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Effects of Lobeline, a Nicotinic Receptor Agonist, on Learning and Memory

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DECKER, M. W., M. J. MAJCHRZAK AND S. P. ARNERIĆ. *Effects of lobeline, a nicotinic receptor agonist, on learning and memory.* PHARMACOL BIOCHEM BEHAV **45**(3) 571–576, 1993.—The effects of (−)-lobeline were assessed in two learning and memory tasks in which nicotine-induced enhancement of performance has previously been demonstrated. Lobeline (19 μmol/kg, IP) administered immediately after inhibitory (passive) avoidance training improved retention performance assessed 24 h later, as rats that received this dose of lobeline took significantly longer to enter the shock compartment on the test day than rats that had been treated with vehicle. Pretraining lobeline treatment (1.9 μmol/kg, IP) significantly improved performance of rats with septal lesions in a spatial discrimination water maze, a finding confirmed when rats were retrained using new spatial locations and vehicle and lobeline treatments were reversed in a crossover design. The effective dose of lobeline in the inhibitory avoidance task was about 10-fold higher than that generally reported for nicotine, and direct comparison of the suppression of locomotor activity shortly after administration of nicotine or lobeline also revealed a 10-fold greater potency for nicotine. In contrast, no difference was found between the effective dose of lobeline in the current study and that we previously found with nicotine in the water maze. These findings suggest that lobeline's effects on the performance of learning and memory tasks may be similar to those of nicotine. Coupled with previous reports that lobeline does not produce the nicotine cue in drug discrimination experiments, this study also suggests that nicotinic receptors involved in the modulation of memory processes may be distinct from those involved in producing the nicotine cue.

Nicotinic receptor agonists Lobeline Nicotine Learning Memory Locomotor activity Water maze Inhibitory avoidance

(−)-LOBELINE is a compound that binds to nicotinic cholinergic receptors with high affinity and enters the brain readily upon systemic administration (20,21). Still, it does not substitute for nicotine in drug discrimination procedures and does not antagonize the ability of nicotine itself to produce the nicotine cue in these studies (21,23). This set of findings suggests that lobeline is a potent nicotinic ligand with neither agonist nor antagonist activity in this paradigm. Differences in the behavioral effects of lobeline and nicotine in drug discrimination experiments suggests the need to compare the effects of these two compounds on other behavioral measures.

Of particular interest among the behavioral effects of nicotine are its effects on learning and memory. Nicotine improves the performance of experimental animals in a variety of learning and memory tasks. In rodents, nicotine improves the retention of shock avoidance training (12,19) and reduces errors in the radial arm maze (14). In primates, nicotine improves the performance of both young and aged monkeys in a delayed match-to-sample task (4,9). Furthermore, nicotine improves spatial memory performance in rats with lesions of cholinergic basal forebrain structures (7,13). Lobeline, on the other hand, has not been extensively tested in memory tasks. Both lobeline and nicotine have been reported to reduce error rates in an operant discrimination task, although lobeline appears to be less potent than nicotine in this task (11). In this experiment, however, several other compounds similarly improved performance on this task, including chlordiazepoxide, a benzodiazepine anxiolytic agent that impairs spatial memory performance in rats (17). Thus, it is perhaps unlikely that the drug-induced improvement of discrimination performance in this task is indicative of enhanced learning and memory.

Given the differences in the effects of lobeline and nicotine in drug discrimination experiments and the limited information regarding the relative effects of these two nicotinic agents on learning and memory, we evaluated the learning and memory effects of lobeline. For purposes of comparing lobeline's effects with those produced by nicotine, two learning and memory tasks were selected on which we have previously reported effects with nicotine—inhibitory avoidance in normal rats (16) and spatial discrimination water maze performance in rats with septal lesions (7). In addition, the effects of these two compounds on locomotor activity, a behavior also af-

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fected by nicotinic receptor stimulation, were directly compared.

METHOD

Subjects

Male, Long-Evans rats (Charles River) weighing from 250–350 g were used in the experiments. Rats were maintained in a climate-controlled facility with a 12 L : 12 D cycle. Behavioral testing was conducted during the light portion of the day.

Surgery

Lesions of the septal area were produced by delivering radiofrequency current under stereotaxic control. Rats were anesthetized with pentobarbital (55 mg/kg, IP), and the electrode was placed in the septal area using the coordinates 0.5 mm anterior to bregma, 0.0 mm lateral to the midline, and 6.5 mm ventral to the skull surface. Current sufficient to maintain a temperature of 61 °C at the electrode tip was passed for 25 s. Sham surgery was conducted by lowering an electrode to a point 1.0 mm above the target location for the lesions but passing no current. At the end of the behavioral experiments, rats were sacrificed and the lesions verified histologically.

Water Maze Training

Beginning 10–14 days after surgery, rats were trained in a spatial discrimination version of the Morris water maze, as previously described (7). Rats were first trained to find a visible escape platform in a round pool (180 cm in diameter and 60 cm high) filled to a depth of 37 cm with water (26 ± 1 °C) rendered opaque by the addition of powdered milk. Following this habituation training, rats were trained on the spatial discrimination water maze. In this task, two visible platforms similar in appearance to the platform used in cue training were used, but only one of the platforms provided a means of escape from the water: The other was made of expanded polystyrene and did not support the animal's weight. The position of each platform remained constant in relation to extramaze cues available in the room during training. Rats were given six trials per day, with the start location being changed from trial to trial. Contacts with the incorrect platform were scored as errors.

On each of the first 4 days of training, (−)-lobeline (0, 1.9, or 19 μmol/kg) was administered 15 min before training (n = 4–5 per group). A six-trial retention test session was conducted on the fifth day. No additional drug was injected before this retention test session. Beginning 10 days after the original training, rats that had received either vehicle or the lower dose of lobeline were retrained using two new platform locations. During training on this new spatial discrimination problem, a crossover design was used for drug treatment—rats received the drug treatment opposite that received during initial training [i.e., rats originally trained under 1.9 μmol/kg lobeline received vehicle injections before training in this phase and rats originally trained using vehicle injections received 1.9 μmol/kg (−)-lobeline during the retest]. The general procedures used during retraining were the same as those used for initial training.

Inhibitory (Passive) Avoidance

Unoperated, naive rats (n = 15 per group) were used in this experiment. Animals were trained using an automated avoidance training system (Gemini, San Diego Instruments, San Diego, CA). Training was initiated by placing the rat in a 21 × 25 × 17-cm brightly lit chamber. After a delay of 10 s, a guillotine door leading to darkened chamber of the same size automatically opened. When the rat crossed completely into the dark chamber, the door was closed and a scrambled, constant-current (0.8 mA) foot-shock was delivered through a grid floor for 2 s. After termination of the foot-shock, the rat was immediately removed from the apparatus, given an injection of (−)-lobeline (0, 0.62, 1.9, 6.2, and 19.0 μmol/kg, IP), and returned to its home cage. Retention of the training experience was measured 24 h later by again measuring the rat's latency to enter the dark compartment. Longer latencies on this second exposure were interpreted as indicating better retention of the training experience. Because posttraining injections were used, rats were not under the direct influence of drug during either training or retention testing. This procedure therefore allows for an assessment of drug effects on posttraining memory consolidation processes.

Locomotor Activity

Open-field locomotor activity was measured in naive rats (n = 6–8 per group) beginning 2 min after an injection of (−)-nicotine (0, 1.9, or 6.2 μmol/kg, IP) or (−)-lobeline (0, 6.2, 19, or 62 μmol/kg, IP). Horizontal activity counts in the 41 × 41-cm open field were recorded for 60 min in 10-min bins using Digiscan activity monitors (Omnitech Electronics, Columbus, OH).

Statistics

Initial acquisition data from the water maze were analyzed using a three-way repeated-measures analysis of variance (ANOVA), with session as the repeated measure and drug dose and lesion as between-group measures. Performance during the retention session (the session not immediately preceded by drug injection) was analyzed separately using a two-way ANOVA. The crossover water maze data were analyzed using session and drug as the within-subject measures and lesion as the between-group measure. In this analysis, data from both the initial and retraining sessions were included.

Because the latency data derived from the inhibitory avoidance experiment were not normally distributed, these data were analyzed nonparametrically using the Mann–Whitney U-test.

Locomotor activity was analyzed using a two-way repeated-measures ANOVA with drug dose as the between-group measure and time as the within-group measure.

Drugs

(−)-Lobeline (HCl salt; Sigma Chemical Co., St. Louis, MO) was dissolved in distilled water and (−)-nicotine (hydrogen tartrate salt; Sigma) was dissolved in 0.9% sterile saline. Both drugs were injected IP. The doses were selected based upon previous experience with (−)-nicotine (1.0 mg nicotine base = 6.2 μmol). Control injections consisted of vehicle (1.0 ml/kg).

RESULTS

Locomotor Activity

As can be seen in Fig. 1, both nicotine and lobeline significantly affected locomotor activity [for nicotine: drug effect, $F(2, 21) = 2.46$, $p > 0.10$; time effect, $F(5, 105) = 14.67$, $p < 0.0001$; and nicotine × time interaction, $F(10, 105) = 7.79$, $p < 0.0001$; for lobeline: drug effect, $F(3, 21) = 2.00$, $p > 0.10$; time effect, $F(5, 105) = 80.81$, $p < 0.0001$; and lobeline × time interaction, $F(15, 105) = 2.51$, $p < 0.01$].

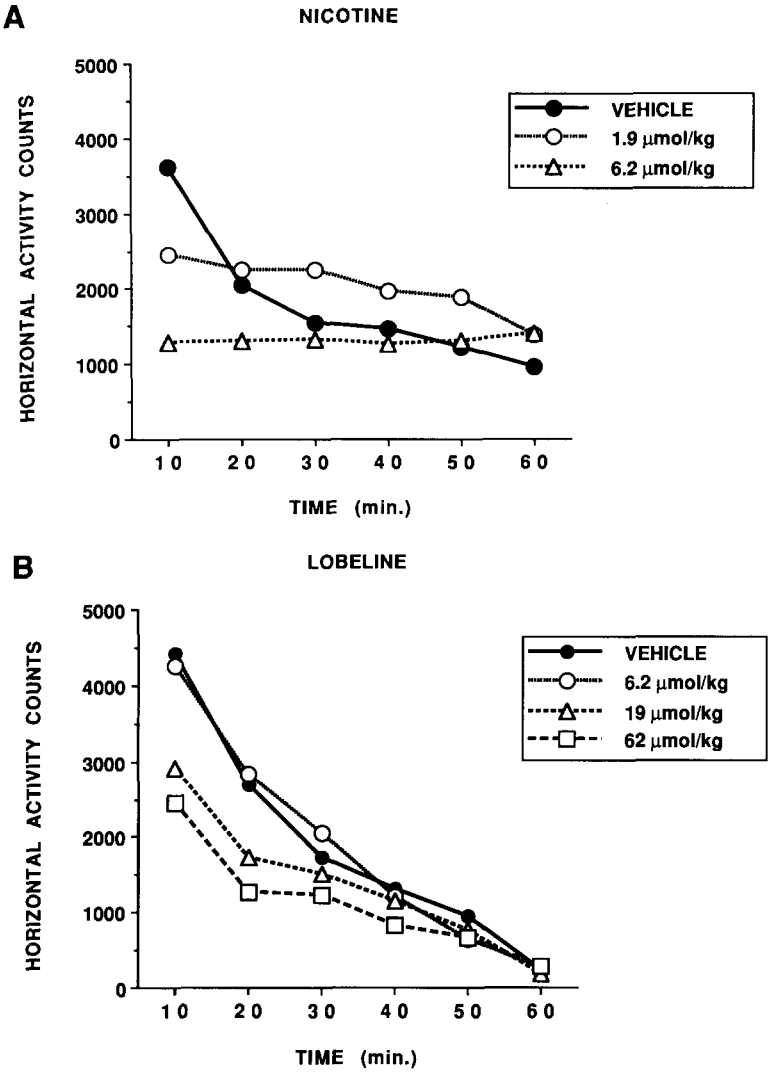

FIG. 1. Locomotor activity in rats after IP administration of (A) nicotine or (B) lobeline during a 60-min session in an open field. Both compounds reduced locomotor activity in the early portion of the session, although with different potency. n = 6–8 per group.

For both compounds, a reduction in locomotor activity that was restricted to the early part of the session was noted. Comparison of Figs. 1A and 1B, however, reveals that nicotine was at least 10 times more potent than lobeline on a molar basis in reducing locomotor activity.

Inhibitory (passive) Avoidance

Posttraining administration of lobeline improved retention of inhibitory avoidance training (Fig. 2), an effect that was only significant at 19.0 μmol/kg ($U = 66, p < 0.05$).

Histology

The lesions in this experiment were of moderate size and primarily affected the medial portion of the septal area. Involvement of the lateral septum was observed in only a few rats. Little damage to the anterior commissure was noted; however, some lesions extended caudally into the most rostral aspects of the fimbria/fornix. Two animals were excluded from the behavioral analysis on the basis of histology, one because no lesion could be detected and the other because the lesion was too far posterior. Two animals with small but well-placed lesions were included. Ratings of the lesions were done without knowledge of the behavioral results.

Spatial Discrimination Water Maze

Analysis of the initial training data on the water maze reveals neither a lesion effect, $F(1, 21) = 2.31, p > 0.10$, nor a lobeline effect, $F(2, 21) = 2.46, p > 0.10$, but a significant lesion × lobeline interaction, $F(2, 21) = 4.43, p < 0.025$. Figure 3 illustrates the performance of animals during initial training. Here, it can be seen that septal lesions impaired the performance of rats given control injections and that lobeline differentially affected the performance of sham and lesioned rats. The performance of sham rats was unaffected by the

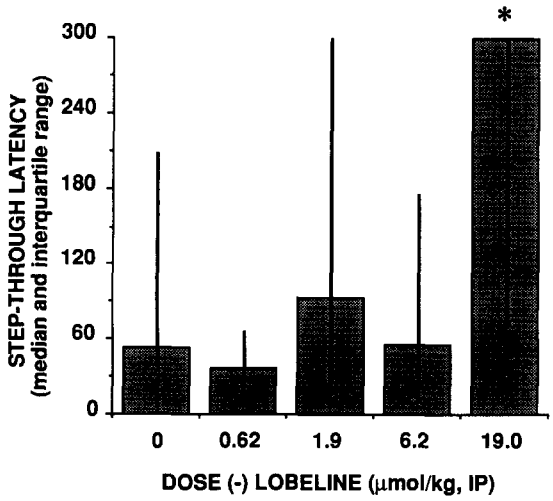

FIG. 2. Retention test performance of rats that received lobeline immediately after training. The highest dose tested significantly enhanced retention test performance. *Significantly different from saline group, $p < 0.05$ by Mann-Whitney U. $n = 15$ rats per group.

lower dose but tended to be impaired by the higher dose. The performance of lesioned rats was improved by the lower dose of lobeline. In addition, the effect of lobeline varied as a function of training day, resulting in a significant lobeline × training day interaction, $F(6, 63) = 4.34$, $p < 0.005$. Lobeline appeared to produce greater effects toward the end of training.

Analysis of the performance of these animals on day 5, when no drug injections were made, revealed a pattern of performance similar to that found on day 4, as a marginally significant lesion × lobeline effect, $F(2, 21) = 3.34$, $p < 0.06$, was obtained (data not shown).

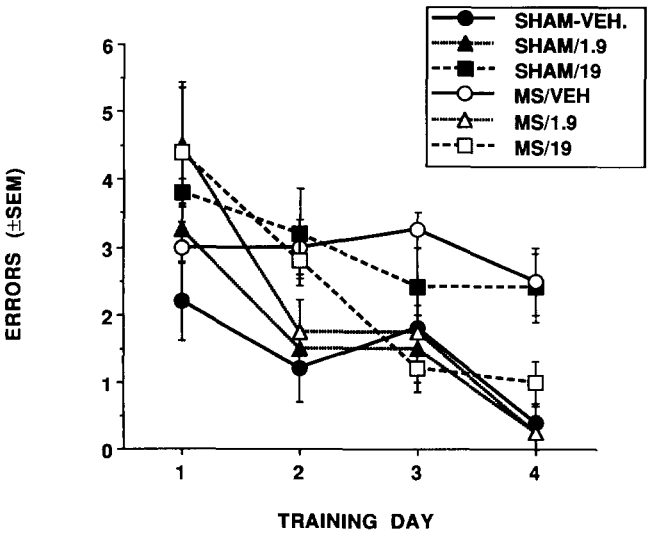

FIG. 3. Mean errors (±SEM) during initial acquisition of the spatial discrimination water maze. The middle dose significantly improved the performance of rats with septal lesions. The higher dose was less effective and actually impaired the performance of sham-operated rats. $n = 4$–5 per group.

When animals receiving the low dose of lobeline and vehicle injections were retrained to new platform locations in a crossover design, the performance-enhancing effects of lobeline on septal-lesioned rats was confirmed. The analysis of this crossover experiment reveals a significant lesion effect, $F(1, 15) = 30.56$, $p < 0.001$, and a significant lobeline × training day interaction, $F(3, 45) = 5.12$, $p < 0.005$. By the last day of training, the lobeline-induced enhancement of performance was quite pronounced in septal-lesioned rats (Fig. 4).

DISCUSSION

In this study, we demonstrated cognitive-enhancing effects of (−)-lobeline that were comparable to those we previously found for (−)-nicotine using these same tasks (7,16). The similarities in the behavioral results we obtained with these two compounds in the current study contrast with the marked differences reported in drug discrimination experiments, differences we also observed in our laboratory using drug discrimination techniques (unpublished data). These two sets of findings suggest that the mechanisms underlying the behavioral effects of nicotinic receptor stimulation may be task dependent. Alternatively, lobeline and perhaps even nicotine may produce cognitive effects through actions at nonnicotinic receptors.

Posttraining administration of lobeline improved retention of inhibitory avoidance in the current experiment just has we previously reported with nicotine (16). The effective dose of lobeline, however, was at least 10-fold higher than the posttraining dose of nicotine typically required to improve inhibitory avoidance performance (12,16). This lower potency of lobeline relative to nicotine on this task is comparable to the relative potency of these two compounds we observed in their effects on locomotor activity. Here, too, lobeline effects were comparable to those obtained with nicotine but were only

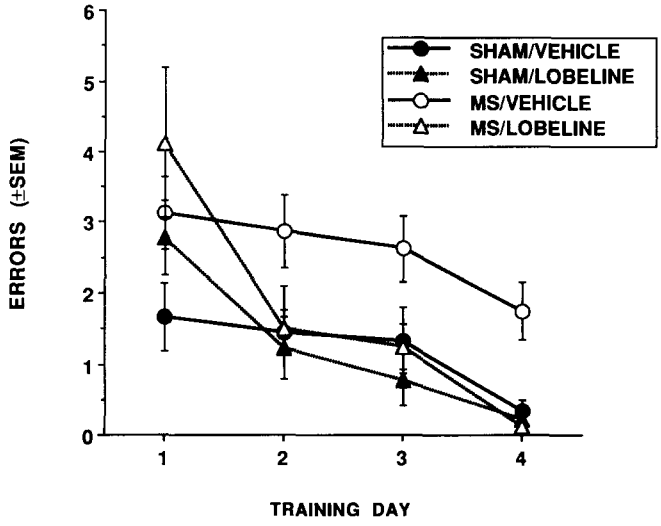

FIG. 4. Mean errors across 4 training days in the spatial discrimination water maze in a crossover study. Rats receiving 0 or 1.9 μmol/kg lobeline in the experiment depicted in Fig. 3 were trained to a new set of platform locations and received the drug treatment opposite that received during initial acquisition. Shown here are the cumulative results from both phases of this crossover experiment. Lobeline at this dose did not affect the performance of sham-lesioned rats but improved the performance of septal-lesioned rats. $n = 8$–9/group.

observed at higher doses. The differences in potency between lobeline and nicotine in these two tasks are consistent with binding and pharmacokinetic data available on these compounds (21).

The mechanisms by which nicotinic receptor stimulation enhances retention of inhibitory avoidance is not known. One potential mechanism would be through nicotine-induced release of catecholamines (10). Brioni et al. (2) suggested dopamine release is important in the effect of pretraining administration of nicotinic agonists on retention of inhibitory avoidance training in mice. In support of this hypothesis, they demonstrated that the ability of nicotinic agonists to release dopamine from striatal slices, and presumably other dopamine terminals, is correlated with the ability of these compounds to improve retention of inhibitory avoidance training. Consistent with this interpretation, the enhanced retention of inhibitory avoidance performance induced by pretraining injections of nicotine can be substantially attenuated by dopamine blockade (2). It is unclear, however, whether mechanisms involved in nicotine-induced enhancement of the retention of inhibitory avoidance training found with pretraining injections in mice are the same as those mediating the enhancement found in rats receiving posttraining injections in the current study. Indeed, our finding that lobeline and nicotine have similar effects on retention upon posttraining administration in rats would be inconsistent with the involvement of catecholamine release in the effect we observed because lobeline does not appear to cause the release of catecholamines (3,26).

The disparity between nicotine and lobeline effects on dopamine release might also explain an apparent difference in the pattern of effects of these compounds on locomotor activity. As can be seen in Fig. 1, both nicotine and lobeline reduced locomotor activity during the early part of the session. However, the effects of these two compounds during the latter part of the session are somewhat different. Nicotine (at 1.9 μmol/kg) appeared to elevate locomotor activity toward the end of the session whereas no such tendency was noted with lobeline. This biphasic locomotor response to acute nicotine in drug-naive rats is well documented (5), and it is believed that the late-developing increase in locomotor activity is related to stimulation of dopamine release (5,24). Thus, because lobeline is relatively ineffective in releasing dopamine it is not surprising that the late-developing activation of locomotor activity found in nicotine-treated rats was not observed in our lobeline-treated rats. Given that nicotine-induced dopamine release may be important in producing the nicotine cue in drug discrimination experiments (24), lobeline's relative inability to release dopamine may also explain its failure to produce the nicotine cue.

Similar to its ability to improve retention of inhibitory avoidance performance, lobeline enhanced the water maze performance of septal-lesioned animals, an effect comparable to that we previously reported for nicotine using exactly these same procedures (7). Similarities in the pattern of effects produced by these two compounds were also noted. In the current study, rats with septal lesions were impaired in acquiring a spatial discrimination in the water maze, an impairment similar to that we previously reported with septal lesions (7,8). Pretraining injections of lobeline improved performance in lesioned rats, and these improvements were maintained even in a subsequent test session conducted with no drug injection. Thus, once the spatial discrimination was acquired, lobeline was not required for continued accurate performance. In contrast, lobeline-treated animals were impaired when subsequently trained on a new spatial discrimination without additional lobeline. This pattern of effects is the same as that we previously reported for nicotine and consistent with the interpretation that the nicotinic cholinergic receptor ligands nicotine and lobeline improve water maze performance via similar mechanisms.

Interestingly, the higher dose of lobeline actually impaired the performance of sham-lesioned rats in the water maze task. Conceivably, this could have been due to nonspecific effects on performance variables such as motivation and sensorimotor function, as this dose of lobeline tended to reduce locomotor activity in the open field. Alternatively, the impaired performance in sham-lesioned rats receiving the high dose of lobeline could be due to lobeline's effects at NMDA receptors. Nicotinic agonists appear to bind to NMDA receptors (1,6), with lobeline binding with more than 10-fold greater affinity than (−)-nicotine (1). Electrophysiological results suggest that these nicotinic agonists may be functional antagonists at the NMDA receptor (1). Potent NMDA antagonists, such as AP-5 and MK-801, impair performance on the water maze (18,22), just as the high dose of lobeline did in the current experiment. It is unclear, however, whether the 19-μmol/kg dose of lobeline that impaired the water maze performance of sham-lesioned rats in our experiment would be high enough to effect significant blockade of central NMDA receptors. It should be noted that our finding that this same dose of lobeline enhanced retention of inhibitory avoidance training in normal rats is not necessarily incompatible with NMDA receptor blockade because posttraining systemic administration of NMDA receptor antagonists does not appear to affect retention of inhibitory avoidance training (25).

If the effects of nicotine and lobeline are mediated by actions at nicotinic receptors, the mechanism by which nicotinic receptor stimulation improves the performance of septal-lesioned rats is unclear. As in the case of inhibitory avoidance, the positive results with lobeline would make it unlikely that catecholamine release induced by nicotine underlies the beneficial effects of nicotine in the water maze because lobeline does not induce the release of catecholamines. Potency differences between lobeline and nicotine are apparent in their ability to enhance retention of inhibitory avoidance but not in their ability to enhance the water maze performance of septal-lesioned rats. Comparisons of potency were made across studies, but if the relative potencies of these two compounds are indeed task related it would suggest that the mechanisms by which nicotinic receptor stimulation improves performance in the water maze and retention of inhibitory avoidance may differ. Findings of similarities in the effects of nicotine and lobeline on the behavioral measures we examined contrast with earlier reports that lobeline does not substitute for nicotine in drug discrimination experiments. These disparate sets of results suggest the involvement of multiple nicotinic receptor subtypes in the behavioral effects of nicotinic agonists. Nicotinic receptor subtypes in the brain have been identified using molecular biological techniques (15), but, unfortunately, functions for these receptors have not yet been established and selective ligands for these receptor subtypes have not yet been identified. Further work will therefore be necessary before it can be determined if nicotinic receptor diversity is important in the different behavioral pharmacology of lobeline and nicotine.

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