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Nicotine–Dizocilpine Interactions and Working and Reference Memory Performance of Rats in the Radial-Arm Maze

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LEVIN, E. D., C. BETTEGOWDA, T. WEAVER AND N. C. CHRISTOPHER. *Nicotine–dixocilpine interactions an working and references memory performance of rats in the radial-arm maze.* PHARMACOL BIOCHEM BEHAV **61**(3) 335–340, 1998.—Both nicotinic cholinergic and NMDA glutaminergic systems are important for memory function. Nicotine has been found repeatedly to significantly improve working memory performance in the radial-arm maze. The NMDA antagonist dizocilpine has been found to impair working memory performance. There is neuropharmacological evidence that these two systems are functionally related. Nicotine is potent at releasing many transmitters including glutamate. The current study was conducted to examine the interaction of nicotinic and NMDA systems with regard to working and reference memory. Rats were trained on a working/reference procedure on a 16-arm radial maze. After acquisition, they were administered nicotine (0, 0.2, and 0.4 mg/kg) and dizocilpine (0, 100, and 200 μg/kg) alone or in combination in a repeated measures, counterbalanced design. As seen previously, nicotine at a dose of 0.2 mg/kg caused a significant improvement in working but not reference memory performance in the radial-arm maze. The 200 μg/kg dose of dizocilpine made the rats nonresponsive on the maze so that choice accuracy could not be assessed. The 100 μg/kg dose of dizocilpine caused significant impairments in both working and reference memory. The 0.4 mg/kg dose of nicotine significantly attenuated the dizocilpine-induced deficit in both working and reference memory. NMDA blockade impairs working and reference memory and blocks the expression of the working memory improvement caused by 0.2 mg/kg of nicotine. However, a higher dose of 0.4 mg/kg of nicotine is effective at attenuating the dizocilpine-induced deficit, even though this dose alone is not effective in improving performance. A second study examined the effects of a lower dose range of dizocilpine. Comensurately smaller memory impairments were seen with lower doses of dizocilpine down to 12.5 μg/kg, which did not produce any significant effects on memory performance or response latency. Nicotine had a more modest effect in attenuating the smaller deficits caused by these lower doses of dizocilpine. These studies provide evidence for important interactions between nicotinic and NMDA systems with regard to memory function. © 1998 Elsevier Science Inc.

Nicotinic Cholinergic NMDA Glutaminergic Nicotine Dizocilpine Working memory Reference memory Memory Radial-arm maze

BOTH nicotinic acetylcholine (ACh) (3,6,13,15) and NMDA glutamate receptor (10) systems have been found to be important for memory function. These systems have direct interactions via nicotine-induced glutamate release (20). The interaction of nicotine and glutamate has been posited as an important basis for nicotine's reinforcing effects (20). Nicotinic–glutamatergic interactions may also be important for nicotine-induced improvements in cognitive function.

It has been shown in numerous studies that nicotine administration improves memory performance in rats, monkeys, and humans [for review see (3,13)]. In addition, other nicotinic agonists such as lobeline (8), dimethylethanolamine (DMAE) (19), ABT-418 (7), and GTS-21 (25) have also been found to be effective in improving memory performance. In a series of studies, we have found both acute nicotine injections and chronic nicotine infusion to improve memory performance in the eight-arm radial maze (15). This effect is blocked by coadministration of the nicotinic antagonist mecamylamine (16,18). Using a larger 16-arm radial maze, we have recently found that both acute and chronic nicotine-

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induced memory improvements are selective for working vs. reference memory (11,12).

Nicotine has its effects by triggering the release of several neurotransmitters including acetylcholine and dopamine as well as glutamate (20,24). Nicotine interacts with other transmitter systems in its cognitive enhancing effects. Acute nicotine-induced radial-arm maze memory improvement is attenuated by coadministration of the muscarinic ACh antagonist scopolamine (18). Acute nicotine administration potentiates the memory improving effects of dopaminergic agonists (14,17). The interactions of nicotinic and NMDA systems with regard to memory function has not been well characterized.

The NMDA glutamate receptor system has been demonstrated in several studies to be important for memory function. Wozniak et al. (26) found that 200 μg/kg but not 100 μg/kg of the NMDA antagonist dizocilpine impaired working memory performance in an eight-arm radial maze. The 200-μg/kg dose also had motor as well as memory impairing effects. Ward et al. (23) found that 500 but not 100 and 330 μg/kg doses of dizocilpine impaired radial-arm maze choice accuracy. Dizocilpine significantly impaired working memory function in the radial-arm maze when testing was conducted in an unfamiliar environment but not in a familiar environment (4,22). Cole et al (5) found that both 100 and 200 μg/kg of dizocilpine caused significant deficits in an operant delayed-matching-to-position task in a delay-independent manner. The deficits caused by dizocilpine may be nonspecific in nature, given the motor effects and lack of delay dependent effects.

There were three goals of the current study. The first was to replicate the selective effect of acute nicotine improving working memory but not reference memory performance in the 16-arm radial maze. The second was to determine the relative effect of the NMDA antagonist dizocilpine on working vs. reference memory in the 16-arm radial maze. The third was to determine the interactive effects of nicotine and dizocilpine in the radial-arm maze. The results should give an insight into the mechanism by which both nicotine and dizocilpine function and provide further data as to possible the therapeutic value of nicotine to attenuate memory impairment.

METHOD

Subjects

Young adult female Sprague–Dawley strain rats (Zivic-Miller, Allison Park, PA) were used in the present experiment ($n = 24$). They were kept on a reverse 12-h on:12-h off light cycle (lights on at 0600 h). The rats were housed in groups of three in plastic cages with wood shavings. They had ad lib access to water. They were fed daily approximately 15 g of Purina rat chow after testing such that their weights were kept at 80–85% of free-feeding levels. This feeding schedule began before the beginning of training and continued throughout the experiment.

Radial-Arm Maze

Behavioral testing was conducted on a radial 16-arm maze constructed of wood and painted black. The central arena was 50 cm in diameter and 16 10 × 60 cm arms extended radially; food cups were located 2 cm from the distal end of each arm. There were transparent plastic barriers along the sides of the proximal portion of each arm to prevent the rats from jumping from one arm to another. The maze was positioned 30 cm above the floor in a testing room, which contained many extramaze visual cues. The rats were trained for 2–4 days per week for 18 sessions over a period of 2 months. For each session, the same 12 arms were baited at the beginning of the session with a half piece of cereal (Kellogg's Froot Loops) testing working memory, leaving four arms always unbaited testing reference memory. At the start of the session, the rat was placed in a circular plastic ring at the center of the maze for 10 s to eliminate any bias of placement. The ring was then removed, and the rat completed the task once all the baited arms were entered, or 10 min had passed. Repeated entries into baited arms were considered working memory errors, and entries into unbaited arms were considered reference memory errors. The latency measure was the total time the rat took to finish the maze divided by the number of total entries into an arm.

Drug Treatment

After the 18 sessions of acquisition in which no drug injections were made, the rats began the drug studies. In Study 1 ($n = 12$), the drug treatments consisted of (−)nicotine ditartrate at doses of 0, 0.2, and 0.4 mg/kg, (+)dizocilpine maleate at doses of 0, 100, and 200 μg/kg, and every combination of the two drugs for nine total dose combinations. In Study 2 ($n = 12$), the drug treatments consisted of (−)nicotine ditartrate at doses of 0, 0.2, and 0.4 mg/kg, (+)dizocilpine maleate at doses of 0, 12.5, 25, and 50 μg/kg and every combination of the two drugs for 12 total dose combinations. All doses were dissolved in 0.9% saline and injected subcutaneously 20 min before the rats were tested. Each rat was given at least 48 h between injections to ensure that the effects of the previous injection had dissipated. Each rat was tested two to three times per week over a period of a month.

Statistics

The choice accuracy and response duration measures were assessed by a within subjects design analysis of variance. The hypothesis was that dizocilpine would impair performance and nicotine would attenuate that effect. Thus, planned comparisons were made between dizocilpine given alone and the saline control injection and between dizocilpine given alone and dizocilpine given together with nicotine. A p-value less than 0.05 (two tailed) was considered significant. A p-value between 0.10 and 0.05 (two tailed) was considered to be suggestive of an effect.

RESULTS

Nicotine Effects

In the two studies there were a total of 24 rats ($n = 12$ in each study). The doses of nicotine were common in the two studies. An analysis of the effects of nicotine showed that there was a significant effect of nicotine with working memory errors, $F(2, 44) = 5.22$, $p < 0.01$. Planned comparisons of each nicotine dose to the saline control showed a significant ($p < 0.005$) reduction in working memory errors caused by the 0.2 mg/kg dose of nicotine (Fig. 1). The 0.4 mg/kg dose of nicotine caused a slight mean reduction in working memory errors, but this was not significantly different from saline. With reference memory errors there was a nearly significant ($p < 0.06$) effect of 0.2 mg/kg nicotine treatment reducing error relative to saline (Fig. 1). Again, the higher dose of 0.4 mg/kg was ineffective. There was a highly significant effect of nicotine on response latency, $F(2, 44) = 13.70$, $p < 0.0005$. Planned comparisons showed that relative to saline (20.6 ± 1.9 s per

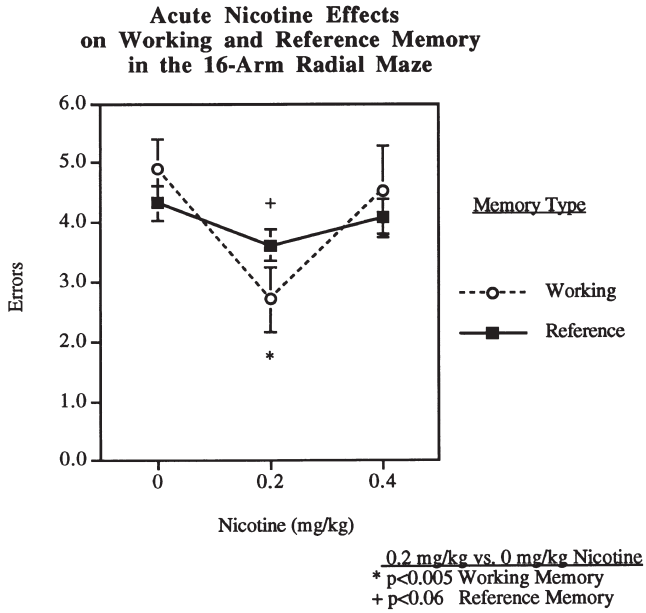

FIG. 1. Acute nicotine effects in rats from Studies 1 and 2 ($n = 24$) on working and reference memory performance in the 16-arm radial maze (mean ± SEM). The 0.2 mg/kg dose of nicotine caused a significant ($p < 0.005$) decrease in working memory errors and a nearly significant ($p < 0.06$) decrease in reference memory errors.

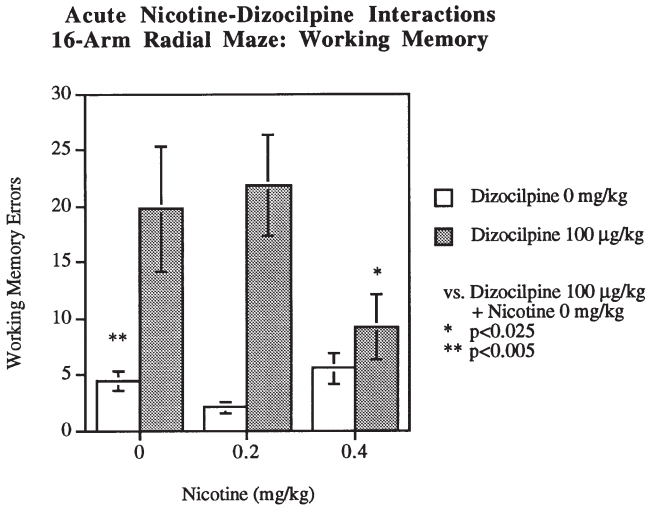

FIG. 2. Interactions between acute nicotine and dizocilpine ($n = 9$) on working memory performance in the 16-arm radial maze (mean ± SEM). The 0.1 mg/kg dose of dizocilpine caused a significant ($p < 0.005$) increase in working memory errors relative to the saline injected control. This effect was significantly ($p < 0.025$) attenuated by 0.4 mg/kg of nicotine.

entry), significantly faster response was seen with 0.2 mg/kg of nicotine (15.2 ± 1.1 s per entry, $p < 0.0005$) and 0.4 mg/kg of nicotine (14.9 ± 0.9 s per entry, $p < 0.0005$).

Study 1, High-Dose Dizocilpine–Nicotine Interactions

The 200 µg/kg dose of dizocilpine caused considerable disruption of performance in all 12 of the rats such that memory performance could not be assessed. The lower 100 µg/kg dose did not cause nearly as much disruption, but there were three rats that did not finish the task at this dose and could not be included in the analysis. Thus, $n = 9$ for analyses of the nicotine–dizocilpine interactions.

With working memory, the main effect of dizocilpine was significant, $F(1, 8) = 15.54$, $p < 0.005$, reflecting an overall dizocilpine-induced working memory deficit (Fig. 2). The overall nicotine main effect was not significant. There was a significant dizocilpine × nicotine interaction, $F(2, 16) = 4.34$, $p < 0.05$. The planned comparisons showed that without nicotine, 100 µg/kg dizocilpine caused a significant working memory impairment relative to saline ($p < 0.005$). There was no significant attenuation of this effect with the 0.2 mg/kg dose of nicotine but the higher dose of 0.4 mg/kg of nicotine did significantly ($p < 0.025$) attenuate the dizocilpine-induced working memory deficit (Fig. 2).

With reference memory, the main effect of dizocilpine was significant, $F(1, 8) = 14.60$, $p < 0.01$, reflecting an overall dizocilpine-induced reference memory deficit. The overall nicotine main effect and dizocilpine × nicotine interaction were not significant. The planned comparisons showed that without nicotine, 100 µg/kg dizocilpine caused a significant working memory impairment relative to saline ($p < 0.005$). There was no significant attenuation of this effect with the 0.2 mg/kg dose of nicotine, but the higher dose of 0.4 mg/kg of nicotine did significantly ($p < 0.025$) attenuate the dizocilpine-induced reference memory deficit (Fig. 3).

With response latency, there was a nearly significant main effect of dizocilpine, $F(1, 8) = 4.34$, $p < 0.08$) reducing response latency (Fig. 4). Planned comparisons showed a significant speeding of response caused by 100 µg/kg of dizocilpine relative to saline ($p < 0.025$). Nicotine coadministration did not attenuate this effect.

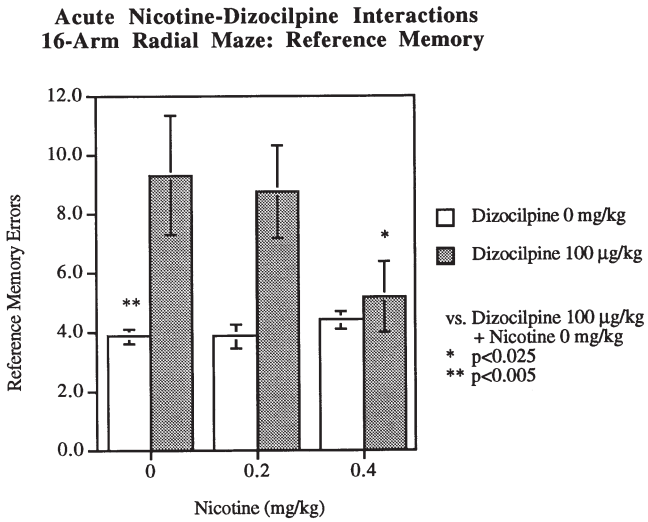

FIG. 3. Interactions between acute nicotine and dizocilpine ($n = 9$) on reference memory performance in the 16-arm radial maze (mean ± SEM). The 0.1 mg/kg dose of dizocilpine caused a significant ($p < 0.005$) increase in working memory errors relative to the saline injected control. This effect was significantly ($p < 0.025$) attenuated by 0.4 mg/kg of nicotine.

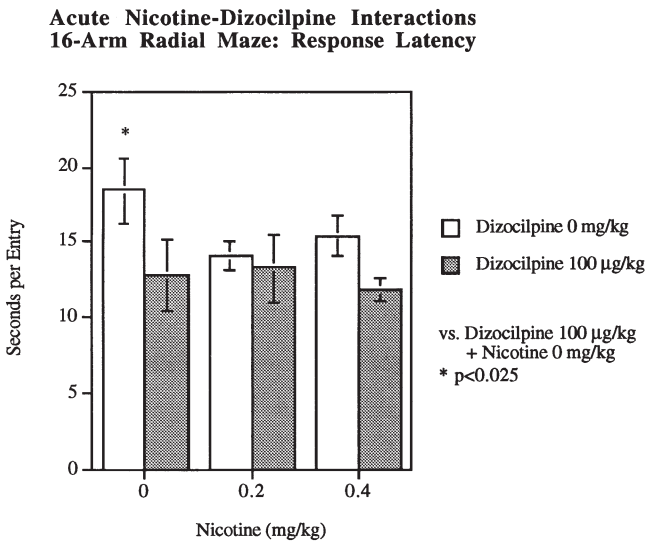

FIG. 4. Interactions between acute nicotine and dizocilpine ($n = 9$) on response latency in the 16-arm radial maze (mean ± SEM). The 0.1 mg/kg dose of dizocilpine caused a significant ($p < 0.025$) decrease in latency vs. saline injected control.

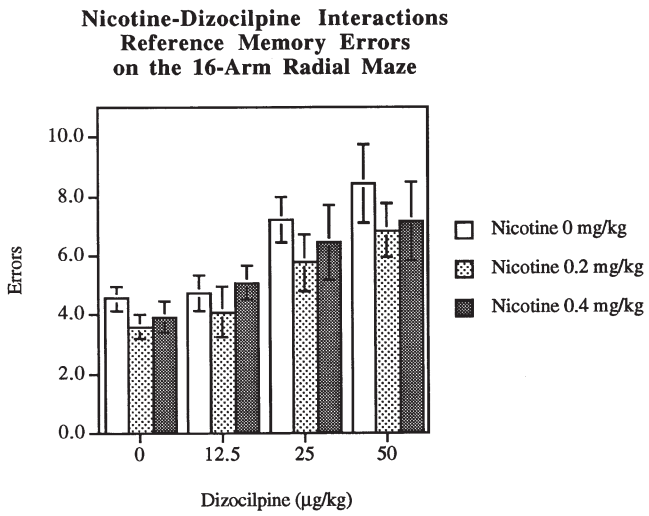

FIG 6. Interactions between acute nicotine and dizocilpine ($n = 12$) on reference memory in the 16-arm radial maze (mean ± SEM). The 25 and 50 µg/kg doses of dizocilpine caused significant ($p < 0.05$) increases in reference memory errors relative to the saline injected control. The 0.2 mg/kg dose of nicotine had a nearly significant ($p < 0.06$) attenuation of the dizocilpine-induced reference memory deficit.

Study 2, Low-Dose Dizocilpine–Nicotine Interactions

With working memory, there was a significant effect of dizocilpine ($F(3,33)=14.54$, $p < 0.0005$) impairing performance (Fig. 5). No effect of the 12.5 µg/kg dose was seen, but both the 25 µg/kg ($p < 0.0005$) and 50 µg/kg ($p < 0.0005$) dizocilpine doses caused significant impairments relative to the saline injection condition. Both 0.2 and 0.4 mg/kg of nicotine caused a slight attenuation of these deficits but the effect was not significant.

With reference memory, a similar pattern of effects was seen (Fig. 6). There was a very significant main effect of dizocilpine, $F(3, 33) = 7.62$, $p < 0.0005$. Significant deficits were caused by 25 µg/kg ($p < 0.05$) and 50 µg/kg ($p < 0.005$) dizocilpine, but the 12.5 µg/kg dose was ineffective. The 0.2 mg/kg dose of nicotine caused a nearly significant ($p < 0.06$) attenuation of the dizocilpine-induced deficit. The 0.4 mg/kg dose of nicotine caused a slight attenuation of the dizocilpine deficits but the effect was not significant.

With latency, both nicotine, $F(2, 22) = 15.42$, $p < 0.0005$, and dizocilpine, $F(3, 33) = 15.67$, $p < 0.0005$, had significant main effects (Fig. 7). The 12.5 µg/kg dizocilpine dose did not

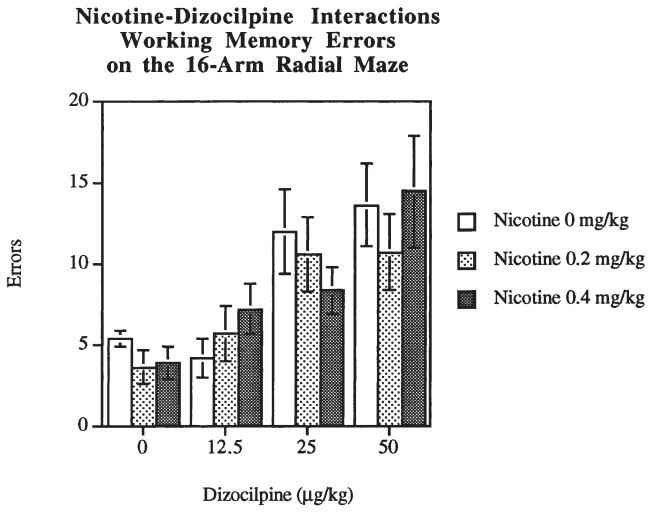

FIG. 5. Interactions between acute nicotine and dizocilpine ($n = 12$) on working memory in the 16-arm radial maze (mean ± SEM). The 25 and 50 µg/kg doses of dizocilpine caused significant ($p < 0.0005$) increases in working memory errors relative to the saline injected control.

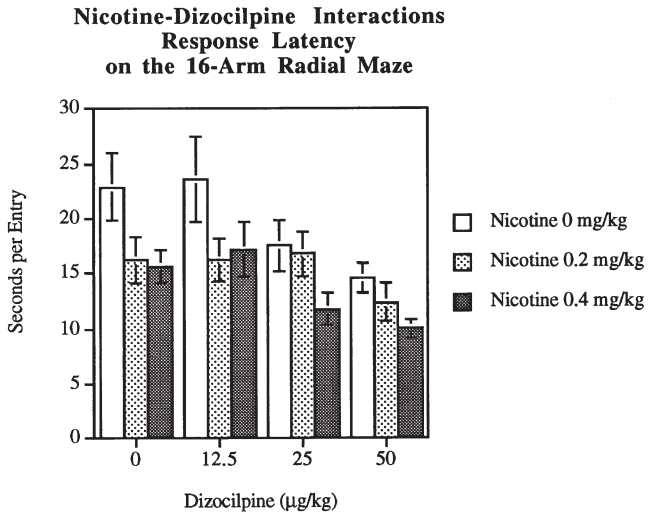

FIG. 7. In Study 2 ($n = 12$), both acute nicotine and dizocilpine significantly ($p < 0.0005$) decreased response latency in the 16-arm radial maze (mean ± SEM). The 25 and 50 µg/kg doses of dizocilpine, but not the 12.5 µg/kg dose significantly ($p < 0.05$) reduced response latency. Both the 0.2 and 0.4 mg/kg doses of nicotine caused significant ($p < 0.025$) decreases in latency relative to the saline injected control.

significantly affect latency, but both the 25 μg/kg ($p < 0.05$) and the 50 μg/kg ($p < 0.005$) dizocilpine doses significantly lowered latencies. Both the 0.2 mg/kg ($p < 0.025$) and the 0.4 mg/kg ($p < 0.01$) doses of nicotine significantly lowered latencies.

DISCUSSION

The present study showed that nicotine can attenuate the memory impairment caused by the NMDA antagonist dizocilpine. As seen previously, nicotine by itself caused a significant improvement in working memory performance, whereas reference memory performance was not significantly affected. Dizocilpine caused a significant deficit in both working and reference memory. Coadministration of nicotine significantly attenuated both working and reference memory deficits caused by a high dose of dizocilpine.

As previously demonstrated by McLamb et al. (21), this study found that dizocilpine causes an impairment in cognitive performance as demonstrated by the increase in the mean number of working and reference errors with a dose of 100 μg/kg of dizocilpine. As suggested by Wozniak et al., a dose of 200 μg/kg of dizocilpine may be too high for rats and causes loss of motor control and creates an appearance of intoxication (26). Nicotine, however, did appear to attenuate this loss of motor control, as the rats were able to move with greater ease and stayed on the maze longer before falling off the edge when given the combination of dizocilpine and nicotine. In contrast to the current study, Wozniak et al. (26) did not find 100 μg/kg of dizocilpine to cause significant deficits on memory performance in the radial-arm maze. However, they used an easier task in an eight-arm maze that did not require simultaneous performance of working and reference memory components. Hönack and Lösher (9) found that female rats were more sensitive than males to the hyperactivity caused by dizocilpine. Given that Wozniak et al. (26) used male rats and we used female rats, the differing results of the studies may have been due to the greater susceptibility of females to dizocilpine.

Nicotine did not seem to have its effects of attenuating the dizocilpine-induced memory deficit by mere additive behavioral effects. The dose of nicotine that was effective in reducing working memory errors when given alone (0.2 mg/kg) was ineffective in attenuating the dizocilpine-induced deficit. It took the higher dose of nicotine (0.4 mg/kg) to provide this effect. Interestingly, the 0.4 mg/kg dose of nicotine when given alone did not significantly improve working memory performance. This may have been due to the inverted U-shaped dose–effect function, which is often seen with memory-enhancing drugs. The 0.2 mg/kg dose of nicotine effectively reversed the dizocilpine-induced deficit in reference memory. The fact that this dose of nicotine did not by itself have any significant effect on reference memory errors is also evidence against the possibility of mere additive behavioral effects of nicotine and dizocilpine.

The choice-accuracy deficit caused by 100 μg/kg of dizocilpine was evident with both working and reference memory. It also caused a significant hyperactivity. There is the possibility that the dizocilpine-induced choice-accuracy deficit was not due to memory impairment but secondary to motor or perceptual impairment. The nicotine-induced attenuation of the choice-accuracy impairments did not seem to be secondary to nicotine effects on motor activity, because there was no evidence for nicotine-induced attenuation of the dizocilpine-induced hyperactivity. Nicotine itself increased the speed of response, but this was not additive with the similar dizocilpine effect.

The second study provided a more detailed description of the dose–response curve for lower doses of dizocilpine. No effects of 12.5 μg/kg of dizocilpine were seen for working memory, reference memory, or response latency. Increasing effects were seen for the 25- and 50-μg/kg doses that produced deficits more modest than the 100-μg/kg dose used in Study 1. There was some evidence for attenuation of the dizocilpine-induced deficit caused by these lower doses, but the effects were more modest than those seen in the high dose study.

In these studies, the animals were pretrained so that drug effects on memory performance would be assessed during the stable asymptotic postacquisition phase of performance. The within-subjects counterbalanced design was used so that possible carryover drug effects would not be confounded with order of treatment dose. At least 2 days were interposed between drug doses to minimize carryover effects.

Nicotine may have counteracted the dizocilpine-induced memory deficits through its action in stimulating glutamate release (20). However, because nicotine and NMDA receptors are similar in structure, crossreactivity of ligands for these receptors may also be involved in the observed interactions. Nicotine has effects at the NMDA receptor, and dizocilpine has effects at nicotinic receptors (1,2). The ultimate mechanisms underlying these interactions awaits further study.

The current study showed that nicotine attenuated the working and reference memory impairments caused by dizocilpine. This provides information concerning the dual involvement of nicotinic and NMDA systems in the neural bases of memory function. These results also provide a further demonstration of the efficacy of nicotine in reversing memory impairment and provides information concerning the possible therapeutic use of nicotine or other nicotinic drugs to treat cognitive dysfunction.

ACKNOWLEDGEMENTS

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