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BRIEF COMMUNICATION

Effects of the Dopamine D-2 Receptor Agonist, LY 171555, on Radial Arm Maze Performance in Rats

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LEVIN, E. D. AND R. E. BOWMAN. *Effects of the dopamine D-2 receptor agonist, LY 171555, on radial arm maze performance in rats.* PHARMACOL BIOCHEM BEHAV **25**(5) 1117–1119, 1986.—Rats trained to run through an 8-arm radial maze for food reinforcement were injected with a broad range of doses of the dopamine D-2 receptor agonist, LY 171555. Deficits were detected by the choice measures of entries to repeat and arms entered in the first eight choices. There was a dose-related increase in latency to finish the maze even though there was no significant increase in the number of choices needed to finish the maze.

Radial arm maze LY 171555 Dopamine D2 Agonist

DOPAMINE (DA) systems have been found to be involved with accurate choice performance in the radial arm maze. The DA receptor blocker, haloperidol, impairs performance when given acutely [4] or chronically [12]. The DA agonist, amphetamine, impairs memory performance in the radial arm maze [2, 3, 8, 11], but only when a delay is imposed between choices [2,9]. DA systems appear to contain at least two receptor types: D-1 and D-2 [10]. Drugs which differentially affect these receptors differ both in their biochemical [16] and behavioral effects [1]. The selective D-2 agonist, LY 171555 [17], has been found to cause hyperactivity [6,7] similar to the nonspecific DA agonist, amphetamine. However, the effects of this D-2 agonist on cognitive functions have not yet been investigated.

METHOD

The subjects were 19 male Sprague-Dawley rats (Holtzman, Madison, WI), 120–200 days of age, housed singly with a 12:12 light:dark cycle. Tests were conducted during the light phase. The rats were kept at approximately 85% of their ad lib weight and were fed daily after testing. Thirty minutes before each of the five daily sessions, one dose (0, 0.03, 0.1, 0.3 or 1.0 mg/kg) of the DA-D2 receptor agonist LY 171555 (Eli Lilly, Indianapolis) mixed in 1 ml/kg of normal saline was injected IP in a randomized order.

The rats were tested in an 8-arm radial maze with a central platform 34 cm across and arms 10.5 cm wide and 42 cm long. The top of the maze, 10 cm high, was clear so that the rats could make use of extramaze visual cues. Before each session the maze was wiped with a 1% acetic acid solution to help mask odor cues. Entries were scored when the rat first put its nose half-way down an arm. The first entry into each arm was rewarded with a 45 mg Noyes food pellet. Reentries were not rewarded. The session lasted until all eight arms had been entered or 600 seconds had elapsed. Prior to the onset of drug administration the rats were tested in the maze for 35 sessions without injections followed by five sessions with injections of saline. The measures consisted of arm entries until a choice was repeated (entries to repeat), the number of different arms chosen in the first eight entries (arms in first eight), number of entries until all eight arms were chosen (entries/session) and latency in seconds to enter all eight arms. If the rat had a perfect session, the number of entries to repeat was assigned to be eight.

The response accuracy and latency data were evaluated by orthogonal contrasts within an overall analysis of variance. The orthogonal contrasts were: saline vs. all drug

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TABLE 1

EFFECTS OF LY 171555 ON RADIAL ARM MAZE PERFORMANCE MEANS ± STANDARD ERROR OF THE MEAN

		mg/kg LY 171555			
Measure	Saline	0.03	0.10	0.30	1.00
Entries to Repeat	7.6 ± 0.2†	6.8 ± 0.3	7.1 ± 0.3	6.9 ± 0.3	6.5 ± 0.3
Arms in First 8	7.6 ± 0.1*	7.4 ± 0.1	7.4 ± 0.2	7.3 ± 0.2	7.1 ± 0.2
Entries to All	8.7 ± 0.3	9.3 ± 0.4	9.5 ± 0.5	9.1 ± 0.3	9.1 ± 0.2
Latency (secs)	78 ± 8‡	121 ± 24§	200 ± 33#	350 ± 36	384 ± 37

Saline vs. All Drug Groups: *$p<0.05$; †$p<0.01$; ‡$p<0.0001$.
0.03 mg/kg vs. Higher Doses: §$p<0.0001$.
0.10 mg/kg vs. Higher Doses: #$p<0.005$.

doses, the 0.03 mg/kg dose vs. the three higher doses, the 0.1 mg/kg dose vs. the two higher doses and the 0.3 mg/kg dose vs. the highest dose (1.0 mg/kg). The first contrast would indicate whether there was an overall effect of the drug, while the subsequent contrasts would indicate whether there were differential effects with progressively higher doses.

RESULTS

Most of the rats performed the task of entering all eight arms in under ten minutes, except for two at the 0.3 mg/kg dose and four at the 1.0 mg/kg dose. The missing data for these animals at these doses was filled in with the mean of the group. The means and standard errors for all of the response measures are presented in Table 1. With entries to repeat, comparison of saline with the combined drug conditions showed that LY 171555 caused a significant deficit of about 10%, $F(1,18)=11.87$, $p<0.005$. There was a modest appearance of a dose-effect function, but none of the contrasts comparing the progressively higher drug doses were significant. With the number of arms chosen in the first eight entries, comparison of saline with the combined drug conditions showed that LY 171555 significantly impaired performance, $F(1,18)=5.95$, $p<0.025$. Performance at all of the drug doses was worse than at saline, but none of the comparisons between the different doses of LY 171555 were significant. With the entries to choose all eight arms measure, none of the comparisons were significant. There was a very striking dose-effect of LY 171555 increasing latency. The comparison of saline with the combined drug condition was very significant, $F(1,18)=90.11$, $p<0.0001$. There was a significant effect of the comparison of the 0.03 mg/kg dose with the higher doses, $F(1,18)=51.45$, $p<0.001$, and a significant effect of the comparison of the 0.1 mg/kg dose versus the higher two doses, $F(1,18)=16.16$, $p<0.005$. The last comparison between the two highest doses was not significant.

DISCUSSION

Over a 33-fold range of doses, LY 171555 impaired choice accuracy and slowed response speed in the radial arm maze. Several possibilities exist for the basis of the impairment in choice accuracy: the increase in response latency, possible anorectic effects and cognitive impairment. The LY 171555-induced increase in latency most likely did not in itself account for the impaired choice accuracy. Spatial memory of rats in the radial arm maze has been found to remain unimpaired after imposed delays of two minutes [13,15] or fifteen minutes [14]. With extended training it has been found that rats can remember very well even when delays of several hours are imposed [5]. Given that the average increase in latency by the highest dose of LY 171555 was only a little more than five minutes, it seemed unlikely that the increased response time would in itself impair choice accuracy. Another possibility is that LY 171555 may have acted as an anorectic agent like amphetamine, and that the increased latency was a consequence of decreased motivation for the food rewards. However, since the rats did not leave more rewards uneaten after injections of LY 171555 than after saline injections, this seems unlikely. Cognitive dysfunction remains as a likely basis of the impairment in choice behavior. Disruption of response patterning could be a basis for the cognitive impairment, but analysis of the most common beneficial strategy, choosing adjacent arms, showed that there was actually a significant increase, $F(1,18)=4.94$, $p<0.05$, in the use of this strategy with the highest two doses.

The LY 171555-induced deficit in choice accuracy occurred in the present study with no delays imposed between choices in contrast to the adverse effect of amphetamine which has only been found to occur when delays are imposed [2,9]. The selectivity of the LY 171555 as a D-2 dopamine receptor agonist [19] may have been crucial in producing the deficit. Concurrent stimulation of the D-1 receptor or noradrenergic receptors by amphetamine may have made it less effective in disrupting choice performance when no delay was imposed. On the other hand, the increased response latencies caused by LY 171555 may have effectively imposed enough of a delay between choices to elicit a deficit. The combination of a cognitive impairment and reduced response speed may have been sufficient to impair choice accuracy in the radial arm maze test without imposed delays.

The dose-related slowing due to LY 171555 in the present study stands in contrast to the finding of hyperactivity at similar doses in other studies [6,7]. The increased number of arm entries to complete the maze when treated with LY 171555 was far too small to account for the increased latencies. The difference in behavioral tests may account for the divergent results. In the above-mentioned experiments, the rats were allowed to habituate to the apparatus for 1 hour before injection and after injection activity counts were

cumulated for 2.5 hours. In contrast, in the present study, the rats were placed in the apparatus only 30 minutes after injection of the drug and tested for a period of not exceeding ten minutes. In the present study, the rats injected with LY 171555 were observed to engage in vigorous, almost stereotypic sniffing, which may have accounted for the slower locomotor speed with increasing doses. This stereotypic sniffing may not have occurred in the previous experiments [6,7] because the rats had already thoroughly explored the environment during the hour prior to drug administration. The effect of LY 171555 on locomotor activity when a rat is initially placed in an environment might be quite different from its effect on activity after a rat has been in an environment for an extended period of time.

This study demonstrated that the selective D2 agonist, LY 171555, has consistent effects of increasing response latency and impairing choice accuracy in the radial arm maze. Given that selective agonists and antagonists of the dopamine D1 and D2 receptors have been developed, the participation of each of these receptors in the cognitive deficits produced by the more nonspecific drugs amphetamine and haloperidol can be investigated. The subtypes of dopamine receptors may have quite different roles in the cognitive functioning necessary for radial arm maze performance.

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