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Effects of Dopamine Agonists on Delayed Response Performance in Chronic Low-Dose MPTP-Treated Monkeys

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SCHNEIDER, J. S., Z.-Q. SUN AND D. P. ROELTGEN. *Effects of dopamine agonists on delayed response performance in chronic low-dose MPTP-treated monkeys.* PHARMACOL BIOCHEM BEHAV **48**(1) 235-240, 1994.—Monkeys exposed to low doses of the dopaminergic neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) develop difficulty in performing a previously learned delayed response (DR) task. In the present group of animals, performance deficits were manifested as a combination of mistakes or incorrect responses and no response errors, trials on which the animals failed to respond. Methylphenidate and the dopamine D_2 receptor agonist LY-171555, at low doses, decreased the number of no-response errors but not mistakes. The partial D_1 agonist SKF-38393 had no effects on no-response errors or mistakes. Thus, behavioral deficits associated with decreased task persistence may be amenable to treatment with dopamine agonists, and particularly D_2 agonists, while cognitive performance per se may not be improved by such drugs. The similarities between this primate model and the cognitive/behavioral deficits associated with early Parkinson's disease and attention deficit hyperactivity disorder suggest that this may be a useful model for testing hypotheses concerning the pharmacological treatment of these disorders.

Cognition Monkey Basal ganglia 1-Methyl-4-phenyl-1,2,3,6-tetrahydro-pyridine Dopamine

MANY studies have examined motor aspects of parkinsonism in monkeys exposed to the dopaminergic neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (8,12,14,38 39), but few studies have examined cognitive aspects of MPTP-induced parkinsonism in monkeys devoid of significant motor impairment (33,47). Such studies are of obvious importance, in view of the demonstration of specific cognitive deficits in early Parkinson's disease patients (17,22) and in humans exposed to MPTP but asymptomatic for motor impairment (44).

Previously, we have reported that monkeys exposed to the dopaminergic neurotoxin MPTP, either acutely (37) or chronically (35) develop deficits in operant (37) or cognitive (35) task performance. These deficits either precede (37) or occur independent of the development of gross parkinsonian motor deficits (35).

In one study (37), monkeys exposed to MPTP developed dificulty in maintaining responding on an operantly conditioned forearm reaching task and appeared inattentive and distracted during testing sessions. Monkeys would typically initiate task performance in a normal manner but would stop after only a few trials and would need to be refocussed on the task by the experimenter. Post-MPTP performance was also characterized by many no-response errors, where the animal would initiate a trial but not complete the response.

A later study (35) showed that monkeys exposed chronically to low doses of MPTP developed deficits in performing delayed response (DR) and delayed alternation tasks but not a visual discrimination task. In addition to these cognitive deficits, the behavior of these monkeys was also characterized by inattentiveness and increased distractability in the testing situation, as well as apparent increased frustration (i.e., violent outbursts directed at the testing equipment after a series of incorrect responses) at the inability to correctly perform DR and delayed alternation trials. Performance deficits were characterized by a combination of incorrect responses and no-response errors (i.e., if a monkey did not respond to any

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particular trial within 30 s, a no-response error was noted). Neurochemical analyses of the brains of these animals showed a profound decrease in dorsal caudate dopamine and norepinephrine levels with less severe catecholamine depletions in other striatal regions and in frontal cortical regions (34).

Recently, chronic low-dose (CLD) MPTP-treated monkeys have been discussed not only as a model for early parkinsonism (35), but also as a potential model for attention deficit hyperactivity disorder (ADHD) (32). Similarities in the nature of the cognitive and behavioral deficits across these clinical conditions (32) suggest that they might have similar physiological underpinnings involving hypofunction of basal ganglia (and perhaps, in particular, nigrostriatal) dopamine function.

In view of the dopaminergic dysfunction known to exist in chronic low-dose (CLD) MPTP-treated monkeys, the present study was designed to assess the effects of the dopamine agonist apomorphine, the stimulant methylphenidate (releases norepinephrine and dopamine), LY-171555 (D_2 agonist), and SKF-38393 (partial D_1 agonist) on DR performance in CLD MPTP-treated monkeys. Methylphenidate was chosen because of its use in treating ADHD and because we have previously proposed the CLD MPTP-treated monkey as a possible animal model of ADHD (32). The antiparkinson activity of dopamine agonists has been primarily attributed to the D_2 receptors (5,6), while the role of D_1 receptors is less clear. SKF-38393 is only a partial D_1 receptor agonist and fails to relieve parkinsonian motor symptoms in monkeys (6,11,27) and humans (7). However, full D_1 agonists such as dihydrexidine (48) and SKF-82958 (13) may have antiparkinsonian effects on nonhuman primates. The effects of specific or partial dopamine receptor agonists on cognitive deficits associated with human parkinsonism or MPTP-induced parkinsonism in monkeys are not known.

METHOD

Delayed Response Testing

Three adult Macaque nemistrina monkeys (two females, one male) were trained to perform a delayed response (DR) task as previously described (35). Briefly, animals were trained and tested on DR while seated in a restraining chair placed inside a modified Wisconsin General Test Apparatus (4,35). Each monkey sat behind an opaque screen that when raised, allowed access to a sliding tray that contained recessed food wells and identical sliding Plexiglas covers that served as stimulus plaques that could be displaced by the animal to obtain rewards (raisins). Monkeys were trained to retrieve a raisin from one of the food wells after observing the experimenter bait one of the wells. Right and left wells were baited in a balanced order. Each daily session consisted of 25 trials. Animals were trained until performance with a 5 s delay was 90% correct or better for at least 5 consecutive days. A response was scored a mistake if the monkey made its response choice to a well that was not baited with reward. A no-response error was scored if the monkey failed to respond to a trial within 30 s.

Once animals were performing at criterion level, MPTP administration began. MPTP-HCl was administered intravenously two or three times per week while animals were under light anesthesia (3% halothane/oxygen/nitrous oxide mixture) and seated in the restraining chair. Personnel administering MPTP wore a disposable gown, latex gloves, and a face mask with a splash shield. Following administration of the toxin, the syringe used was filled with a saturated solution of potassium permanganate (to oxidize any remaining MPTP), capped, and discarded as hazardous waste. Waste pans located beneath the animal's cages and excreta were sprayed with the postassium permanganate solution prior to disposal of the excreta. Care was taken not to generate aerosols during cage cleaning. MPTP was administered to each animal in doses ranging from 0.05 mg/kg at the start of the study to 0.175 mg/kg. By the time drug testing comenced, animals had received cumulative MPTP doses of 15.2, 25.4, and 34.9 mg over periods of 82, 194, and 240 days. The different total amounts of MPTP administered reflect the variability in individual animal sensitivity to the toxin. Although animals received different total amounts of toxin over different time periods, the nature of the cognitive deficits, as discussed below, were similar in all animals. Pharmacological data were obtained after animals consistently showed at least a 15% performance deficit on DR.

Drug Administration

On drug treatment days, animals were tested for DR performance, administered drug, and retested on DR performance. Animals were tested approximately once every 3 weeks for performance after saline injections to control for effects of receiving an injection and to control for possible changes in performance when tested a second time in 1 day. A minimum of 3 days separated drug trials in any particular animal. Drug test sessions were conducted only if subjects met the 15% or more performance deficit requirement on any particular day. The order of drug and dose administration was determined quasi-randomly (1). Each dose of each drug was tested at least twice in each animal.

D_1/D_2 agonist. The D_1/D_2 receptor agonist apomorphine and the stimulant methylphenidate (which is not strictly a D_1/D_2 agonist, but for the purposes of this study, will be grouped together with apomorphine to distinguish the actions of these drugs from the selective dopamine receptor agonists discussed below) were diluted in sterile saline (containing 0.2% ascorbic acid for apomorphine) and injected intramuscularly 15 to 20 min prior to DR testing. Drug doses were 0.025 to 0.10 mg/kg for apomorphine and 0.1 to 0.6 mg/kg for methylphenidate. The doses and injection times were selected on the basis of previous data that suggested effective doses and injection times for these same drugs for eliciting contralateral rotation in monkeys with unilateral dopamine depletions (unpublished observations). Apomorphine hydrochloride and methylphenidate hydrochloride were purchased from Research Biochemicals, Inc.

Dopamine D_2 agonist. The dopamine D_2 agonist LY-171555 was diluted in sterile saline and injected intramuscularly at doses of 0.01 to 0.05 mg/kg, 15 to 20 min prior to DR testing. LY-171555 was obtained from Research Biochemicals, Inc.

Dopamine D_1 agonist. The partial dopamine D_1 agonist SKF-38393 was administered intramuscularly in sterile saline at doses of 0.25 to 2.0 mg/kg, 15 to 20 min prior to DR testing. SKF-38393 was obtained from Research Biochemicals, Inc.

Data Analysis

Delayed response performance on drug was compared with matched control performance obtained on the same day prior to drug administration. The number of mistakes and no-response errors were tabulated for each test session. All animals served as their own controls and statistical analyses consisted of analysis of variance, repeated measures design with post hoc comparisons (Bonferroni *t*-test).

RESULTS

Monkeys were trained to perform DR for an average of 7 months (±2) and had a mean baseline performance of 96.8% correct responses (±3.4) prior to MPTP exposure. As described previously (35), all monkeys given chronic administration of low doses of MPTP developed difficulties in performing the DR task. Initially, monkeys made primarily mistakes on DR but over time (and with additional MPTP treatment) settled into a performance routine in which they typically first made a number of mistakes followed by a number of no-response errors. The no-response errors typically appeared after a number of incorrect responses were made. While these two error types were produced by all animals, the relative proportion of the two error types varied somewhat across animals and testing sessions.

Prior to MPTP administration, monkeys never made no-response errors, although they occasionally made mistakes (mean no-response errors/session during baseline ± SD = 0 ± 0; mean number of mistakes/session during baseline ± SD = 0.8 ± 0.4). However, after chronic exposure to MPTP, animals made both no-response errors and mistakes (see predrug test results in Figs. 1 and 2). On trials where no-response errors were made, animals were observed to be inattentive and looking around the testing chamber rather than focusing their attention on the response tray.

As described previously, no-response errors did not seem to be related to motor impairment. Often, when monkeys would not respond to the task, they would move with normal speed and agility to retrieve a raisin placed on top of one of the sliding Plexiglas covers.

D_1/D_2 Agonists

Apomorphine and methylphenidate resulted in fewer no-response errors at low doses (0.025 mg/kg for apomorphine; 0.3 mg/kg for methylphenidate) compared to performance in the nondrug condition (Fig. 1), although this was statistically significant only for methylphenidate. Animals generally appeared to be more attentive and focused on the task after administration of these drugs and particularly after methylphenidate. At a high dose (0.1 mg/kg) apomorphine resulted in more no-response errors than in the nondrug condition. This appeared to be due to excessive hyperactivity and decreased attentiveness in all monkeys tested.

Methylphenidate (at 0.3 mg/kg) was more effective than apomorphine, at the doses used, in restoring response maintenance or persistence to normal levels. While animals made fewer no-response errors with this drug than with apomorphine, the number of mistakes made either increased or remained the same as in the nondrug condition (Fig. 2).

Dopamine D_2 Agonist

Administration of LY-171555 at low doses (0.01 mg/kg) also caused a significant decrease in the number of no-response errors as compared to the nondrug condition. There were no significant differences between the ability of LY-171555, the nonspecific agonist apomorphine, or methylphenidate to decrease the number of no-response errors produced on the DR task. While LY-171555 improved response maintenance or persistence, it did not result in any significant decrease in the number of mistakes produced by the monkeys.

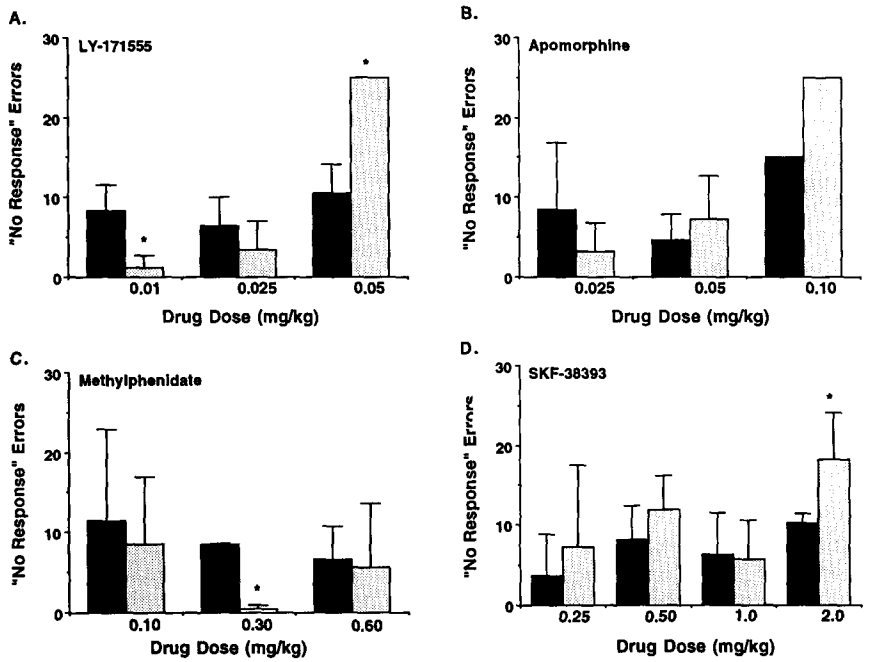

FIG. 1. Mean number (±SD) of no-response errors made on delayed response prior to (solid bar) and after (stippled bar) drug treatment. Nonspecific or D_2 dopamine agonist drugs (A, B, and C), at low doses, resulted in animals making fewer errors of omission during a 25 trial test session (*$p < 0.05$). At high does, LY-171555 and apomorphine (A and B) caused hyperactivity and no task performance. The partial D_1 agonist SKF-38393 did not result in fewer no-response errors at any of the doses tested. However, a high dose of this drug resulted in hyperactivity and deterioration of task performance.

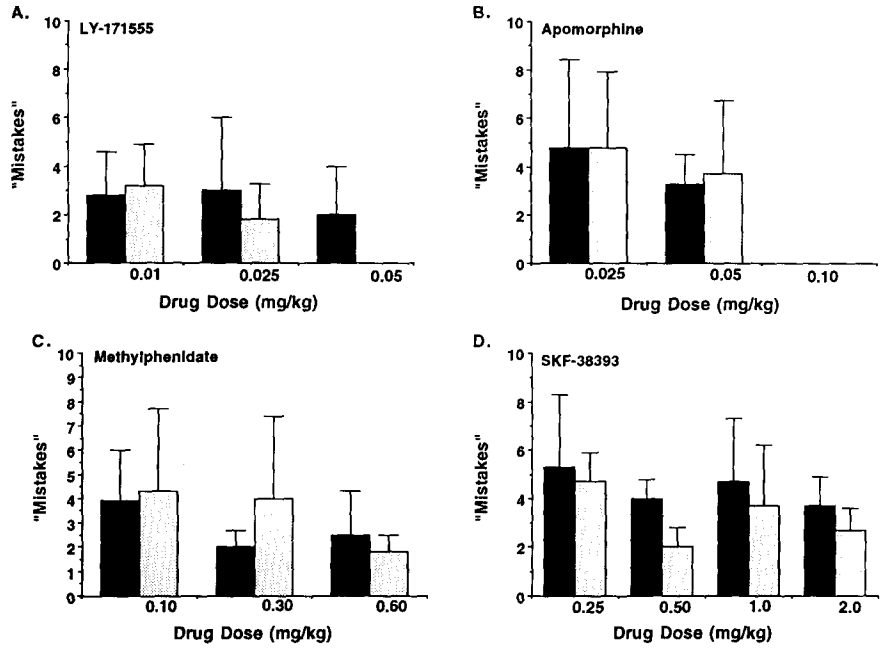

FIG. 2. Mean number of mistakes (± SD) made on delayed response prior to (solid bar) and after (stippled bar) drug treatment. None of the drugs tested significantly reduced the number of mistakes made during a 25 trial delayed-response test session. At high doses, LY-171555 (A) and apomorphine (B) resulted in hyperactivity and no responses were made by any of the monkeys to task presentation.

After administration of a high dose of LY-171555, monkeys became unresponsive to the DR task, due to excessive hyperkinesia and inattentiveness.

Dopamine D_1 Agonist

Unlike the D_2 agonist, the partial D_1 agonist SKF-38393 had no effect on the number of no-response errors except at the highest dose administered (2.0 mg/kg). At this dose, monkeys became mostly unresponsive to the task due to excessive hyperactivity and inattentiveness. SKF-38393 also had no effect on the number of mistakes made during performance of the DR task.

Saline Controls

Approximately once every 3 weeks DR performance was measured prior to and after receiving saline injection. There were no significant differences in task performance or the types or numbers of errors produced in pre- and postsaline test sessions [mean (± SD) pre- and postsaline no-response errors = 6.0 ± 1.6 and 5.2 ± 1.2, respectively; mean (± SD) pre- and postsaline mistakes = 3.8 ± 1.1 and 4.2 ± 1.8, respectively]. This suggests that positive drug effects were not due to practice effects and negative drug effects could not be explained by satiation effects. Some alpha-2 adrenergic agonists have been shown to have residual cognitive effects up to a week after treatment (1,2). However, there are no data to indicate that the dopaminergic drugs used in the present study have such long-lasting effects. The preinjection results in the present study suggest that if such effects exist, they are insignificant in terms of the tasks used in this study.

DISCUSSION

As shown by us previously, monkeys with monoaminergic deficits as a consequence of MPTP exposure have difficulties in performing previously learned operant (37) and cognitive (35) tasks, have response maintenance problems (37), and generalized attention deficits (35,37). These behavioral disturbances have been observed in monkeys prior to appearance of parkinsonian motor deficits (37) or in monkeys that remained motor asymptomatic throughout the study (35). In the present study, similar to previous performance (35,36), the animals had no difficulty performing a visual discrimination task that required the same reaching response as the DR task. Drug effects on this normal task performance were not assessed in the present study. The visual discrimination was performed accurately during the same time periods that the animals performed poorly on DR. Therefore, it is unlikely that the observed DR deficits were due to motor or visual impairments.

The DR deficits described in this paper have been reported previously in monkeys exposed chronically to low doses of MPTP. The present group of chronic low dose (CLD) MPTP monkeys made a combination of mistakes or incorrect responses and no-response errors or errors of omission on the DR task. The present results show that treatment with methylphenidate or a dopamine D_2 receptor agonist LY-171555 can, at low doses, decrease the number of no-response errors but not significantly improve task performance. While the D_1/D_2 agonist apomorphine tended to decrease the number of no-response errors at a low dose, this was not a statistically significant effect. The lack of effect with apomorphine compared to methylphenidate and LY-171555 may relate to the

ability of apomorphine to act as a D_2 agonist and D_1 antagonist in vivo in primates (6).

Administration of the partial D_1 agonist SKF 38393 had no effects on task performance except at a high dose, at which it may not be selective and at which D_2 receptor stimulation was possible. SKF-38393 is only a partial D_1 receptor agonist and only weakly stimulates adenylate cyclase activity in vitro (19), and in primates, may act as a D_1 receptor antagonist rather than as an agonist (6,27,29). Therefore, firm conclusions regarding the role of D_1 receptors in the presently examined cognitive deficits awaits further testing with a full D_1 receptor agonist such as dihydrexidine (25). While errors of omission seem to be responsive to dopamine receptor stimulation [most likely D_2 subtype, and perhaps to a lesser extent D_3 receptors, which may also be stimulated by LY-171555 (40)], cognitive ability is not significantly influenced. That is, while under the influence of nonspecific agonists or a D_2 agonist, CLD MPTP monkeys generally performed more trials on the DR task than in the nondrug condition, but did not necessarily perform the trials correctly.

We have previously noted similarities between the behavioral deficits observed in CLD MPTP monkeys, patients with early Parkinson's disease, and people with attention deficit hyperactivity disorder (ADHD) (32). ADHD, believed to be primarily a dopaminergic/noradrenergic deficit (42,43,50), is characterized by inattention, overactivity and impulsivity, executive function (cognitive) deficits, and motor persistence problems (26,32,49). Parkinson's disease, primarily a dopaminergic deficit, is characterized by sensorimotor disinhibition (9), poor attention (22), increased distractability (41), poor persistence and impaired executive functions (46), and cognitive impairments similar to those found in ADHD (49,50). It has further been noted that many years prior to manifestation of overt parkinsonian motor signs, a Parkinson's disease patient was described as looking vacant, unresponsive, and inattentive, displaying restless, irritable, and impatient behaviors, and had a disinclination to continue motor tasks (21). Furthermore, both parkinsonism and a behavioral disorder resembling ADHD occurred after the influenza epidemic in the early part of the 20th century (16,20,45).

The present finding that some dopamine agonists may be able to decrease the number of no-response errors produced by CLD MPTP monkeys while not necessarily increasing the proportion of correct responses made on DR may have clinical analogs. Hyperactive children who produced numerous errors of omission on a cancellation task produced significantly fewer omission errors (i.e., failures to respond) after methylphenidate treatment (10). Methylphenidate also decreased the number of omission errors and increased the amount of time on task in ADHD children performing a Continuous Performance Task (3,31). In a classroom setting, methylphenidate treatment caused ADHD children to attempt more arithmetic problems but did not increase the proportion of problems solved correctly (28). Furthermore, as the dose of methylphenidate was increased, the number of problems attempted decreased (28). Similar data from Parkinson's disease patients is not available, because tests with these particular outcome measures are not typically administered to Parkinson's disease patients.

Although neurochemical analyses of the brains of the monkeys used in this study have not yet been performed, previous analyses of the brains of CLD MPTP monkeys with cognitive and no or minimal motor deficits have shown there to be primarily a caudate dopaminergic deficiency, and to lesser extents, caudate and cortical noradrenergic deficiencies (34). Similar neurochemical findings have been reported in other monkeys asymptomatic for MPTP parkinsonism (15,30). In this regard, the striatum in Parkinson's disease is also characterized by similar monoaminergic deficiencies (18), as have been suggested to be involved in ADHD (42,43,51). Lou et al. (24) have also shown there to be decreased blood flow in the striatum in ADHD, that can be reversed with methylphenidate treatment, further suggesting a role of the striatum in this disorder.

In summary, the results of this study suggest that task persistence or attention may be improved with some drugs that influence the dopamine system, particularly those that activate D_2 receptors, but that those same drugs may not significantly improve cognitive performance. The present results also suggest a possible link between the dopamine system, parkinsonism, and ADHD, and further support the use of the CLD MPTP monkey as a model for studying behavioral disorders linked to dopamine system dysfunction.

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