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Effects of Ketamine and L-Glutamic Acid Diethyl Ester on Spatial and Nonspatial Learning Tasks in Rats

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LALONDE, R. AND C. C. JOYAL. *Effects of ketamine and L-glutamic acid diethyl ester on spatial and nonspatial learning tasks in rats.* PHARMACOL BIOCHEM BEHAV **44**(3) 539–545, 1993.—An NMDA antagonist, ketamine, at the highest dose tested (15 mg/kg), impaired the acquisition of a hole-board spatial learning task but not the acquisition of a left–right alternation task. A non-NMDA (quisqualate) antagonist, L-glutamic acid diethyl ester (LGDE), did not impair the acquisition of either task. Both drugs had effects on different aspects of a go–no go discrimination task and a straight runway task, ketamine tending to activate and LGDE tending to slow rats. These results concur with previous research regarding the sensitivity of some spatial tasks to NMDA antagonism. Non-NMDA antagonists affect behavior without causing spatial deficits.

Ketamine L-Glutamic acid diethyl ester NMDA Glutamate Excitatory amino acids

KETAMINE is a noncompetitive antagonist of the NMDA receptor (3,25). NMDA antagonists like dizocilpine (MK-801) act as neuroprotective agents in various pathologic conditions, including hypoglycemia (29) and ischemia (13,22). Renewed interest in ketamine, no longer much used clinically as an anesthetic because of unacceptable side effects such as agitation and hallucinations, may be generated in the context of finding drugs with clinical potential for neuroprotectant activity. Ketamine is also a serotonin reuptake blocker (17), but this effect has been detected at high doses (80 mg/kg).

Despite the clinical potential of NMDA blockers, there is increasing evidence that these drugs impair learning. Deficits in active and passive avoidance learning (5,8,9,24,26), spatial learning (2,15,19,21,28), olfactory learning (23), and taste aversion learning (27) have been reported after NMDA blockade. Learning deficits have also been reported in the case of non-NMDA glutamate antagonists such as the quisqualate antagonist L-glutamic acid diethyl ester (LGDE) (11,14).

To increase our understanding of the effects of NMDA and non-NMDA glutamatergic blockade on learning processes, the effects of ketamine on the acquisition of spatial and nonspatial tasks were compared to the effects of LGDE. Spatial tasks included hole-board and alternation learning, whereas nonspatial tasks included go–no go discrimination learning and a straight runway test.

Hole-board learning required retrieving food pellets among four holes in a 4 × 4 matrix (20). This is considered a spatial task in that with repeated trials animals learn to avoid empty holes and visit food-filled holes, distinguishable only by their spatial configuration in the matrix. This form of learning is mediated by the hippocampus (20). In the second spatial task, spatial alternation, rats must alternate left–right choices in a T-maze for food reward. Left–right alternation is a test of working (trial dependent) memory. Because NMDA antagonists impair both Morris maze (considered a reference memory task) and radial maze learning (a working memory task) (2,15,19,21,28), it is worthwhile to discover a spatial task not sensitive to NMDA antagonism to understand the mechanism of action of these drugs. Left–right alternation is a simple version of radial maze performance, requiring a win-shift strategy with two choices instead of the usual eight.

The two nonspatial tasks (go–no go discrimination learning and straight runway testing) were chosen to delineate whether tasks measuring running speed are differentially sensitive to NMDA as opposed to non-NMDA antagonism. The go–no go task measures the ability to respond to a positive stimulus (S+), associated with the reward, and withhold responding to the negative stimulus (S−), associated with a lack of reward (1,6,7). Because NMDA blockade causes disinhibitory effects as assessed by the conflict procedure (4), it was hypothesized that disinhibitory effects would also be found in the go–no go paradigm. As a further test of possible disinhibitory tenden-

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cies of NMDA blockade, the straight runway test was used under both reinforcing and extinction conditions.

Ketamine and LGDE dose ranges in the present experiments were chosen on the basis of significant effects on learning tasks in past experiments (2,11,14,15).

METHOD

Subjects

Four series of twenty-eight male Sprague-Dawley rats (Charles River, St. Constant, Quebec), kept in a temperature- and humidity-controlled room and weighing about 280 g at the start of testing, were used. Because of the number of subjects required in different tasks, no attempt was made to test gender differences. Upon arrival at the laboratory, they were first kept together in group cages and then separated into individual cages just before testing. Food (Purina Rat Chow) was restricted so that animals were fed for approximately 1 h/day, with water available at all times.

Apparatus

Two straight runways of identical size (81.5 × 8.5 × 10.2 cm) were used for go–no go discrimination learning and runway learning. The floor of the runway in the go–no go task was either covered with a sheet of waxed paper or uncovered. In the runway task, the runway was always uncovered.

The hole-board apparatus was a 70 × 70-cm wooden box (height of walls = 30 cm, distance between holes = 9 cm) containing a 16-hole 4 × 4 matrix. Each hole measured 4 cm in diameter and was 2 cm deep.

The T-maze was made of transparent plastic (stem = 81.5 × 8.5 cm, arms = 30 × 8.5 cm, height of walls = 10.2 cm). Food cups made of aluminum were found at the end of each arm.

Procedure

Go–no go learning. To habituate rats to the general conditions of the experiment, they were placed in either runway (both uncovered at this time) with 45-mg food pellets (Dustless Noyes Precision Food Pellets, Technolab, Montreal) available throughout the runway. Following this habituation period, rats were randomly assigned to four groups (n = 7) according to doses of ketamine (Ketalar, Parke-Davis, Montreal): 0 (0.9% saline), 5, 10, and 15 mg/kg IP, injected each day 20 min before testing (injection volume: 1 ml/kg for the 5- and 10-mg/kg doses and 1.5 ml/kg for the 15-mg/kg dose, calculated from the base). A separate group of rats (n = 7) was injected each day IP with LGDE (Sigma Chemical Co., St. Louis, MO, injection volume: 1 ml/kg) at either 0, 120, 240, or 360 mg/kg 30 min before testing. Significant behavioral effects were detected at these dose ranges and postinjection intervals in past studies (2,11,14,15).

Rats were trained (12 trials per day = 6 S+ and 6 S− trials with no intertrial interval) to discriminate between the S+ runway and the S− runway (for four rats in each group, the S+ was the runway without the waxed paper and for the remaining three the S+ was the runway with the waxed paper). The runways were placed side by side and their positions reversed from day to day to minimize learning by means of spatial discrimination. The goal of this paradigm is for the rat to discriminate between runways on the basis of intramaze cues (wax vs. nonwax conditions), not on the basis of extramaze visuospatial cues.

Food cups were placed at the end of each runway so that during an S+ trial the rat found a single pellet in the cup whereas during an S− trial no pellet was given. The sequence of S+ trials was determined by sequences 1-3-2-4-5 drawn from Fellows (10). Latencies were measured with a maximum cut-off point of 30 s for each trial. Rats were placed in the runway with their face toward the cup and the time taken for them to run and then place their snout in the cup was the latency measure. There were 4 days of testing in each experiment.

Hole-board learning. After go–no go learning, the same series of rats (but randomly assigned to different groups) performed the hole-board test. A period of 2 weeks intervened between each test to reduce the chance of long-term drug effects from the first experiment. Rats were habituated to the hole-board for 8 days. During the first 4 days, they were placed in the box seven at a time for 15 min. During the following 4 days, they were placed one at a time for 5 min. Noyes pellets were scattered throughout the box, especially in the holes.

On each day of training, 20 min before the session, rats were injected IP with ketamine (0, 5, 10, and 15 mg/kg). In a separate experiment, the other series of rats were injected IP with LGDE (0, 120, 240, and 360 mg/kg) 30 min before each session. There were four food-filled holes, two at the center and two at the periphery of the matrix (using rows A–D from top to bottom and numbers 1–4 from left to right, the food-filled holes were the following = A1, B3, C2, and D4). Rats were placed at the bottom of the hole-board (nearest row D) and the number of errors recorded. An error was defined as the number of pokes in an empty hole. A trial ended whenever all four pellets were retrieved. There was no time limit to a trial but an overall limit of 15 min/day for each rat. If a rat fell short of the number of trials planned for the day, additional trials were added on the following day so that each rat received the same number of trials at the end of training. Few animals fell short of the required trials per day. Holes A1, B3, C2, and D4 were baited in every trial. When a trial was completed, the animal was lifted from the hole-board and placed in a waiting cage until the hole could be rebaited and the floor washed clean with water to minimize odor cues. Hole visits were recorded by observational (nonautomated) means. Any visit to an empty hole counted as an error. If a rat visited the same hole χ times, then that constituted χ errors, whether the hole was previously baited or not. There were four trials a day for 4 days in the ketamine experiment and five trials a day for 5 days in the LGDE experiment. The LGDE experiment was performed first and because performance seemed to plateau on day 4 the last day was deleted in the ketamine experiment. All rats completed the required number of trials.

Spatial alternation learning. A new series of rats performed spatial alternation and runway tests. Fifty-six rats (n = 7) received either ketamine (0, 5, 10, and 15 mg/kg, IP) 20 min before testing or LGDE (0, 120, 240, and 360 mg/kg, IP) 30 min before testing. Rats were habituated to the T-maze by placing them three to four at a time for 10 min during 4 days and one at a time for 5 min during 4 additional days. Beginning on day 9, rats were given 20 trials a day until reaching the criterion of 18/20 correct responses. Food cups were placed at the end of each arm. A Noyes pellet was given whenever a rat alterned choices in the maze arms. The rat was first given a free pretrial run where food could be found on either arm. Then, for 20 trials the pellet was found on the opposite arm of the previous trial. A correction procedure was used in that whenever an error occurred the rat was rewarded for

entering the correct maze arm. If, for example, a rat turned left instead of the correct right arm, the pellet was kept in that arm until the rat retrieved it. A second left turn was counted as a second error.

Straight runway testing. Two weeks after the alternation task, rats (randomly assigned to different groups) performed the straight runway task. A period of 2 weeks intervened between tasks. After 4 days of habituation (2 days two at a time and 2 days one at a time), rats were put in the same straight runway as used in the go-no go paradigm except the floor was always uncovered. On day 1, food was placed at the end of the runway for six trials. On day 2, an extinction procedure was used in that the pellet was no longer present at the end of the runway. Latencies for each day were calculated. Rats received either ketamine or LGDE at the same dose range as outlined above.

Statistical Analysis

Go-no go learning. Discrimination ratios were tabulated according to an adaptation of an equation described by Alescio-Lautier et al. (1). The ratio on a given day was the sum total of the latencies during the S− trials divided by the total of the latencies during S− and S+ trials multiplied by 10 {discrimination ratio = [(S−)/(S−) + (S+)] × 10}. A high discrimination ratio is an indication of good learning. The results of days 1-2 and 3-4 were combined. Separate analyses were performed for the latencies during S+ trials as opposed to S− trials. Discrimination ratios were analyzed by parametric tests such as analysis of variance (ANOVA) following the Greenhouse-Geisser correction procedure, while the latency data were analyzed by nonparametric tests. The Wilcoxon rank sum test was used as a multiple-comparison test with a correction for significance at 0.05/3 (number of comparisons of interest) = 0.01 (16).

Other tests. Parametric measures were analyzed by ANOVA (with repeated measures), Newman-Keuls tests, or paired *t*-tests. Nonparametric measures were analyzed by Kruskal-Wallis and Wilcoxon tests. The latter measures were used when variances were heterogeneous, as in the case of latencies.

RESULTS

Body Weight and General Health

In no experiments did ketamine and LGDE cause a decrease in body weight or impair general health in any way ($p > 0.05$). The 5- to 15-mg/kg dose range for ketamine and the 120- to 360-mg/kg dose range for LGDE seemed apt to permit the study of exploratory behaviors and cognition. No ataxia was evident. From general behavioral observations, there was no obvious cumulative carry over effect across days.

Go-No Go Learning

Discrimination ratios for the placebo groups in each experiment were nearly identical (Table 1). However, latencies for the LGDE experiment were higher (Table 2). We ascribe this to the fact that the preexperimental habituation of animals was more successful in the ketamine experiment. We performed the LGDE study first and found rats tentative in their approach to either runway. We therefore extended this period in the ketamine experiment.

In the ketamine experiment, there was an increase in discrimination ratios on days 3-4 in comparison to days 1-2, $F(1, 24) = 10.25$, $p < 0.01$. The increase in discrimination ratios on the part of the placebo group, $t(6) = 4.4$, $p < 0.01$, was mainly due to a decrease in S+ latencies over days, $W + (7) = 0$, $p < 0.01$, the increase in S− latencies over days not being significant, $W + (7) = 6$, $p > 0.05$. There was an increase in discrimination ratios at 5, $t(6) = 2.6$, $p < 0.05$, and 10, $t(6) = 2.03$, $p < 0.05$, but not at 15 mg/kg (Table 1). Rats at 15 mg/kg ketamine ran slightly though not significantly faster than control rats in all parts of the experiment, the main result being a lack of decrease in S+ latencies over days, $W + (7) = 9$, $p > 0.05$.

TABLE 1

MEAN (SD) DISCRIMINATION RATIOS OF RATS ($n = 7$) TREATED WITH KETAMINE OR LGDE FOR 4 DAYS DURING ACQUISITION OF THE GO-NO GO SUCCESSIVE DISCRIMINATION LEARNING TASK

Drug Groups (mg/kg)	Days 1-2	Days 3-4
Ketamine		
0	5.6 (1.6)	7.2 (1.3)*
5	5.7 (1.0)	7.2 (1.2)†
10	5.7 (1.6)	6.7 (1.8)†
15	5.8 (1.7)	5.8 (2.3)
LGDE		
0	5.9 (1.0)	7.1 (0.9)*
120	5.9 (0.7)	5.9 (1.2)
240	5.8 (1.0)	6.3 (0.9)
360	6.0 (0.9)	6.2 (0.7)

*$p < 0.01$ vs. days 1-2.
†$p < 0.05$ vs. days 1-2.

An increase in discrimination ratios on days 3-4 in comparison to days 1-2 for the placebo group was also found in the LGDE experiment, $t(6) = 7.18$, $p < 0.001$. However, none of the drugged groups showed an increase in discrimination ratios over days (Table 1). Only the placebo group had a decrease in S+ latencies over time, $W + (7) = 2$, $p < 0.05$. None of the groups had an increase in S− latencies over time. Kruskal-Wallis tests indicated no dose effects for either S+ or S− latencies on days 1-2 or 3-4 ($p > 0.05$). The net effect of LGDE was thus to eliminate the decrease in S+ latencies over time.

Hole-Board Learning

There was a drop in the number of errors (pokes in non-food holes) over days in the ketamine experiment, $F(3, 63) = 4.07$, $p < 0.05$. There was a significant dose effect, $F(3, 63) = 4.2$, $p < 0.05$, but not a significant interaction, $F(9, 63) = 0.52$, $p > 0.1$. The Newman-Keuls multiple-comparison test revealed an increase in errors on the part of the 15-mg/kg ketamine group (Table 3) in comparison to the placebo group ($p < 0.05$). A decrease in the number of errors over days also occurred in the LGDE experiment, $F(4, 96) = 19.95$, $p < 0.001$ (Table 3). However, there was no dose effect, $F(3, 96) = 0.33$, $p > 0.1$, or interaction, $F(12, 96) = 1.12$, $p > 0.1$.

Spatial Alternation

All rats reached the 18/20 criterion in both experiments. Neither ketamine, $F(3, 24) = 0.33$, $p > 0.1$, for trials to criterion, $F(3, 24) = 0.19$, $p > 0.1$, for errors to criterion, nor

TABLE 2

MEAN (SD) LATENCIES FOR REWARDED (S+) AND NONREWARDED (S−) TRIALS DURING ACQUISITION OF THE GO-NO GO SUCCESSIVE DISCRIMINATION LEARNING TASK IN RATS (n = 7) TREATED WITH KETAMINE OR LGDE

	S+ Latencies		S− Latencies	
Drug Groups (mg/kg)	Days 1-2	Days 3-4	Days 1-2	Days 3-4
Ketamine				
0	122.6 (63.2)	75.1 (66.3)*	160.7 (78.0)	182.3 (86.5)
5	91.9 (48.9)	52.9 (28.6)	120.0 (48.2)	139.4 (59.4)
10	49.4 (21.0)†	35.7 (19.7)	72.1 (47.1)†	94.7 (75.3)
15	79.6 (38.6)	65.7 (28.7)	106.4 (48.3)	112.1 (74.0)
LGDE				
0	202.4 (111.6)	141.6 (72.5)‡	251.0 (73.8)	283.0 (60.2)
120	197.6 (82.6)	234.0 (109.5)	260.6 (71.9)	282.0 (73.5)
240	158.3 (61.9)	164.7 (71.2)	202.4 (93.4)	270.7 (83.5)
360	205.0 (97.7)	190.6 (73.4)	278.6 (53.7)	294.0 (60.9)

*$p < 0.01$ vs. days 1-2.
†$p < 0.01$ vs. 0 mg/kg.
‡$p < 0.05$ vs. days 1-2.

LGDE, $F(3, 24) = 0.23, p > 0.1$, for trials, $F(3, 24) = 0.75$, $p > 0.1$ for errors, had an effect on acquisition of the left-right spatial alternation task (Table 4).

Straight Runway

On day 1, rats found food at the end of a straight runway. On day 2, food was no longer present (extinction session). Ketamine had no effect on running latencies on day 1, $H(3) = 0.38, p > 0.1$, for the first three trials, $H(3) = 0.77, p > 0.1$, for the last three trials (Table 5). However, on day 2, while running latencies were three times higher for the placebo group during the last three trials in comparison to the first three trials, $W + (7) = 0, p < 0.01$, the extinction effect was not evident in the case of the ketamine groups, $W + (7) = 4$ for 5 mg/kg, $W + (7) = 5$ for both 10 and 15 mg/kg, all $p > 0.05$. Although latencies were lower for the 10- and 15-mg/kg groups on the last three trials of day 2 than the placebo group, the dose effect was not significant, $H(3) = 2.81, p > 0.1$. LGDE slowed running speeds on the last three trials, $H(3) = 7.9, p < 0.05$, but not the first three trials, $H(3) = 5.16, p > 0.05$, of day 1, especially at 360 mg/kg, $R1(7,7) = 38, p < 0.05$. Rats under LGDE were slower during extinction, $H(3) = 8.76, p < 0.05$, at 240, $R1(7,7) = 36, p < 0.05$, and 360 mg/kg, $R1(7,7) = 36, p < 0.05$. The placebo group showed evidence of extinction as assessed by an increase in latencies on the last three trials in comparison to the first three trials, $W + (7) = 1, p < 0.05$. This was not the case for 120-, $W + (7) = 12, p > 0.05$, and 240-mg/kg, $W + (7) = 4, p > 0.05$, groups because of slower initial running speeds. The 360-mg/kg LGDE had the highest initial latencies, yet showed evidence of extinction, $W + (7) = 3, p < 0.05$.

TABLE 3

MEAN (SD) NUMBER OF ERRORS OF RATS (n = 7) DURING ACQUISITION OF SPATIAL LEARNING IN A HOLE-BOARD TASK UNDER KETAMINE (FOUR TRIALS A DAY FOR 4 DAYS) OR LGDE (FIVE TRIALS A DAY FOR 5 DAYS)

	Days					
Drug Groups (mg/kg)	1	2	3	4	5	Mean Values
Ketamine						
0	66.1 (11.2)	54.1 (17.9)	44.1 (15.8)	46.6 (13.5)	–	52.8 (17.1)
5	69.7 (31.9)	72.6 (24.9)	47.6 (9.3)	66.6 (26.3)	–	64.1 (26.5)
10	71.9 (17.1)	53.4 (9.4)	50.9 (16.7)	48.1 (14.3)	–	56.0 (17.4)
15	85.0 (38.6)	75.9 (21.5)	68.3 (27.9)	55.1 (14.8)	–	71.1 (29.3)*
LGDE						
0	82.4 (12.2)	64.7 (10.7)	52.3 (8.8)	56.3 (13.5)	47.3 (9.5)	60.6 (17.5)
120	82.3 (33.3)	57.9 (16.1)	61.7 (17.7)	54.6 (11.6)	48.6 (10.5)	61.0 (22.0)
240	72.9 (9.5)	64.9 (12.2)	64.9 (21.0)	45.3 (12.5)	45.9 (11.7)	58.7 (18.0)
360	75.1 (16.7)	74.0 (15.7)	50.1 (5.3)	46.3 (13.5)	40.4 (6.3)	57.2 (19.1)

*$p < 0.05$.

TABLE 4

MEAN (SD) NUMBER OF TRIALS AND ERRORS TO CRITERION OF RATS (n = 7) DURING ACQUISITION OF A LEFT-RIGHT SPATIAL ALTERNATION TASK IN A T-MAZE

Drug Groups (mg/kg)	Trials to Criterion	Errors to Criterion
Ketamine		
0	78.0 (71.9)	25.9 (24.8)
5	83.3 (49.7)	26.4 (16.2)
10	88.1 (28.3)	26.9 (4.6)
15	107.6 (76.9)	32.4 (21.9)
LGDE		
0	58.3 (45.6)	16.7 (11.6)
120	57.7 (35.5)	16.1 (10.5)
240	60.1 (40.6)	19.6 (11.1)
360	71.9 (34.1)	24.6 (13.6)

Because LGDE but not ketamine increased latencies on the last three trials of day 1, the analysis of extinction data for the LGDE groups must take into account that baseline levels of performance were not the same for the placebo group as opposed to the LGDE groups. Instead of continuing the day 1 experiment until perhaps the LGDE groups reached similar latency measures, rats were immediately run on an extinction session on the following day. In both placebo groups, latencies on the last three trials of day 1 were nearly identical to the first three trials of day 2 (Table 5). The latencies of the LGDE groups on the first three trials of day 2 were higher but not significantly so. LGDE was evaluated in the extinction condition in any case because we wanted to evaluate acute effects to the drug in two experimental conditions. To evaluate the effects of LGDE strictly on extinction, one would need to run all rats for food reward on day 1 and inject LGDE on day 2.

DISCUSSION

Previous experimentation in rats has shown that ketamine increases motor activity as assessed by a photocell unit at 7.5 and 15 mg/kg (18). Higher doses either increase (12) or decrease (2) motor activity. In the present studies, ketamine tended to activate. This result was found in the extinction session of the straight runway test, where ketamine at all doses eliminated the increase in running latencies observed in the control group during trials of nonreward. Moreover, at the highest dose (15 mg/kg) ketamine, contrary to control rats, did not increase discrimination ratios over days in the go–no go discrimination learning task. Although the drug did not significantly decrease either S+ or S− latencies, both latencies were slightly lower during the initial sessions in such a manner that S+ latencies were not significantly lowered over days, the main reason whereby control rats increased their discrimination ratios.

In spatial learning tests, ketamine increased the number of errors in the hole-board task (only at 15 mg/kg) but had no effect in the left-right alternation task. The increase in pokes into empty holes in the hole-board task induced by ketamine is ascribed to a spatial learning defect. There was a considerable decrease in errors over days for all groups, meaning that animals learned to avoid those holes. We do not ascribe the deficit to a decrease in motivation (hunger) because: 1) Animals completed all required trials; 2)there was no body weight change in any ketamine experiment; 3) animals performed well on spatial alternation testing. Impaired acquisition of spatial tasks such as the Morris water maze and the radial maze has been found with ketamine and other NMDA receptor antagonists (2,15,19,21,28). The hole-board test seems a spatial memory task sensitive both to NMDA antagonism and hippocampal lesions (20). However, ketamine did not impair acquisition of spatial alternation in a T-maze, a working memory task but simpler than the radial maze. It is possible that the lack of impairment in spatial alternation is due to the simplicity of the task, placebo rats reaching a strict 18/20 criterion within 60–80 trials (3–4 days of testing).

In the go–no go and straight runway tasks, ketamine caused hyperactivity in some periods but not others. Therefore, the deficit in hole-board testing may also be ascribed to disinhibitory tendencies, much like hippocampal damage (20). However, there was no disinhibition in the go–no go discrimination as defined by a selective decrease in S− latencies, a result found with minor tranquillizers (6,7). On the other hand, rats under ketamine did not show the extinction effect in runway testing, an indication of perseveration. Spatial er-

TABLE 5

MEAN (SD) RUNNING LATENCIES OF RATS IN A STRAIGHT RUNWAY TASK FOR FOOD REWARD (DAY 1) AND DURING TRIALS OF NONREWARD (EXTINCTION) (DAY 2)

	Food Reward		Extinction	
Drug Groups (mg/kg)	First Three Trials	Last Three Trials	First Three Trials	Last Three Trials
Ketamine				
0 (n = 6)	40.7 (17.7)	27.2 (10.5)	20.1 (8.2)	64.2 (38.3)
5 (n = 7)	36.4 (29.5)	47.1 (32.6)	45.0 (55.3)	85.7 (52.6)
10 (n = 7)	22.6 (21.9)	38.4 (44.7)	13.9 (13.3)	36.3 (27.0)
15 (n = 7)	24.0 (12.9)	39.6 (16.4)	16.6 (12.1)	26.7 (20.8)
LGDE				
0 (n = 7)	50.9 (34.7)	33.1 (24.7)	34.6 (18.7)	56.6 (22.9)
120 (n = 7)	31.3 (11.3)	24.1 (12.3)	55.6 (31.4)	66.3 (46.6)
240 (n = 7)	80.7 (44.8)	73.7 (43.3)	86.1 (39.4)	110.3* (50.3)
360 (n = 7)	79.0 (43.4)	79.6* (39.4)	94.4 (39.9)	133.7* (62.2)

*$p < 0.05$ vs. 0 mg/kg.

rors and perseveration errors appear to be present in both rats injected with ketamine and rats with hippocampal lesions.

Contrary to ketamine, LGDE tended to decrease motor activity, although the effect was mild and situation specific. LGDE at 360 mg/kg increased running latencies during the last three trials of the acquisition phase (with food present at the end of the runway), a time when latencies for the control group were at their minimum. LGDE at 240 and 360 mg/kg also decreased running speeds during the extinction session (with food not present at the end of the runway), a time when reduced speed was appropriate. However, baseline levels were not the same for placebo and LGDE groups during extinction. LGDE did not increase either S+ or S− latencies in the go-no go discrimination task. However, none of the groups under LGDE had a significant decrease in S+ latencies or an increase in discrimination ratios over time. The drug may therefore cause a subtle slowing of motor activity, being evident at times where control rats increase their running speeds at their maximal point, for example, during the last trials of the straight runway task or during the go periods in later sessions of the go-no go task. The lack of a decrease in S+ latencies over time in the absence of initial increase in S+ latencies is evidence of a learning (acquisition) deficit. High latencies on the last three trials of straight runway testing is also evidence of an acquisition deficit. It is also possible that the drug caused an acute effect on motivational levels. We do not think the drug caused a generalized decrease in motivation after multiple injections because it did not impair hole-board or spatial alternation testing and did not reduce body weight in any experiment.

The differential effects of ketamine as opposed to LGDE in the hole-board underline the sensitivity of NMDA antagonism in spatial learning. LGDE, contrary to ketamine, did not impair the acquisition of an adaptation of the Morris water maze task (with a rectangular rather than a circular water basin) (15). However, LGDE caused a mild impairment in a concept learning version of the same task (15). LGDE has also been reported to impair the acquisition of a bar-pressing task (11) and a visuotactile discrimination learning task (14). The effects of NMDA antagonists in these two tasks have not been evaluated. Overall, the results indicate that spatial tasks are sensitive to NMDA receptor antagonism. These drugs cause similar deficits to those of rats with hippocampal lesions (19). This result may be due in part to the high number of NMDA receptors in the hippocampus [see (19) for a discussion on this parallel]. However, it is possible to consider that some spatial tasks are not sensitive to NMDA receptor antagonism, as in the spatial alternation test reported here, possibly due to the simplicity of the task. On the other hand, it remains to be determined whether non-NMDA receptor antagonism causes spatial learning defects. LGDE did not impair the acquisition of water maze (15), hole-board, and spatial alternation testing (present study). This result may indicate that spatial tasks are more sensitive to NMDA than non-NMDA receptor antagonists. However, use must be made of new drugs with more potent and selective non-NMDA antagonist properties than LGDE to verify this hypothesis. In the dose range tested so far, LGDE can cause behavioral effects such as decreased runway speeds (present study) and impairments in a bar-pressing (11) and a nonspatial discrimination test (15) without causing spatial deficits.

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