administered both alone and in combination with levonantradol. Two tests were used to evaluate changes in motor function: the immobility (ring stand) test and the catalepsy (bar) test. Levonantradol increased immobility and catalepsy in a dose-dependant manner. Both the D_2 agonist quinelorane and the D_1 agonist 6-Br-APB were able to attenuate the motor dysfunction caused by levonantradol. Administration of the D_1 antagonist SCH23390 enhanced the effects of levonantradol, producing a leftward shift of the log dose–response curve. These results differ from the augmentation by D_2 agonists of the hypoactivity induced by levonantradol in non-human primates [Meschler JP, Clarkson FA, Mathew PJ, Howlett AC, Madras BK. D_2, but not D_1 dopamine receptor agonists potentiate cannabinoid-induced sedation in nonhuman primates. J Pharmacol Exp Ther 2000;292:952–9], suggesting that conclusions about the interactions between the dopamine and cannabinoid receptor motor systems in rodents may not extend to primates.

Keywords: Cannabinoid receptors; D_1 dopamine receptors; D_2 dopamine receptors; Basal ganglia; Motor dysfunction

CB_1 cannabinoid receptors are found throughout the brain in locations including the hippocampus, cerebellum, and the basal ganglia [9,15,16]. The CB_1 cannabinoid receptor is found most densely in the nuclei of the basal ganglia especially in the striatum [8,28,32] where it is thought to modulate motor activity [10]. The striatum also contains a high density of D_1 and D_2 dopamine receptors [13,33] that stimulate motor activity through the direct and indirect pathways, respectively, in the basal ganglia [1,26]. Herkenham et al. [8] found that cannabinoid receptors as well as D_1 and D_2 receptors were depleted upon lesion of the body of the striatum with ibotenic acid but not by lesion of the striatal dopaminergic input neurons with 6-OH-DOPA. This suggests that these receptors may be co-localized on the same populations of intrastriatal neurons but not on the presynaptic dopaminergic terminals [8]. Co-localization of dopamine and cannabinoid receptors has been suggested by signal transduction studies in rat striatal slices [3].

The dopaminergic antagonist haloperidol has been documented to produce catalepsy when administered to rodents [25,31]. Cannabinoid agonists produce an immobility and catalepsy as well [4,23,27], although the cannabinoid-induced catalepsy appears to be accompanied by a hypersensitivity to external stimuli that can disrupt the cataleptic behavior [12]. Early studies noted a synergism between the cannabinoid agonists and D_2 antagonists to produce a cataleptic response in rodents. In reserpinized rats, deficient of dopamine, the cataleptic effects of the cannabinoid agonist Δ^9-tetrahydrocannabinol were greatly enhanced [23]. Pretreatment of rats with Δ^9-tetrahydrocannabinol potentiated the hypokinesia produced by the D_2 dopamine

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receptor antagonist haloperidol [2]. The D_2 receptor antagonist raclopride acted synergistically with the cannabinoid agonist CP55940 to produce catalepsy in rats [2].

In this study, we investigated the interactions between the D_1, D_2 and cannabinoid receptor systems on catalepsy and immobility in mice. We show that both a D_2 and a D_1 agonist could attenuate the behavioral effects of the cannabinoid agonist levonantradol. SCH23390, a D_1 antagonist, increased the apparent ED_{50} of levonantradol when co-administered at a dose of SCH23390 that had no behavioral effects when administered alone. Thus, both D_1 as well as D_2 receptors act to modulate cannabinoid-induced motor dysfunction.

1. Methods

1.1. Drugs

Quinelorane was a gift from Eli Lilly, (Indianapolis, IN) and levonantradol was a gift from Pfizer (Groton, CT). 6-Br-APB (3-allyl-6-bromo-7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin) and SCH23390 were purchased from RBI (Natick, MA). All drugs were administered intraperitoneally 30 min before testing time. Drugs were administered in a vehicle of 90% saline, 5% ethanol and 5% Tween-80.

1.2. Behavioral tests

Sexually mature male ICR mice weighing between 25 and 35 g were purchased from Harlan (Indianapolis, IN). The animals were housed in a temperature-controlled environment with lights on at 6:00 A.M. and off at 6:00 P.M. Mice were tested between 8:00 A.M. and 11:00 A.M. The ring stand immobility test was performed according to Pertwee [27]. Briefly, a ring (8 cm in diameter) was placed on a ring stand 35 cm above the counter top. The mouse was positioned with front and rear paws on the ring, and the amount of time the animal remained immobile was recorded for a 5-min testing period. Immobility was counted if the animal was entirely immobile including lack of whisker movement; however, respiratory movements or sagging from the ring stand was not counted as movement. The test was generally ended at 5 min and the fraction of time the animal was immobile was recorded as the immobility index. If the animal escaped five times prior to the end of the 5-min test, the test was terminated and the time the animal remained immobile was divided by the total time of the test to determine the immobility index. However, if the animal escaped more than five times within the first 2.5 min, the data from that subject was not recorded.

The bar test, a measure of catalepsy, was adapted from Moss et al. [23]. A bar (0.5 cm in diameter) was horizontally positioned 6 cm above the counter top. The animal's front paws were placed on the bar and the hind paws were rested on the counter. Time was recorded until the mouse placed both front paws onto the counter top. The maximum allowable time was 5 min, at which time the test was ended and a score of 300 s was recorded.

Animals were also videotaped in an open field for a 5-min session and rated by an observer blind to the experimental conditions. Behaviors that were recorded included the number of rearing and grooming episodes, the fraction of time immobile, and whether or not rigid joint locomotion was observed.

1.3. Data analysis

Each point represents mean values from three to six animals, and the error bars represent the S.E.M. For log dose–response curves having more than four points on the curve, parameters for a sigmoidal curve were generated by non-linear regression analysis (Graph Pad's Prism). Other figures show point-to-point connection of the data points without analysis. Statistical analyses were performed by ANOVA and Dunnett's test was used to compare treatment groups with control groups (Graph Pad's Prism).

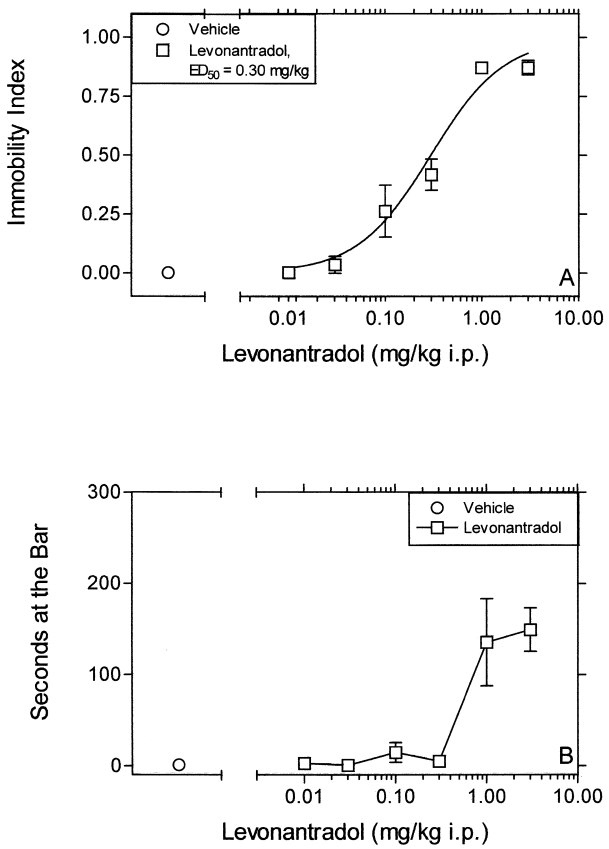
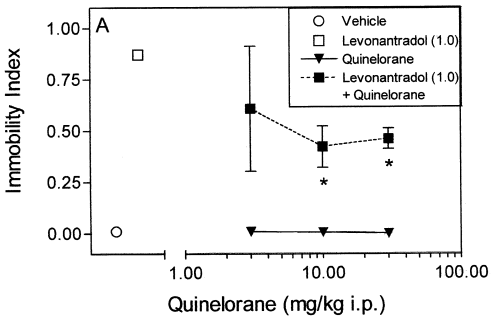


Fig. 1. Log dose–response relationships of levonantradol to produce (A) immobility and (B) catalepsy. Mice were administered the indicated doses of levonantradol intraperitoneally, and after 30 min, were tested in (A) the ring stand test, and (B) the bar test, as described in the text.

2. Results

Previous experiments performed at Pfizer Central Research demonstrated that the cannabinoid agonist, levonantradol, elicited analgesia and hypoactivity in rodents and analgesia and ataxia in dogs [17]. Levonantradol injected intravenous also elicits a tetrad of behavioral changes, including immobility (ED_{50} of 0.085 mg/kg), analgesia (ED_{50} of 0.01 mg/kg), decreased spontaneous activity (ED_{50} of 0.004 mg/kg), and decreased rectal temperature (effects classically known to be elicited by cannabinoid receptor agonists) in ICR mice [14]. Fig. 1 shows that levonantradol administered intraperitoneally produced an increase in the immobility index in the ring stand test (Fig. 1A) and an increase in catalepsy in the bar test (Fig. 1B) in a dose-dependent manner. The ED_{50} was 0.3 mg/kg for immobility, and appeared to be somewhat greater for catalepsy.

We next wanted to define the interactions between the CB_1 receptor and D_2 receptor-mediated responses. Quinelorane has been shown to be a highly potent and selective D_2 receptor agonist [6]. Quinelorane, administered to mice at doses of 0.03 to 30 mg/kg ip, did not cause any significant changes in motor activity as compared to vehicle



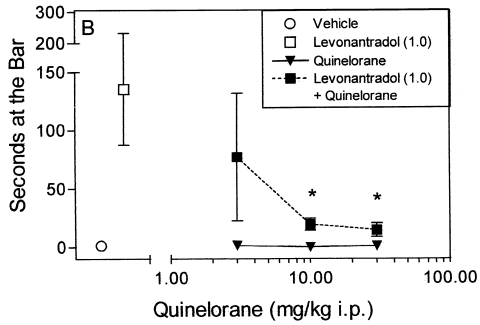
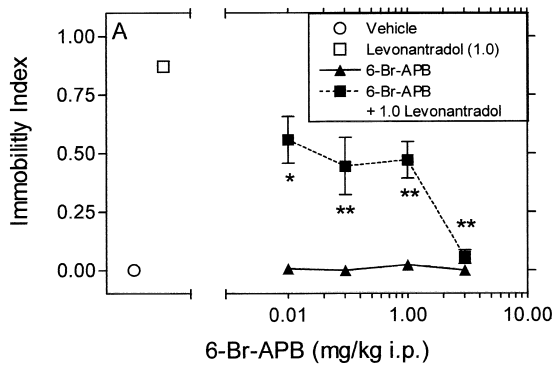


Fig. 2. Effects of the D_2 agonist, quinelorane, to attenuate the behavioral effects of an ED_{90} dose of levonantradol (1.0 mg/kg) in (A) the ring stand test, and (B) the bar test. Levonantradol (1 mg/kg) and quinelorane (at the indicated doses) were co-administered, and mice were tested 30 min later as described in the text. Statistically significant difference from levonantradol alone is denoted with an * ($P<.05$).



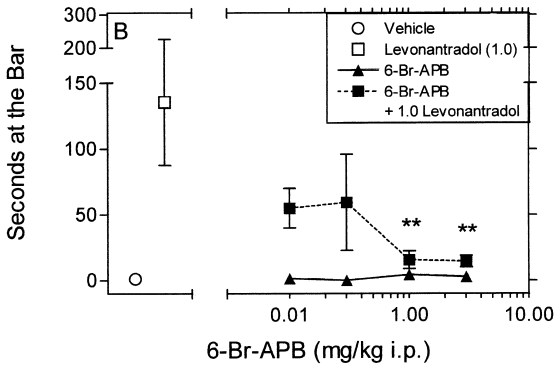


Fig. 3. Effects of the D_1 agonist, 6-Br-APB, to reverse levonantradol-induced motor behaviors in (A) the ring stand test, and (B) the bar test. Levonantradol (1 mg/kg) and 6-Br-APB (at the indicated doses) were co-administered, and mice were tested 30 min later as described in the text. Statistically significant differences from levonantradol alone are denoted by * ($P<.05$) or ** ($P<.01$).

(data not shown). Quinelorane at increasing doses appeared to reverse the effects of a submaximal (0.1 mg/kg ip) dose of levonantradol (data not shown); however, none of the points reached statistical significance. A dose of levonantradol at or above the ED_{50} (1.0 mg/kg) produced a robust increase in the immobility index and catalepsy in the ring stand and bar tests, respectively (Fig. 1A and B). Quinelorane was able to significantly and dose-dependently attenuate immobility and catalepsy produced by this dose of levonantradol (Fig. 2). At the highest dose tested (30 mg/kg), quinelorane could not completely reverse the effects of levonantradol on the immobility index (Fig. 2A), whereas this dose completely reversed levonantradol-induced catalepsy (Fig. 2B).

In order to determine the interactions of a D_1 agonist with levonantradol-induced immobility and catalepsy, we used the D_1 agonist, 6-Br-APB [24], which had no effect on these parameters when administered alone (Fig. 3). 6-Br-APB reversed levonantradol-induced immobility and catalepsy in a dose-dependent manner (Fig. 3A and B). 6-Br-APB was able to completely reverse both levonantradol-induced immobility and catalepsy at the highest dose of 6-Br-APB tested (3 mg/kg ip). We next wanted to determine the nature

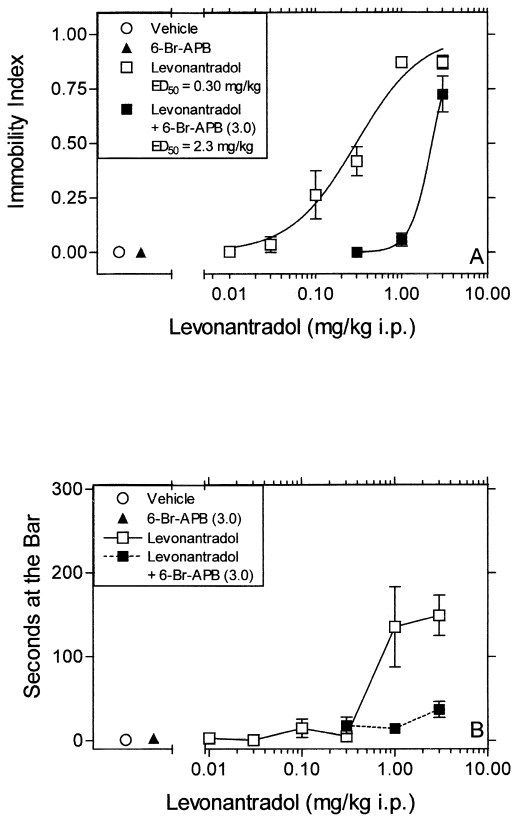


Fig. 4. Apparent physiologically competitive interaction between the D_1 agonist 6-Br-APB and levonantradol in (A) the ring stand test, and (B) the bar test. Levonantradol (at the indicated doses) and 6-Br-APB (3 mg/kg) were co-administered, and mice were tested 30 min later as described in the text. The curves in (A) could be compared, yielding ED_{50} values (with 95% confidence intervals) of 0.30 (0.20 to 0.44) mg/kg in the absence, and 2.3 (1.9 to 2.7) mg/kg in the presence of 3 mg/kg 6-Br-APB.

of the antagonism of levonantradol-induced catalepsy and immobility by 6-Br-APB (Fig. 4). In the ring stand immobility test, 3.0 mg/kg 6-Br-APB significantly shifted the levonantradol log dose–response curve to the right, increasing the ED_{50} approximately 10-fold. The observation that the antagonism was surmountable by increasing stimulation of the CB_1 receptor suggests that this interaction was physiologically competitive. This characterization could not be confirmed in the bar test, in which 3 mg/kg 6-Br-APB completely reversed the catalepsy induced by the highest dose of levonantradol (3.0 mg/kg ip). Higher doses of levonantradol were not attempted because we had previously observed convulsions in rats receiving 10 mg/kg ip levonantradol (A.C. Howlett, unpublished observations).

To further characterize the D_1 interactions with cannabinoid-induced behaviors, we determined the effects of co-administering levonantradol with a D_1 antagonist, SCH23390 [11]. SCH23390 administered alone did not produce significant immobility or catalepsy at the dose tested (0.3 mg/kg ip) (Fig. 5). When SCH23390 (0.3 mg/kg ip) was combined with increasing doses of levonantradol, the ED_{50} in the ring stand test for immobility was shifted only about 2-fold. However, the Hill coefficient, indicative of the slope of the curve, increased 2-fold, suggesting that the interaction may be described as increasing in apparent cooperativity (Fig. 5A). In the bar test for catalepsy, SCH23390 (0.3 mg/kg ip) appeared to shift the log dose–response relationship of levonantradol to the left. However, the interaction is complex because SCH23390 also appeared to increase the maximum response to levonantradol (Fig. 5B). In both tests of motor dysfunction, the D_1 antagonist can be said to "augment" the response to levonantradol.

The immobility and catalepsy produced by levonantradol and the attenuation of these effects by a D_2 or a D_1 agonist were noted in a behavioral rating scale (data not shown). Videotape analysis of the animals (rated by an observer blind to the experimental conditions) demonstrated inactivity in levonantradol-treated mice and an attenuation of this effect after D_1 or D_2 agonist treatment. No significant changes occurred in grooming or rearing behavior except in the mice treated with high doses of levonantradol. Those mice failed to exhibit movement over 90% or more of the

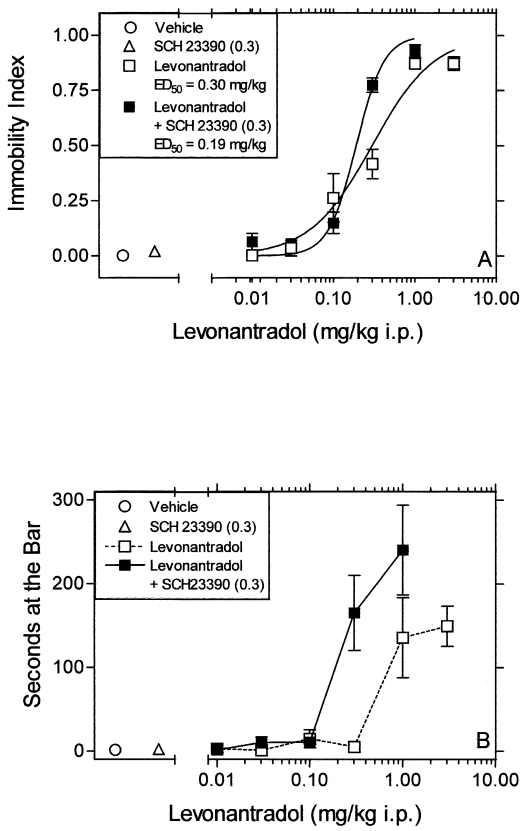


Fig. 5. Effects of the D_1 antagonist SCH23390 to augment the behavioral effects of levonantradol in (A) the ring stand test, and (B) the bar test. Levonantradol (at the indicated doses) and SCH23390 (0.3 mg/kg ip) were co-administered, and mice were tested 30 min later as described in the text. The curves in (A) exhibited ED_{50} values (with 95% confidence intervals) of 0.30 (0.20–0.44) mg/kg in the absence and 0.19 (0.16–0.22) mg/kg in the presence of 0.3 mg/kg SCH23390. Hill coefficients of the curves were (with 95% confidence intervals) 1.14 (0.68–1.6) in the absence and 2.55 (1.9–3.2) in the presence of 0.3 mg/kg SCH23390.

testing period, and therefore, grooming and rearing behaviors were suppressed. Rigid joint locomotion occurred in some subjects treated with levonantradol but this behavior occurred too inconsistently to draw any conclusions using this testing parameter.

3. Discussion

Two important conclusions about the interactions between cannabinoid and dopamine receptor regulation of motor function can be drawn from these data. First, because a D_2 agonist could partially reverse the effects of the cannabinoid agonist levonantradol, these two receptor systems appear to interact in the rodent by exerting opposing influences in regulating motor activity. Consistent with this finding, the cannabinoid agonist CP55940 was reported to potentiate the catalepsy response to the D_2 antagonist raclopride [2]. Second, our finding that a D_1 agonist completely reversed the effects of the cannabinoid agonist in both the catalepsy and immobility tests suggests that the D_1 and cannabinoid receptor systems interact in an opposing manner in rodent brain. One limitation in the interpretation is that the tests for immobility and catalepsy do not ascertain motor hyperactivation (i.e., no score can be reduced below 0). Hyperactivity elicited by dopaminergic agonists may counteract the hypoactivity of cannabinoid agonists without the necessity of the two opposite effects resulting from interactions at the same neurons or even the same pathways. We addressed this in two ways. First, a D_1 antagonist augmented the response to levonantradol, suggesting that the endogenous activation of a D_1 receptor exerts a restraining influence on the levonantradol response. Second, we videotaped these animals in an open field for the 5-min period just prior to the tests for catalepsy and immobility, and quantitated their scores for spontaneous activity and vertical rearing. Quinelorane and 6-Br-APB failed to produce significant changes in the parameters tested at the dose ranges that reversed the effects of levonantradol.

Taken together, these data suggest that there is a reciprocal modulation of motor activity between the dopamine and cannabinoid receptor systems. The exact nature of the interaction can only be speculated from the present results. One mechanism might be that the cannabinoid and dopamine receptors responsible for the effects of these respective drugs coexist on the same neurons, and the interaction is at the signal transduction level. We have investigated this cellular interaction at the level of adenylyl cyclase in striatal membrane vesicle preparations, and found that D_1 agonists could stimulate adenylyl cyclase and cannabinoid agonists could inhibit this stimulation (Meschler and Howlett, submitted). D_2 agonists exhibited the same inhibition of adenylyl cyclase as cannabinoid agonists. Thus, biochemically, the D_1 and D_2 effects oppose each other, and cannot account for the behavioral effects that both dopamine receptor subtypes have in common to oppose cannabinoid effects. It is possible that alternative signal transduction mechanisms may regulate the responses, or difference neuronal populations may be involved.

The interactions between cannabinoid and dopaminergic systems may occur at the synaptic level, in which case the anatomical location may be within any of the specific basal ganglia nuclei including the striatum, the globus pallidus, and the substantia nigra pars reticulata [7,20,22,30]. Intra-striatal injections of cannabinoid agonists produced catalepsy that could be blocked by the release of dopamine in response to amphetamine [7]. Depletion of dopaminergic input into the striatum with reserpine produced a hypersensitivity to the cataleptic effects of microinjection of the cannabinoid agonist levonantradol into the striatum [22]. Unilateral microinjection of the cannabinoid agonist CP55940 into the globus pallidus produced ipsilateral turning behavior that is consistent with inhibition of motor output by disinhibition of the substantia nigra pars reticulata [30]. Furthermore, the turning behavior could be attenuated by the D_2 agonist quinpirole, suggesting reciprocal regulation in the globus pallidus [30]. Unilateral microinjection of CP55940 into the subthalamic nucleus resulted in ipsilateral turning, consistent with stimulation of substantia nigra pars reticulata neurons and subsequent depression of motor function [20]. WIN55212-2 administered intraperitoneally increased the spontaneous firing rate of neurons in the substantia nigra pars reticulata [20], thus decreasing the motor output from the basal ganglia.

In contrast to the evidence of inhibition of motor activity by cannabinoid and opposition by dopamine receptors, there is also evidence suggesting that the cannabinoid receptor system stimulates motor activity and is antagonized by dopamine receptor systems. Intrastriatal microinjection of the cannabinoid agonist CP55940 induced contralateral turning, consistent with an increase in motor stimulation from the basal ganglia [29]. This stimulation of motor activity by CP55940 could be blocked by co-injection of the D_2 dopamine receptor agonist quinpirole [29]. Microinjection of the D_1 agonist SKF82958 into the striatum inhibited movement and this inhibition was antagonized by co-injection of CP55940 [29]. In the globus pallidus, the cannabinoid agonist WIN55212-2 antagonized striatal inhibition of globus pallidus firing [21], which might be expected to result in an increased pallidal release of GABA at the subthalamic nucleus, suppression of subthalamic and substantia nigra pars reticulata activity, and a subsequent increase in motor activity. Because contralateral turning in response to microinjection of cannabinoid agonists into the globus pallidus was not observed, this latter scenario based upon suppression of the striatopallidal pathway is probably not a dominant influence on the motor behavior. Unilateral microinjection of the cannabinoid agonist CP55940 into the substantia nigra pars reticulata produced contralateral turns consistent with sti-

mulation of motor activity [30]. Lastly, microinjection of the D_2 agonist quinpirole into the substantia nigra pars reticulata produced ipsilateral turns consistent with an inhibition of motor activity [30]. The response to the D_2 agonist could be reversed by co-injection with the cannabinoid agonist CP55940 [30].

These reports suggest that cannabinoid receptors in different nuclei within the basal ganglia nuclei and under different situations (i.e. evoked stimulation vs. spontaneous activity) may elicit distinctly opposite influences on motor behavior. Furthermore, it appears that the cannabinoid receptors in different nuclei within the basal ganglia may be modulated by the dopamine receptor systems differentially. Our study demonstrates that the dominant effect of a cannabinoid agonist in the intact rodent is to inhibit motor function as evidenced by hypokinesia. Furthermore, the overall effect of either D_1 or D_2 dopamine agonists is to reverse this hypokinesia produced by cannabinoid agonists. One might presume therefore that the major influence of cannabinoid inhibition of motor activity resides at the level of the globus pallidus, which could be the site of D_2 receptor partial suppression. A second site of cannabinoid-induced immobility would be at the level of the substantia nigra pars reticulata, where cannabinoid agonists could counteract the effects of D_1 agonists to activate motor activity via the striatonigral pathway.

Cannabinoid agonists have been studied for their therapeutic utility in motor disorders associated with basal ganglial dysfunction [5]. Treatment of Tourette's syndrome with marijuana has been investigated [5]. We must warn that extrapolation to the clinical setting of the conclusions that agonist stimulation of D_1 and D_2 receptors oppose the motor disruptive effects of the cannabinoid agonists in rodent brain is not warranted. In contrast to the effects observed in rodents, levonantradol failed to produce catalepsy in non-human primates [18] as did the dopaminergic antagonist haloperidol [18]. The behavioral response to levonantradol in primates was to reduce general and locomotor activity and to increase ptosis [19]. We found that the D_2 agonists quinelorane (used in the present study) and the clinically useful D_2 agonist pergolide significantly augmented the suppression of general and locomotor activity induced by levonantradol [19]. In that same protocol, the D_1 agonist SKF81297 had no effect on the response to levonantradol [19]. These species differences point to the complexity of the interactions within the basal ganglia and suggest that pathways that dominate motor behavior in rodents may not exert the major influence on motor behaviors in primates.

Acknowledgments

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