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Lobeline-induced learning improvement of rats in the radial-arm maze

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Abstract

Lobeline is a nicotinic ligand with some nicotine-like effects, but with some atypical effects as well, including actions as a nicotinic antagonist. Lobeline, like nicotine, has been found to significantly improve memory function as well as provide anxiolytic-like effects in the elevated plus maze. Lobeline effects on learning remain to be fully characterized. Nicotine has been found to improve learning of shock avoidance tasks. Other nicotinic agonists also have been shown to improve learning performance. However, this effect is limited. In some tasks, nicotine has been found to cause deficits. In the current study, effects of lobeline and nicotine injections were assessed in a repeated acquisition procedure in the radial-arm maze for 3 weeks of drug administration. Lobeline (0.3 and 0.9 mg/kg) improved learning on the radial-arm maze. Neither nicotine dose (0.1 and 0.3 mg/kg) improved learning. This nicotine dose range was previously found to improve post-acquisition working memory performance in the radial-arm maze. The atypical effects of lobeline may underlie its greater efficacy than nicotine for improving repeated acquisition. The effect of lobeline improving learning may be useful in the development of novel treatments for learning deficits.

Keywords: Lobeline; Learning; Repeated acquisition; Radial-arm maze

1. Introduction

Lobeline is an atypical nicotinic ligand derived from the plant *Lobelia inflata* (Taylor, 2001). It has mixed agonist-like and antagonist-like effects as well as additional nonnicotinic effects (Damaj et al., 1997; Dwoskin and Crooks, 2002; Terry et al., 1998). As described below, lobeline has been found to have some effects on cognitive function, which are similar to nicotine. However, given the differences in neuropharmacological actions (Terry et al., 1998), there may be important differences between effects of nicotine and lobeline in terms of cognitive function. The mixed agonist and antagonist properties of lobeline may cause it to have different effects than nicotine on cognitive function.

Nicotinic systems have been shown to be important for a variety of cognitive functions including learning (for reviews, see Decker et al., 1995; Levin and Simon, 1998). Several older studies have shown that acute nicotine injections significantly improved learning in maze tests (Garg, 1969), shuttle box-conditioned response (Evangelista et al., 1970) and transfer of learning (Oliverio, 1968). More recent studies have found that acute nicotine injection improves passive avoidance learning (Sansone et al., 1991; Sasaki et al., 1991) and retention (Nordberg et al., 1985). Nicotine injections also attenuate impaired learning performance in aged rats (Arendash et al., 1995a).

Nicotine dose can be critically important. In general, low doses facilitate while high doses have no effect or impair performance. This has been seen with both passive (Haroutunian et al., 1985) and active avoidance performance (Erickson, 1971; Essman and Essman, 1971; Evangelista et al., 1970; Gilliam and Schlesinger, 1985; Oliverio, 1966). However, nicotine does not invariably improve learning. Nicotine administration has been found to produce repeated acquisition deficit in both C57Bl/6J and DBA/2J mice (Gilliam and Schlesinger, 1985). Thus, repeated acquisition tasks may detect different effects than original learning tasks because of deficits due to proactive interference in which previously learned material which is no longer relevant interferes with learning of newer more relevant material. A repeated acquisition task on the radial-arm maze was used in the current study.

Lobeline is an atypical nicotinic ligand with some effects similar to nicotine and others quite different. Lobeline, like

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other nicotinic agonists, has been found to improve memory. Decker et al. (1993) found that lobeline caused significant improvements in learning in an active step-through avoidance procedure and significantly attenuated Morris water maze learning deficits caused by septal lesions in rats.

The purpose of this study is to assess the potential beneficial effect of lobeline on learning of rats in the radial-arm maze using a repeated acquisition procedure. This procedure has been found to provide a reproducible assessment of learning. Scopolamine, a muscarinic cholinergic antagonist, which is a classic amnestic drug, significantly impairs repeated acquisition accuracy (Peele and Baron, 1988). The selective α7 nicotinic agonist, ARR 17779, was shown in a related study to significantly improve learning in the repeated acquisition procedure on the radial-arm maze (Levin et al., 1999). In the current study, the repeated acquisition test was used as a benchmark for the effects on learning of both nicotine and lobeline.

2. Methods

2.1. Subjects

Adult female Sprague–Dawley rats (Zivic-Miller, Allison Park, PA) were used in the experiments. The rats had ad libitum access to drinking water but were kept on a restricted feeding schedule to maintain their body weights at 80–85% of free-feeding levels, adjusted for growth. The treatment and care of the rats was under an approved protocol of the Animal Care and Use Committee of Duke University in an AAALC-approved facility.

2.2. Drug administration

For 3 weeks of testing, the rats received subcutaneous injections of either lobeline HCl or nicotine ditartrate (Sigma, St. Louis, MO, USA) twice per week. The vehicle was saline. A separate group received saline injections and served as controls. The drug weights were of the salt. Injections were made subcutaneously (1 ml/kg) 20 min before testing. Rats were tested for 3 weeks of drug administration with each group kept on the same drug and dose and for 2 weeks after withdrawal. There were five groups of rats ($N = 10$/group): Saline, Low nicotine (0.1 mg/kg), High nicotine (0.3 mg/kg), Low lobeline (0.3 mg/kg) and High lobeline (0.9 mg/kg). The rats were sorted into matched drug groups based on their repeated acquisition performance prior to the onset of treatment.

2.3. Repeated acquisition radial-arm maze testing

The repeated acquisition learning tests were performed using a black, wooden eight-arm radial maze. The maze was elevated 30 cm off the ground with a central platform 35 cm in diameter and eight arms each 10×80 cm. Each arm contained a food cup at its terminal end. The reinforcers used were 1/2 piece of Kellogg's Froot Loops cereal. In a task patterned after the one developed by Peele, three of the arms of the eight-arm radial maze described above were baited once before each trial (Peele and Baron, 1988). Five trials were run each session separated by 1-min intertrial intervals. The same arms were baited for all of the trials of any single session but the arms baited were changed each session. The rats were allowed up to 180 s to finish each trial. Total errors to select the three baited arms were counted for each trial. If only two of the three baited arms were selected before the 180-s time limit and there were more than eight arm entries in a trial, then the number of errors of entries into unbaited arms (errors of commission) plus the error of omission (not selecting the last baited arm) were added together for the calculation of total errors.

Each of the three arms was baited with a reinforcer. The rat was then placed in a plastic cylinder (30 cm in diameter and 20 cm high) on the central platform. To begin the session, the cylinder was lifted allowing the rat to move freely about the maze. Arm choices were recorded when the rat placed all of its paws into the arm. Only one entry into an arm was rewarded. Reentries into arms previously entered or unbaited arms were counted as errors. The session continued until either the rat entered all of the three baited arms or 3 min elapsed. As a further analysis, errors were categorized into nonrepetitive and repetitive errors. Nonrepetitive errors were those in which the rat entered an

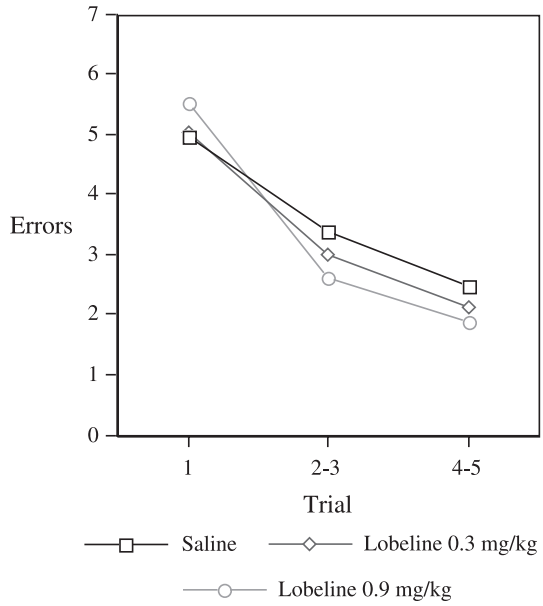

Fig. 1. Lobeline effects on repeated acquisition in the radial-arm maze. Low- and high-dose lobeline effects on the learning curve of repeated acquisition (errors per trial) averaged over the 3 weeks of drug administration. No effects were seen in the first trial when the new problem was initially presented.

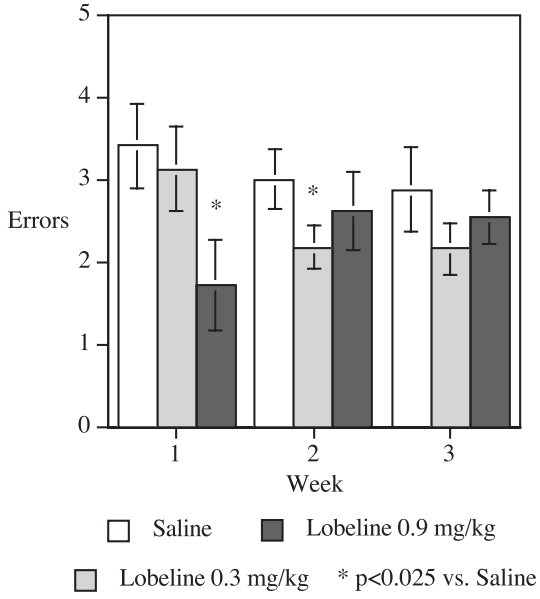

Fig. 2. Lobeline effects on total errors in radial-arm maze repeated acquisition: Trials 2–5. Choice accuracy performance on Trials 2–5 averaged on the repeated acquisition test (total errors per trial) for each of the 3 weeks of lobeline dosing (mean ± S.E.M.).

unbaited arm for the first time during a trial. Repetitive errors were those in which the rat reentered an unbaited arm or a previously baited arm for the second or more time.

2.4. Data analysis

In the radial-arm maze, choice accuracy were measured by errors per trial and choice latency was measured by seconds per entry (i.e., total trial duration/total number of arms entered). Data for each dependent measure were evaluated separately by analyses of variance for between-subjects factors of drug treatment and testing cohort and repeated measures of test trial and week of drug administration. Subsequent planned comparisons were made of controls with the drug-treated groups.

3. Results

Repeated acquisition in the radial-arm maze provided an assessment of the effects of repeated lobeline or nicotine injections on a steady baseline of learning performance. The higher dose of lobeline (0.9 mg/kg) improved learning over the entire course of 3 weeks of treatment to a greater extent than the lower dose (0.3 mg/kg) (Fig. 1). However, both doses produced significant improvements ($P < .025$) relative to control at different times during the 3 weeks of treatment (Fig. 2). In contrast, neither nicotine dose (0.1 and 0.3 mg/kg) significantly affected learning. In fact, both doses of nicotine resulted in a slightly but not significantly higher average number of errors on Trials 2–5 (Control 2.93 ±0.37, Nicotine 0.1 mg/kg 3.41 ± 0.48 and Nicotine 0.3 mg/kg 3.65 ± 0.33 errors per trial).

Analysis of performance during Trial 1 showed no significant of either nicotine or lobeline during the 3 weeks of drug administration or during the 2 weeks after withdrawal. This was not unexpected since this is the first experience each session of the rats on a new problem in the radial maze.

With Trials 2–5, there was a significant Lobeline Treatment × Week interaction [$F(4,14) = 4.10$, $P < .025$]. Follow-up analyses of the drug effects during each week were made.

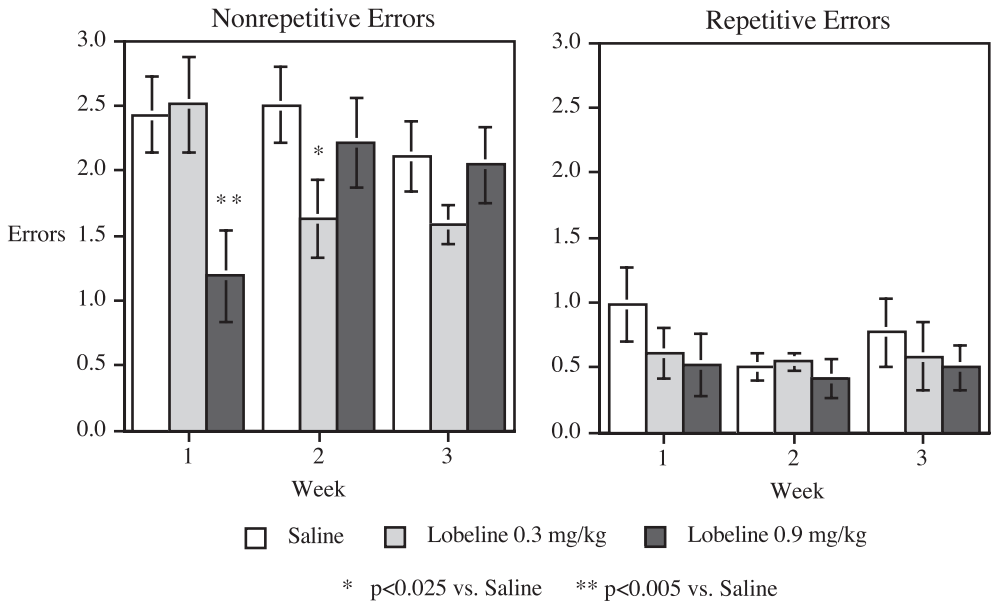

Fig. 3. Lobeline effects on nonrepetitive and repetitive errors in radial-arm maze repeated acquisition: Trials 2–5. Choice accuracy performance on Trials 2–5 averaged on the repeated acquisition test (nonrepetitive and repetitive errors per trial) for each of the 3 weeks of lobeline dosing (mean ± S.E.M.).

As shown in Fig. 2, there was a significant improvement caused by the high dose of lobeline (0.9 mg/kg) relative to the saline-injected control group on Week 1 ($P < .025$). This effect became attenuated and was not significant during the later weeks. The lower dose of lobeline (0.3 mg/kg) had a significantly lower mean error score during Week 2 ($P < .025$).

Total errors can be divided into nonrepetitive and repetitive entry errors. Nonrepetitive entry errors were those of initial entries into nonbaited arms, whereas repetitive entry errors were those of reentries into arms previously chosen during the trial. Lobeline-induced improvements were concentrated in the nonrepetitive errors indicating effects on learning (Fig. 3). With nonrepetitive errors, the Lobeline Treatment × Week interaction was significant [$F(4,14) = 11.56$, $P < .005$]. Follow-up analyses of the drug effects during each week were made. As with total errors, in Week 1 the 0.9 mg/kg lobeline dose showed a significant ($P < .005$) improvement relative to the saline control (Control = 2.43 ± 0.29 and 0.9 mg/kg Lobeline = 1.19 ± 0.86 nonrepetitive errors). Also as with total errors, in Week 2 the 0.3 mg/kg lobeline dose caused a significant ($P < .025$) improvement relative to the saline control group (Control = 2.50 ± 0.29 and 0.3 mg/kg Lobeline = 1.62 ± 0.30 nonrepetitive errors). In contrast, no significant lobeline effects on repetitive errors were seen (Fig. 3).

There was no evidence for a nicotine-induced improvement with either the high or low dose. No significant effects of previous treatment to either lobeline or nicotine relative to control were seen during the 2 weeks of continued testing after withdrawal. No significant lobeline or nicotine effects on response latency were seen either during or after the period of drug administration.

4. Discussion

Nicotine and other nicotinic agonists have been shown to significantly improve cognitive function (Levin and Rezvani, 2000). However, the mechanisms by which these ligands have their functional effects have not been fully determined. Because nicotinic receptors are easily desensitized, it is likely that nicotinic agonists also have desensitizing effects, which provide net antagonist effects. This leaves open the question whether it may be this net antagonist effect which may be critical to some of the potential therapeutic effects of nicotinic agonists. A drug, like lobeline, which has mixed agonist and antagonist effects may have some beneficial cognitive actions.

There is already evidence supporting the therapeutic promise of nicotinic antagonists (Dwoskin and Crooks, 2001). Low doses of the nicotinic antagonist mecamylamine had nicotine-like effects in rats and monkeys (Driscoll, 1976; Driscoll and Battig, 1973; Terry et al., 1999). The effective smoking cessation aid bupropion has been shown to have potent nicotinic antagonist effects (Fryer and Lukas, 1999). ABT-418, which has been found to improve cognitive function, can act to inhibit nicotinic receptor action (Papke et al., 1997). Nicotinic antagonist actions, particularly at the α7 nicotinic receptor site, have been shown to enhance hippocampal LTP (Fujii et al., 2000). Nicotinic antagonistic effects may be an alternative mechanism for nicotinic-mediated cognitive improvement (Newhouse et al., 2001). Net nicotinic antagonist action via nicotinic receptor desensitization or blockade may be important for cognitive improvement in humans (Newhouse and Kelton, 2000). Lobeline has some nicotinic agonist-like actions (Terry et al., 1998) but it also has nicotinic antagonist-like actions (Miller et al., 2000), as well nonnicotinic effects on the metabolism of dopamine at the vescicular monoamine transporter (VMAT2) site (Dwoskin and Crooks, 2002).

This study demonstrated a significant lobeline-induced improvement in learning on the repeated acquisition task in the radial-arm maze. This lobeline-induced learning improvement contrasted with the ineffectiveness of nicotine, which did not cause any sign of improvement and actually showed a trend toward impaired learning in a dose range we have previously shown to improve working memory in the radial-arm maze (Levin and Simon, 1998). Atypical actions of lobeline on nicotinic receptors may underlie this learning improvement. This may provide an important guide for the greater understanding of nicotinic involvement in learning and development of nicotinic treatments for learning impairment.

A critically important aspect of the repeated acquisition test is the fact that it requires repetitive changes in the correct items to be learned task. Despite the widespread finding that nicotine improves original learning (Levin, 1992), nicotine administration has been found in mice to produce deficits in repeated acquisition (Gilliam and Schlesinger, 1985). Repeated acquisition tasks may detect different effects than original learning. The nicotine-induced impairments in repeated acquisition may be related to the enhancement of proactive interference, which has been found to be caused by nicotine (Dunnett and Martel, 1990). In the repeated acquisition task used in the current study, remembering the previously learned problem would interfere with performance on the new problem presented each session.

Interestingly, nicotine has been found in humans to facilitate repeated acquisition (Newhouse et al., 1994). This stands in contrast to the current study in which nicotine was not found to be effective in repeated acquisition. Species differences or task differences in the impact of proactive interference may explain the differences in response.

Different nicotinic receptor subtypes may be important for learning vs. memory. Lobeline may more effectively stimulate nicotinic receptor subtypes important for learning than nicotine. Alternatively, lobeline effects on nonnicotinic receptors may be important for its learning improving effect.

This study sheds light on the differential effects of lobeline and nicotine on learning in rats. The fact that

lobeline significantly improved learning, while nicotine was not effective, provides important information concerning the development of novel nicotinic therapeutic treatments. It also provides important information concerning the basic roles nicotinic systems play in learning function.

Nicotinic agonists other than nicotine have also been found to improve learning performance. Chronic administration of the α7 nicotinic receptor agonist GTS-21 was found to improve learning (Arendash et al., 1995b). GTS-21 was also found to improve eyeblink classical conditioning (Woodruff-Pak et al., 1994). Other nicotinic agonists like nicotine have effects on learning. Epibatidine affected learning in the radial-arm maze in a complex fashion (Levin et al., 1996). Rats were given 0, 0.5 or 1.0 μg/kg of epibatidine in a between-subjects design throughout 24 sessions of radial-arm maze training. The rats given 0.5 μg/kg had a trend toward improved choice accuracy performance relative to control during the middle phase of learning. The higher dose had no apparent effect. A follow-up study was conducted to determine if the transient improvement caused by 0.5 μg/kg of epibatidine during the middle phase of training was due to the chronicity of the treatment or to the phase of training. Rats were pretrained for 12 sessions and then were given 0.5 μg/kg of epibatidine or vehicle injections for an additional 24 sessions of training. In this study, when epibatidine was only given during the middle and later phases of training, no improvement was seen. In fact, a significant epibatidine-induced deficit was seen during the final phase of training. These studies show that the potent nicotinic agonist epibatidine can significantly impair learning in the radial-arm maze. The expression of its effect depends critically on when during training it is given. An atypical nicotinic agonist such as lobeline that appears to cause only limited nicotinic receptor desensitization (Decker et al., 1994) may be of greater utility for improving learning.

The higher dose of lobeline used in the current study did not cause a continuing significant improvement in learning past the first week of administration. In contrast, the α7 nicotinic agonist ARR 17779 (Levin et al., 1999) did cause a persisting improvement for 3 weeks of administration. A fuller dose effect function may uncover the most effective lobeline doses for persisting learning improvement. Either higher or lower doses may be more effective, given the inverted U-shaped dose effect functions often seen with nicotinic drugs. In the current study, the lower lobeline dose of 0.3 mg/kg caused improved learning in Week 2 but not Week 1. There were no signs of residual drug effects or withdrawal effects after cessation of treatment, although the frequency of drug treatment (two times per week) may have limited such effects.

Analysis of the different types of errors provided evidence for a selective effect of lobeline on learning as opposed to working memory. Nonrepetitive entry errors were those of initial entries into nonbaited arms and thus provided the clearest view of the learning taking place. The repetitive entry errors were those of reentries into arms previously chosen during the trial. These were more reflective of working memory function. The finding that lobeline significantly decreased nonrepetitive entry errors but not repetitive entry errors supported a selective effect on learning rather than working memory.

Nicotine-induced learning improvements have been seen in humans as well as experimental animals (Warburton et al., 1986). Importantly, nicotine-induced learning improvements have been found in clinical populations. Nicotine patches in Alzheimer's patients for 8 days caused a significant improvement in repeated acquisition performance accuracy (Wilson et al., 1995). Conversely, the nicotinic antagonist mecamylamine caused a significantly greater learning deficit in Alzheimer's disease patients than in normal elderly adults (Newhouse et al., 1994).

Lobeline is like nicotine in stimulating the release of neurotransmitters (Reavill et al., 1990); however, the mechanism of lobeline in releasing serotonin appears to differ from nicotine and some other nicotinic agonists (Lendvai et al., 1996). Lobeline, like nicotine, stimulates dopamine release from the striatum and norepinepherine from the hippocampus, although unlike nicotine, lobeline effects are independent of calcium (Grady et al., 1992). Both lobeline and nicotine stimulate dopamine release from rat striatal slices but they show differential inhibition of synaptosomal and vesicular dopamine uptake (Teng et al., 1997).

Functional effects of lobeline also shed light on its nicotinic actions. Lobeline, like nicotine, has been shown to have an anxiolytic-like effect on the elevated plus-maze test (Brioni et al., 1993). Both lobeline and nicotine augmented latent inhibition (Rochford et al., 1996). Sensory gating, a form of learning involving habituation to a repeated sensory stimulus is sensitive to nicotinic manipulation. Lobeline has effects like nicotine and opposite to that of the nicotinic antagonist mecamylamine in the rat (Curzon et al., 1994). In contrast, nicotine, but not lobeline, improved retention of the passive avoidance (Brioni and Arneric, 1993).

Lobeline may also have neural effects mediated via nonnicotinic receptor systems. The antinociceptive effect, decreased locomotor activity and decreased body temperature caused by lobeline is not reversed by mecamylamine (Damaj et al., 1997). In a stimulus discrimination task, lobeline, like nicotine, improved discrimination (Terry et al., 1996). However, unlike nicotine, the effect of lobeline was not blocked by coadministration of the nicotinic antagonist mecamylamine. Rao et al. (1997) found effects of lobeline on *N*-methyl-D-aspartate (NMDA)-evoked acetylcholine release in vitro an effect, which did not seem to involve nicotinic mechanisms. It has effects different than nicotine on changes in body temperature and locomotor activity in mice (Decker et al., 1994) and vigilance performance in rats (Turchi et al., 1995). Lobeline has actions promoting dopamine release at the VMAT2 (Teng et al., 1998), which may be useful for treating stimulant abuse (Dwoskin and Crooks, 2002). Lobeline has been shown to block both neurochemical and neurobehavioral effects of the

stimulant amphetamine (Miller et al., 2001) and inhibits amphetamine self-administration (Harrod et al., 2001).

Optimal nicotinic treatment for learning impairment may be different from the optimal treatment for memory or attentional impairments. It is important to specify the nature of the cognitive function being affected. Nicotine itself has been shown to effectively improve working memory, but its actions on learning remain equivocal. Other nicotinic agonists such as lobeline may provide more effective improvement of learning function.

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