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Dihydrexidine, a Full D_1 Dopamine Receptor Agonist, Induces Rotational Asymmetry in Hemiparkinsonian Monkeys

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JOHNSON, B. J., V. PEACOCK AND J. S. SCHNEIDER. *Dihydrexidine, a full D_1 dopamine receptor agonist, induces rotational asymmetry in hemiparkinsonian monkeys.* PHARMACOL BIOCHEM BEHAV **51**(4) 617–622, 1995.—Dihydrexidine (*trans*-10,11-dihydroxy5,6,6a,7,8,12b hexanhyydrobenso-[*a*]phenanthridine) is a full dopamine D_1 agonist. In rhesus macaque monkeys rendered hemiparkinsonian by unilateral intracarotid infusions of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), dihydrexidine (0.15–0.9 mg/kg) elicited dose-dependent contralateral rotation. The effects of dihydrexidine were blocked by pretreatment with the D_1 antagonist SCH 23390 (0.03 mg/kg), but not by the D_2 antagonist raclopride (0.025 mg/kg). These results suggest a functional role for D_1 receptors in stimulating motor behavior in a primate model of Parkinson's disease.

Parkinson's disease Dihydrexidine D_1 agonist Macaque monkey Motor behavior

PARKINSON'S disease is progressive neurological disorder primarily characterized by a loss of dopamine neurons of the substantia nigra pars compacta and a dramatic decrease in striatal tissue dopamine levels (10). At present, the most common treatments of Parkinson's disease include dopamine replacement therapy (levodopa in combination with a peripheral aromatic amino acid decarboxylase inhibitor) and the use of directly acting dopamine agonists that stimulate primarily the D_2 subfamily of dopamine receptors (i.e., bromocriptine), or both D_1 and D_2 receptors (i.e., pergolide). Focus has centered on the dopamine D_2 receptor in the treatment of Parkinson's disease at least in part due to the apparent lack of efficacy of dopamine D_1 receptor agonists in relieving symptoms in patients and in primate models of Parkinson's disease (30).

Until recently, the most commonly used D_1 agonist has been the benzazepine, SKF 38393. SKF 38393 does not seem to have antiparkinsonian effects either in MPTP-treated monkeys (2,3) or in humans with Parkinson's disease (1,6). Indeed, SKF 38393 appears to diminish the antiparkinsonian effect of the D_2 agonist quinpirole (29). SKF 38393 is only a partial D_1 agonist (relative to dopamine) in terms of stimulating adenylate cyclase activity and may even act as a D_1 antagonist in primates (19,20).

Recently, several full (high-potency) agonists selective for the dopamine D_1 receptor have been developed. Early studies of the selective full D_1 agonists A-77636 and SKF 81297 indicated that they relieved parkinsonian symptoms such as poverty of movement and postural abnormalities in monkeys treated with the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (13,28). Dihydrexidine (*trans*-10,11-dihydroxy5,6,6a,7,8,12b hexanhydrobenso-[*a*]phenanthridine), another novel, selective, high-potency dopamine D_1 receptor agonist (15,17), has also been shown to increase blink rate and reduce parkinsonian rating scores in African green monkeys made parkinsonian with MPTP. To further characterize the potential antiparkinsonian effects of dihydrexidine we administered the agent at several doses in monkeys rendered hemiparkinsonian by MPTP. To investigate the functional importance of the D_1 receptor in the effects of dihydrexidine, we also administered the drug in combination with a D_1 (SCH 23390) or D_2 (raclopride) receptor antagonist.

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METHOD

The subjects were five adult male rhesus macaque monkeys (*Macaca mulatta*, weight range 8.9–10.6 kg, age 7–8 years). Animals were allowed ad lib access to food and water and were housed in individual cages in a room with a 12L : 12D cycle. Animals received unilateral retrograde infusions of MPTP HCl (0.4 mg/kg as free base) into the internal carotid artery while the external carotid and superior thyroid arteries were transiently ligated. MPTP was infused over approximately 20 min while animals were under sodium pentobarbital anesthesia. Four animals received a second intracarotid MPTP infusion (0.4 mg/kg) approximately 1 year following the initial infusions. Animals were tested approximately 3 years after induction of the lesion. These animals were used previously in other studies (23).

Drugs used were dihydrexidine (0.15, 0.3, 0.6, 0.9 mg/kg; Interneuron Pharmaceuticals, Inc.); quinpirole (LY 171555; 0.1 mg/kg; Research Biochemicals, Inc.); SCH 23390 (0.03 mg/kg; Research Biochemicals, Inc.); and raclopride (0.025 mg/kg, Astra Pharmaceuticals). All drugs were dissolved in sterile saline and administered by IM injection. Each monkey received all four doses of dihydrexidine and the combination of 0.6 mg/kg of dihydrexidine + SCH 23390 and 0.6 mg/kg dihydrexidine + raclopride in a pseudorandomized (balanced for sequence) manner. Additionally, some subjects received quinpirole or the combination of raclopride + quinpirole. Test sessions were separated by at least 5 days.

Subjects were transported in their home cage to a familiar testing room. Approximately 30 min later subjects were injected with saline and videotaped for 30 min to record baseline behavior. At the end of this 30-min baseline period, dihydrexidine, quinpirole, or one of the antagonists was injected and videotaping continued for another 90 min. If SCH 23390 was used in a given test session, dihydrexidine was administered 10 min following the SCH 23390 injection. In the test sessions in which raclopride was used, dihydrexidine was administered 30 min following the raclopride injection. These time points were determined based on the time course of the effects of the drugs used; dihydrexidine has an onset of within 5 min; SCH 23390 within 10–15 min, and raclopride within 30 min. For purposes of data illustration, time 0 was defined to be the time of dihydrexidine administration.

Videotapes were later analyzed to obtain counts of full 360° ipsilateral and contralateral (to lesion) rotations per 5 min. The extents of dyskinesia and dystonia were also scored for the same time periods. Dyskinesia (random, chaotic alternating flexion and extension of the limbs) and dystonia (repetitive, abnormal posturing caused by extension or flexion of the limbs) were rated on a five-point scale: 0 = absent; 1 = mild and occasional; 2 = moderate and intermittent; 3 = frequent and marked; 4 = continuous.

Drug-induced rotation data were subjected to repeated-measures analyses of variance (ANOVA). When significant drug effects were found, Dunnett's procedure was used to determine which time points differed from baseline. Bonferroni's test was used for planned comparisons of dose and drug combinations. Significance differences were defined to be $p < 0.05$.

RESULTS

Dihydrexidine induced contralateral rotation in a dose-dependent manner (Fig. 1). At a dose of 0.15 mg/kg, no significant rotation was observed. At 0.3 mg/kg, significant contralateral rotation was observed at 5 min ($p < 0.01$) and 10

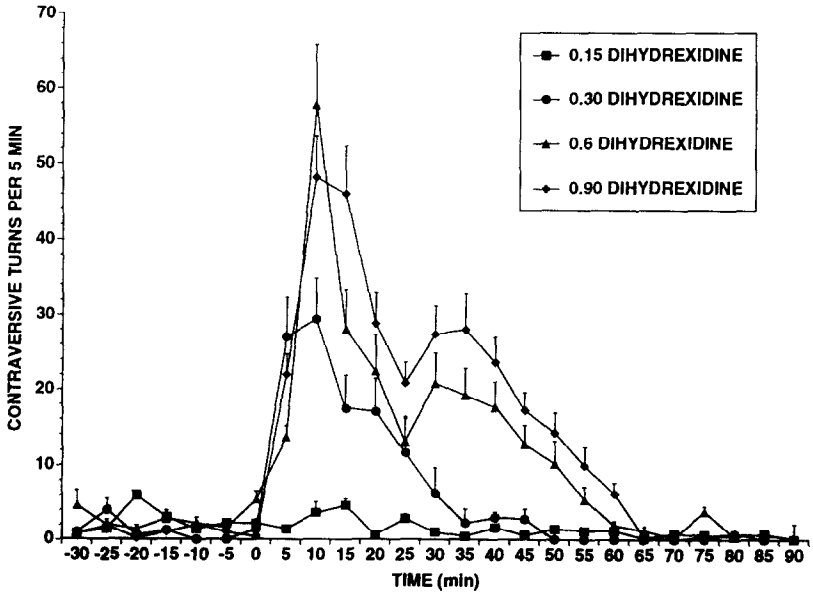

FIG. 1. Effect of dihydrexidine on mean ± SE number of contralateral rotations completed per 5-min period. Data are averages obtained from five monkeys. Saline was administered at time −30 min and dihydrexidine was administered at time 0 min. Dihydrexidine caused a dose-dependent increase in contralateral rotations. At the time of peak effect (10 min), rotations induced by each dose differed significantly from each other, with the exceptions of 0.6 and 0.9 mg/kg, which did not differ from each other, based on Bonferroni's test ($p < 0.05$) and ANOVA.

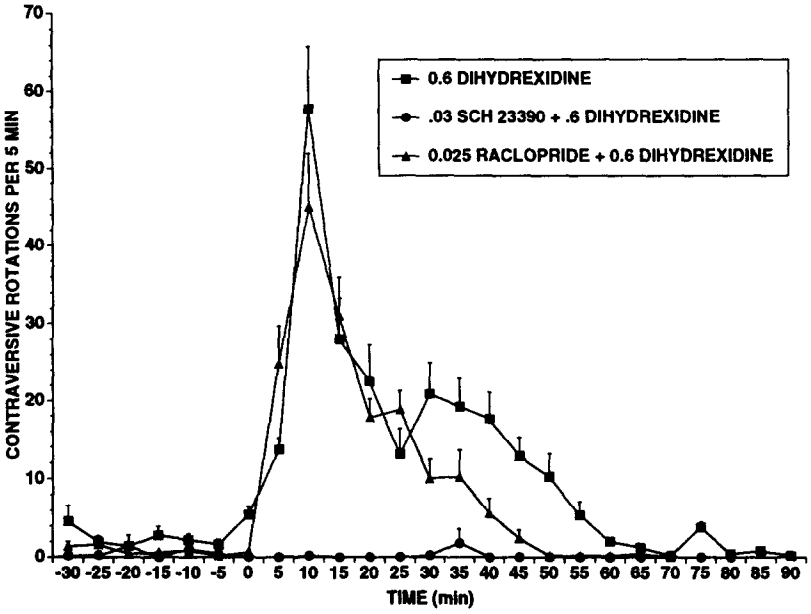

FIG. 2. Effect of dopamine receptor antagonists on mean ± SE dihydrexidine-induced contralateral rotations completed per 5-min period. Data are obtained from five monkeys. Saline was administered at time −30 min, raclopride (D_2 antagonist) at time −20 min, SCH 23390 (D_1 antagonist) at time −10 min, and dihydrexidine at time 0 min. Raclopride had no effect on dihydrexidine-induced rotational asymmetry, whereas SCH 23390 completely blocked dihydrexidine-induced rotations. At the time of peak effect (10 min), dihydrexidine-induced and dihydrexidine + SCH 23390-induced rotations significantly differed from rotations induced by dihydrexidine + SCH 23390 based on Bonferroni's test ($p < 0.05$) and ANOVA.

min ($p < 0.01$) postinjection. The 0.6-mg/kg dose of dihydrexidine appeared to be the peak effective dose and induced contralateral rotation at 5 min ($p < 0.01$), 10 min ($p < 0.01$), and 15 min ($p < 0.05$) postinjection. Dihydrexidine also induced significant contralateral rotation when administered at a dose of 0.9 mg/kg with a profile similar to that observed with the 0.6-mg/kg dose, but with a slightly longer-acting effect. In general, peak drug effect was seen approximately 10 min following drug administration. Saline injections caused no contralateral rotational behavior. None of the dihydrexidine doses induced ipsilateral rotation, dyskinesia, or dystonia.

The D_1 antagonist SCH 23390 effectively blocked contralateral rotation induced by an optimal dose of 0.6 mg/kg dihydrexidine (Fig. 2). The number of contralateral rotations induced by administration of 0.6 mg/kg dihydrexidine alone differed significantly from the number of contralateral rotations induced by the combined administration of 0.03 mg/kg SCH 23390 + 0.6 mg/kg dihydrexidine ($p < 0.001$). In contrast, the D_2 antagonist raclopride had no effect on contralateral rotation induced by 0.6 mg/kg dihydrexidine. The number of contralateral rotations induced by administration of 0.6 mg/kg dihydrexidine alone did not differ from the number of contralateral rotations induced by combined administration of 0.025 mg/kg raclopride + 0.6 mg/kg dihydrexidine. The rotational profile induced by SCH 23390 + dihydrexidine differed from the rotational profile induced by raclopride + dihydrexidine ($p < 0.001$). Following administration of SCH 23390 or raclopride, animals generally sat quietly. Animals remained alert and exhibited occasional spontaneous movements. Neither of the combined dihydrexidine + antagonist treatments induced ipsilateral rotation, dystonia, or dyskinesia.

Quinpirole (0.10 mg/kg) induced contralateral rotation ($p < 0.0001$) with a longer-acting effect than dihydrexidine (Fig. 3). Unlike dihydrexidine, quinpirole produced significant amounts of limb dyskineisa and dystonia, which in part interfered with the rotational response stimulated by this D_2 agonist (mean peak dyskinesia rating = 3.0 ± 0; mean peak dystonia rating = 0.5). The D_2 antagonist raclopride effectively blocked the effect of quinpirole. The number of contralateral rotations induced by administration of 0.1 mg/kg quinpirole alone differed significantly from the number of contralateral rotations induced by the combined administration of 0.025 mg/kg raclopride + 0.1 mg/kg quinpirole ($p < 0.001$).

DISCUSSION

These data suggest that D_1 dopamine receptors, when activated by dihydrexidine, stimulate motor behavior in a primate model of hemiparkinsonism. Dihydrexidine induced dose-dependent contralateral rotation in hemiparkinsonian monkeys that was blocked by pretreatment with the D_1 antagonist SCH 23390 but not by pretreatment with the D_2 receptor antagonist raclopride. These findings are consistent with earlier reports on the effects of dihydrexidine. It was previously reported that dihydrexidine increased blink rate and improved function based on behavioral ratings in African green monkeys treated with MPTP (8,24). These positive effects of dihydrexidine were blocked by the D_1 antagonist SCH 23390, but

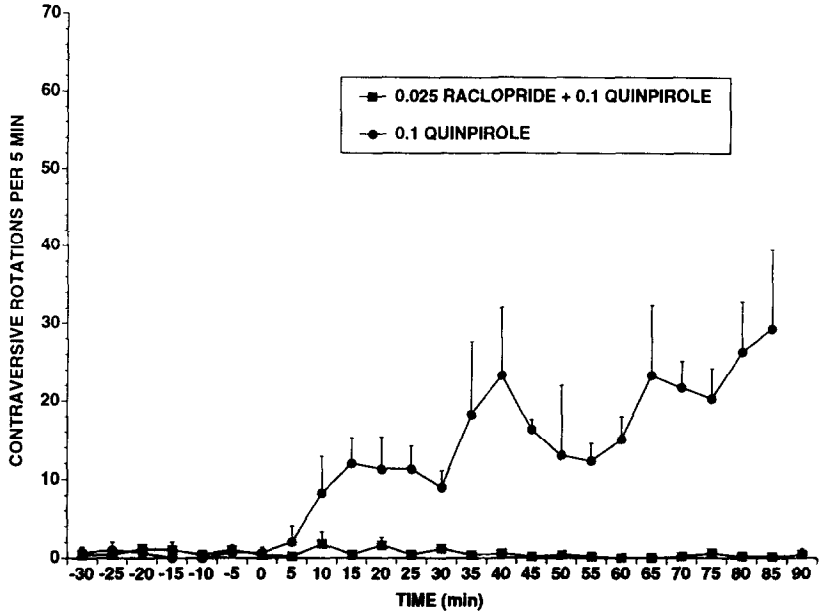

FIG. 3. Effect of quinpirole or the combination of quinpirole + raclopride on mean ± SE number of contralateral rotations completed per 5-min period. Saline was administered at time −30 min, raclopride at time −20 min, and quinpirole at time 0 min. In contrast to its lack of effect on dihydrexidine-induced contralateral rotation, raclopride inhibited rotational asymmetry induced by quinpirole. Quinpirole-induced rotations significantly differed from rotations induced by quinpirole + raclopride based on Bonferroni's test ($p < 0.05$) and ANOVA.

were not altered by the D_2 antagonist remoxipride (8). In naive rats, dihydrexidine increased locomotion, an effect blocked by SCH 23390 but not by remoxipride (7).

One possible explanation for the failure of raclopride to block the dihydrexidine-induced rotation in this study might be that the dose of raclopride used was not optimal. However, this does not seem likely because the same dose of raclopride (0.025 mg/kg) blocked the contralateral rotation induced by 0.05 mg/kg of the D_2 agonist quinpirole. As noted above, other studies have found that remoxipride pretreatment did not block dihydrexidine's effects. The same dose of remoxipride did block the effects of PHNO, a selective D_2 agonist (8). Dihydrexidine does appear to be selective for dopamine receptors, showing little potency at other receptor types (17). Thus, the motor effects of dihydrexidine in primate models appear to be primarily mediated by stimulation of the D_1 receptor.

Several converging lines of evidence suggest that activating the dopamine D_1 receptor may be useful in relieving symptoms of Parkinson's disease. The clinical superiority of L-dopa (which increases activity at both D_1 and D_2 receptor subtypes) over selective D_2 agonists is suggestive in this regard. L-Dopa and mixed D_1/D_2 agonists have greater effects on behavior and glucose utilization than the selective D_2 agonist bromocriptine (16,21,26,27). The D_1 antagonist SCH 23390 produces parkinsonian signs in normal monkeys and increases the severity of symptoms in MPTP-treated monkeys (14,25). Blockade of the D_1 receptor by SCH 23390 attenuates the behavioral response to L-dopa and its effects on glucose utilization in the nigrostriatal system in rats (22). Most significantly, several novel selective full D_1 dopamine receptor agonists show promising preclinical results as antiparkinsonian treatments. For example, SKF 82958 and CY 208-243 have been reported to increase locomotor activity in MPTP-treated marmosets, an effect blocked by pretreatment with SCH 23390 (18,25). Likewise, A-77636, another novel full D_1 agonist, increased locomotion and decreased the severity of parkinsonian symptoms in marmosets treated with MPTP and produced contralateral rotation in rats with unilateral 6-OHDA lesions of the nigrostriatal pathway, effects blocked by SCH 23390 but not by the D_2 antagonist haloperidol (13). SKF 81297 has been reported to induce contralateral rotations and stimulate dominant hand use in MPTP-lesioned rhesus monkeys, an effect blocked by the D_1 antagonist SCH 23390 but not by the D_2 antagonist remoxipride (28). Thus, several novel structurally distinct D_1 agonists appear to have antiparkinsonian effects in a variety of species and animal models of Parkinson's disease. Further, these effects are consistently blocked by the D_1 dopamine receptor antagonist SCH 23390 but are not altered by a variety of D_2 dopamine receptor antagonists.

The most widely used D_1 receptor agonist, SKF 38393, appears to have no antiparkinsonian effects in primate models of Parkinson's disease or in patients with the naturally occurring disorder (3,4,6,9,30). These observations have effectively limited therapeutic approaches aimed at stimulating D_1 activity for the treatment of Parkinson's disease. However, it is likely that SKF 38393's apparent lack of antiparkinsonian effects may be due to its pharmacological profile. The use of SKF 38393 has generated most of the available data concerning the effects of D_1 receptor stimulation on behavior. The vast majority of this work was performed on rodents and may not be applicable to primates. For example, whereas SKF 38393

enhances the action of D_2 agonists in rats (5), it inhibits D_2 agonist effects in primates (3). It has also been suggested that SKF 38393 may be a partial D_1 agonist in rodents but a partial D_1 antagonist in primates (4,18,20). SKF 38393 only weakly stimulates adenylate cyclase activity in vitro (12), stimulates adenylate cyclase activity in rhesus monkey striatum at about 25% of that achieved in rat striatum (19), and stimulates adenylate cyclase activity in squirrel monkey striatum at about 60% of that achieved in rat striatum (11).

Our present results, together with the results from other laboratories, suggest that dihydrexidine or other agonists with full activity on D_1 dopamine receptors are capable of stimulating motor behavior in dopamine-depleted monkeys and thus may be useful in the treatment of human Parkinson's disease. At the least, full D_1 agonists deserve to be studied further to more completely assess their antiparkinsonian and dyskinesia-producing effects in primate models of parkinsonism.

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