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Lobelane decreases methamphetamine self-administration in rats

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Abstract

Lobelane, a minor alkaloid of *Lobelia inflata* and a synthetic, *des*-oxy analog of lobeline, has good affinity for the vesicular monoamine transporter and the dopamine transporter. The current study examined the ability of lobelane to specifically decrease methamphetamine self-administration. Rats were trained on a fixed ratio 5 schedule of reinforcement to self-administer methamphetamine (0.05 mg/kg/infusion, i.v.) or to respond for sucrose pellets. Upon reaching stable responding, rats were pretreated with lobelane (0.1, 1, 3, 5.6, or 10 mg/kg, s.c.) or saline, 15 min prior to the operant session. To assess the effect of repeated lobelane on methamphetamine self-administration, rats were pretreated with lobelane (5.6 or 10 mg/kg, s.c.) for 7 sessions. Behavioral specificity was further investigated by assessing the effects of lobelane (0.1, 1, 3, 5, or 10 mg/kg, s.c.) or saline on locomotor activity. Within the dose range tested, lobelane dose-dependently decreased methamphetamine self-administration, while having no effect on sucrose-maintained responding. Locomotor activity was decreased following only the highest dose of lobelane (10 mg/kg). Across repeated pretreatments, tolerance developed to the effect of lobelane on methamphetamine self-administration, demonstrating that the ability of lobelane to specifically decrease methamphetamine self-administration is a transient effect. Thus, taken together, the results show that although lobelane interacts with the pharmacological targets believed to be responsible for its ability to decrease methamphetamine self-administration, removal of the oxygen functionalities from the lobeline molecule may have afforded a compound with an altered pharmacokinetic and/or pharmacodynamic profile.

Keywords

methamphetamine; self-administration; lobeline; lobelane; pharmacotherapy

1. Introduction

Attention has focused recently on lobeline, the major alkaloidal constituent of *Lobelia inflata* (Indian tobacco), as a potential pharmacotherapeutic agent for the treatment of methamphetamine abuse. Lobeline has been shown to interact with high affinity at the [³H] nicotine binding site, indicating that it has high affinity for $\alpha 4\beta 2^*$ nicotinic acetylcholine receptors (Abood et al., 1989; Damaj et al., 1997; Miller et al., 2000). Behavioral and

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pharmacological evidence suggests that lobeline functions as a nicotinic acetylcholine receptor antagonist (Benwell and Balfour, 1998; Miller et al., 2000; Reavill et al., 1990). In particular, lobeline inhibits nicotine-evoked $^{86}\text{Rb}^+$ efflux from rat thalamic synaptosomes and nicotine-evoked $[^3\text{H}]$ dopamine overflow from rat striatal slices preloaded with $[^3\text{H}]$ dopamine, suggesting it acts functionally as an antagonist at $\alpha 4\beta 2^*$ and $\alpha 6$ -containing nicotinic acetylcholine receptors (Miller et al., 2000).

Lobeline also alters vesicular storage of monoamines by potently inhibiting the $[^3\text{H}]$ dihydroxytetrabenazine binding site on the vesicular monoamine transporter, thus inhibiting $[^3\text{H}]$ dopamine uptake into isolated striatal synaptic vesicles (Teng et al., 1998). Behavioral experiments have shown that lobeline decreases methamphetamine self-administration in rats, an effect that is not surmounted by increasing the unit dose of methamphetamine (Harrod et al., 2001). With repeated administration, lobeline selectively decreases methamphetamine self-administration without altering sucrose-maintained responding, and lobeline is not self-administered by rats, indicating low abuse potential (Harrod et al., 2001; Miller et al., 2003).

The pharmacological mechanism underlying the lobeline-induced decrease in methamphetamine self-administration has been postulated to be due to lobeline-induced perturbations of the fundamental mechanisms of dopamine storage and release (Dwoskin and Crooks, 2002). The rewarding effect of methamphetamine results from increased dopamine release in limbic terminal fields, which is regulated by the vesicular monoamine transporter (Takahashi et al., 1997). Methamphetamine increases extracellular dopamine concentrations by inhibiting the action of the vesicular monoamine transporter which sequesters dopamine into vesicular stores, as well as by inhibiting monoamine oxidase which diminishes dopamine metabolism, thereby making cytosolic dopamine more available for methamphetamine-induced reversal of the plasmalemma dopamine transporter (Dwoskin and Crooks, 2002; Suzuki et al., 1980). Although lobeline inhibits dopamine uptake into synaptic vesicles via the vesicular monoamine transporter, unlike methamphetamine, lobeline does not inhibit monoamine oxidase, and as a result, cytosolic dopamine is rapidly metabolized to dihydroxyphenylacetic acid, leading to a decrease in the cytosolic dopamine pool available for methamphetamine-induced reversal of the dopamine transporter. Thus, in the presence of lobeline, methamphetamine-induced dopamine release into the extracellular space is diminished. The interaction of lobeline at the vesicular monoamine transporter is generally considered to be its most important effect with respect to its attenuation of amphetamine-evoked dopamine release (Dwoskin and Crooks, 2002). In addition to lobeline's interactions with the vesicular monoamine transporter, it also interacts with the dopamine transporter, thus inhibiting $[^3\text{H}]$ dopamine uptake into rat striatal synaptosomes (Teng et al., 1997). Inhibition of the dopamine transporter with GBR-decanoate has been shown to antagonize methamphetamine-evoked dopamine release and has been suggested to be a potential adjunct therapy for methamphetamine addiction (Baumann et al., 2002).

Given these preclinical results, a potentially useful pharmacotherapeutic strategy for treating methamphetamine abuse is to develop an analog of lobeline that selectively and potently inhibits the function of the vesicular monoamine transporter and dopamine transporter, while having little or no effect at nicotinic acetylcholine receptors. Such an analog might be expected to inhibit methamphetamine reward at doses that have minimal cholinergic side effects. In a recent study, structural modification of the lobeline molecule has been shown to afford compounds with differing affinities for nicotinic acetylcholine receptors, the dopamine transporter and vesicular monoamine transporter (Miller et al., 2004). Among these analogs, lobelane, the *des*-oxy analog of lobeline (Fig. 1), was shown to be more potent than lobeline in inhibiting the vesicular monoamine transporter and dopamine transporter, as indicated in $[^3\text{H}]$ methoxytetrabenazine binding assays using vesicle membranes and in decreasing $[^3\text{H}]$ dopamine uptake into rat striatal synaptosomes, but was less potent than lobeline in inhibiting

[³H]nicotine binding to rat striatal membranes (Miller et al., 2004). Taken together, these results indicate that lobelane is more selective for the vesicular monoamine transporter, the proposed pharmacological target for the development of therapeutic agents to treat methamphetamine abuse. Thus, the aim of the current study was to determine if lobelane specifically decreases methamphetamine self-administration in rats across acute and repeated administration.

2. Methods

2.1 General Procedure

2.1.1 Animals—Male Sprague-Dawley rats (225–250g) obtained from Harlan Industries (Indianapolis, IN) were housed individually and allowed to acclimate to the colony for 7 days with *ad libitum* access to food (Purina Rat Chow) and water. Animals were handled for 3 days prior to the commencement of each experiment. The animal vivarium was maintained at 24° C and 45% relative humidity, with lights on 0700–1900 hours. All experiments were conducted during the light phase. All procedures were approved by the University of Kentucky Institutional Animal Care and Use Committee and conformed to the 1996 edition of the *Guide for the Care and Use of Laboratory Animals* (National Institutes of Health).

2.1.2 Drugs—*d*-Methamphetamine HCl was obtained from the National Institute on Drug Abuse (Bethesda, MD., USA) and was mixed in sterile saline (0.9% NaCl). The *des*-oxy lobeline analog, *cis*-lobelane, was synthesized by structural modification of the lobeline molecule according to previously described methods (Zheng et al., 2005). Lobelane pretreatments were administered s.c. in a volume of 3 ml/kg.

2.1.3 Apparatus—Operant chambers (ENV-001, Med Associates, St. Albans, VT) were enclosed in sound-attenuating compartments and were operated by computer interface equipment. A 5 × 4.2 cm opening that allowed access to a recessed food tray was located on the front panel of each operant chamber. Two metal response levers on either side of the food tray were located 7.3 cm above a metal-grid floor. A 28 V white cue light, 3 cm in diameter, was centered 6 cm above each response lever. Drug infusions (0.1 ml over 5.9 sec) were delivered via a syringe pump (Med Associates, PHM-100). A water-tight swivel allowed attachment of the catheter tubing from a 10-ml syringe to the head mount of the rat in the operant chamber.

Locomotor activity was recorded automatically using an animal activity monitoring system with Versamax System software (AccuScan Instruments Inc., Columbus, OH). Rats were placed into a monitoring chamber (42 × 42-cm square and 30 cm high) made of clear acrylic walls and floor. The chamber incorporated a horizontal 16 × 16 grid of photo beam sensors, with each beam located 2.5 cm apart and 7.0 cm above the chamber floor. Horizontal activity was recorded for a 60-min period, comprised of 5-min intervals. Activity was measured by photo beam interruptions and was expressed as total distance traveled (cm).

2.1.4 Methamphetamine Self-Administration—Rats were first trained briefly to respond for sucrose reinforcement (45 mg sucrose pellets, NOYES Co., Inc., Lancaster, NH) as described previously (Harrod et al., 2001). After training, rats were allowed free access to food for the remainder of the experiment. One week after training, rats were surgically implanted with a chronic indwelling jugular catheter. Rats were anesthetized (100 mg/kg ketamine, 5 mg/kg diazepam, i.p.) and implanted with a catheter into the jugular vein that exited through a dental acrylic head mount. The head mount was affixed to the skull with metal jeweler screws. Daily infusions of heparinized saline (0.2 mg/0.1 ml/rat/day) were given to maintain catheter patency. Rats were allowed to recover for 1 week before commencing methamphetamine self-administration sessions.

Rats were first allowed to self-administer methamphetamine (0.05 mg/kg/infusion) on a fixed ratio 1 (FR 1), 20-s signaled time out schedule of reinforcement during daily, 60-min sessions. Drug was infused (0.05 mg/kg per infusion dissolved in saline) following depression of one lever (active lever); responding on the second lever (inactive lever) was recorded, but had no programmed consequence. Each drug infusion was followed by a 20-s signaled timed-out interval that began immediately following completion of the ratio requirement and was signaled by illumination of the lights above the response levers. During this interval, responding on either lever was without consequence. The schedule of reinforcement was incremented across sessions from a FR 1 to a FR 3, and then to a terminal FR 5 schedule. Stable responding was operationally defined as less than 15% variability in the number of infusions earned across three consecutive sessions, a greater than 2:1 ratio of active to inactive responses and at least 10 infusions earned per session. At the end of each experiment, catheter patency was verified with morphine (15 mg/kg, i.v.), which induced a rapid cataleptic response.

2.1.6 Sucrose-Maintained Responding—Rats were reduced to 85% of free-feeding body weight by restricting food access and were shaped to press a lever for contingent sucrose pellet reinforcement (45 mg pellets, NOYES Co., Inc., Lancaster, NH) during the 60-min shaping procedure. Only one lever was available, which was counterbalanced between rats. In subsequent food training sessions, both levers in the operant chambers were available. The schedule of reinforcement was increased across 5 days from a FR 1 to FR 3 and then to a terminal FR 5 schedule. Following acquisition of lever pressing on a FR 5 schedule of reinforcement, the schedule was amended to include a 100-s signaled time out following delivery of a sucrose pellet. Insertion of the long time out was used to equate the number of reinforcers earned between the sucrose and methamphetamine self-administration experiments (Paterson et al., 2003). Stable responding was operationally defined by less than 15% variability in the number of pellets earned across three consecutive sessions, greater than 2:1 ratio of active to inactive responses and at least 10 sucrose pellets earned per session.

2.2 Specific Experiments

2.2.1. Dose Effect of Acute Lobelane on Methamphetamine Self-Administration and Sucrose-Maintained Responding—To determine if lobelane alters the self-administration of methamphetamine, rats (n=8) were pretreated with lobelane (0.1, 1, 3, 5.6, or 10 mg/kg, s.c.) or saline 15 min prior to the operant session using a within-subject Latin square design. Pretreatments were separated by 2 intervening maintenance days of methamphetamine self-administration in order to maintain stable responding for methamphetamine in the absence of lobelane. On each pretreatment session, the number of infusions earned was recorded in 5-min intervals. To determine whether lobelane altered lever pressing for sucrose reinforcement, rats (n=6) trained to lever press for sucrose reward were pretreated with lobelane (0.1, 1, 3, 5.6, or 10 mg/kg, s.c.) or saline 15 min prior to the operant session using a within-subject Latin square design. Pretreatments were separated by 2 intervening maintenance days of sucrose responding in order to maintain stable responding for sucrose in the absence of lobelane.

2.2.2. Dose Effect of Lobelane on Locomotor Activity—Rats (n=6) were habituated to the locomotor activity chamber for 60 min. On the following day, rats were pretreated with lobelane (1, 3, 5.6, or 10 mg/kg, s.c.) or saline immediately prior to placement in the activity monitor for 60 min. Doses were administered according to a within-subject Latin-square design where each animal received each dose of lobelane with 2 days between doses. During these intervening drug-free days, animals were left undisturbed in their home cage.

2.2.3. Effect of Repeated Lobelane on Methamphetamine Self-Administration—To determine if lobelane altered methamphetamine (0.05 mg/kg/infusion) self-administration

across repeated pretreatments, two separate groups of rats ($n = 5\text{--}6/\text{group}$) trained to self-administer methamphetamine on a FR 5 schedule of reinforcement were treated with lobelane (5.6 or 10 mg/kg, s.c.) prior to seven, 60-min sessions. To ensure stable responding for methamphetamine was maintained across the experiment, two intervening maintenance sessions (no pretreatment) occurred between each pretreatment session.

2.3 Statistics

The dose and time course effects of lobelane pretreatment on methamphetamine self-administration were analyzed using a two-way ANOVA with dose and time interval as within-subject factors. Further analyses using 2-way ANOVAs and paired t -tests were conducted to determine significant differences between saline and lobelane at specific doses and time points. To assess the specificity of lobelane to alter methamphetamine self-administration over sucrose-maintained responding, the number of reinforcers earned during the first 15 min of the methamphetamine self-administration and sucrose-maintained responding experimental sessions were assessed. These data were analyzed using a 2-way ANOVA with lobelane dose (0.1, 1, 3, 5.6, and 10 mg/kg, s.c.) or saline as the within-subject factor and reinforcer type (sucrose pellet or methamphetamine infusion) as the between-subject factor for the dose-effect experiments. Following post-hoc analyses, between-group and within-group differences were further assessed using independent and paired t -tests, respectively. The effect of repeated lobelane pretreatment (5.6 and 10 mg/kg) on the number of infusions earned during the first 15 min of methamphetamine self-administration sessions was analyzed using a 2-way ANOVA, with lobelane dose (5.6 or 10 mg/kg) as the between-subject factor and session as the within-subject factor. Planned pair-wise comparisons using paired t -tests were conducted to assess differences between infusions earned during baseline responding and those earned following repeated lobelane pretreatment. All post-hoc analyses incorporated a correction for family-wise error and significance was set at $P < 0.05$.

3. Results

3.1. Dose and Time Course Effects of Lobelane on Methamphetamine Self-Administration

The ANOVA revealed a significant interaction of lobelane dose $\times$ interval [$F(55,385) = 1.88$, $P < 0.001$] on the number of methamphetamine infusions earned (Fig 2). Across the session, saline pretreated rats showed an initial high rate of self-infusions, followed by a decrease to a steady low rate, an effect indicative of drug “loading” on a limited access schedule. This temporal pattern of responding for methamphetamine was not altered significantly by low doses of lobelane (0.1, 1 or 3 mg/kg; results not shown). However, relative to saline, both 5.6 and 10 mg/kg of lobelane decreased methamphetamine self-administration early in the session, but not late in the session. Post hoc analysis indicated significant differences ($P < 0.05$) between saline and 5.6 mg/kg of lobelane at the 5, 10 and 15-min intervals and between saline and 10 mg/kg of lobelane at these time points. Since the effect of lobelane was observed during the first 15 min of the operant session, this time interval was used as a factor for all subsequent analyses.

3.2 Comparison of the Dose Effect of Acute Lobelane on Methamphetamine Self-Administration and Sucrose-Maintained Responding

A 2-way ANOVA revealed a significant interaction of lobelane dose $\times$ reinforcer type [$F(5,60) = 18.74$, $P < 0.001$; Fig 3]. Post hoc analysis indicated a significant decrease in the number of methamphetamine infusions earned relative to the number of sucrose pellets earned following the two highest doses of lobelane tested (5.6 and 10 mg/kg; $P < 0.01$); there was no significant alteration in the number of sucrose pellets earned at any lobelane dose. No differences were observed on the inactive lever in either the methamphetamine or sucrose reinforcement experiments following any dose of lobelane (results not shown).

3.3 Dose Effect of Lobelane on Locomotor Activity

Results from the locomotor activity experiment following lobelane pretreatment are illustrated in Fig. 4. The time interval during the locomotor experiment that coincides with the time interval assessed in methamphetamine self-administration and sucrose maintained responding is 15–30 min. A 1-way, repeated measures ANOVA on activity during this 15-min time interval revealed a near significant decrease in locomotor activity across dose [$F(4,20) = 2.66$, $P < 0.06$]. A pair-wise comparison revealed that lobelane decreased locomotor activity only at the highest dose tested (10 mg/kg; $P < 0.05$).

3.4 Effect of Repeated Lobelane on Methamphetamine Self-Administration

Following stable responding for methamphetamine infusions, separate groups of rats were pretreated with lobelane (5.6 mg/kg or 10 mg/kg) 15 min prior to the operant session for 7 sessions (Fig. 5). A 1-way ANOVA on data from the first 15 min of the session revealed no significant differences between groups on baseline responding. On the pretreatment days, an overall 2-way ANOVA revealed significant main effects of session [$F(7,63) = 6.12$, $P < 0.001$] and dose [$F(1,9) = 5.85$, $P < 0.05$]. Within-subject pair-wise comparisons with the baseline control indicated that 5.6 mg/kg of lobelane pretreatment decreased the number of methamphetamine infusions earned on sessions 1 and 2 ($P < 0.05$) and 10 mg/kg of lobelane decreased the number of infusions earned on sessions 1, 2, and 4 ($P < 0.05$).

4. Discussion

Lobelane, a minor alkaloid of *Lobelia inflata* and a synthetic, *des*-oxy analog of lobeline, has enhanced affinity for the vesicular monoamine transporter and dopamine transporter compared to lobeline (Miller et al., 2004). Both of these transporter proteins are considered therapeutic targets for the treatment of methamphetamine abuse (Baumann et al., 2002; Miller et al., 2004; Partilla et al., 2006). The current experiments assessed the effect of lobelane pretreatment on methamphetamine self-administration, sucrose maintained responding, and locomotor activity in rats. Acute lobelane (5.6 or 10 mg/kg) administration decreased methamphetamine self-administration during the first 15 min of the session, with no change at later time points. This contrasts with the effect of lobeline, which has been shown previously to decrease methamphetamine self-administration during the first 25 min of the session, but then produces a compensatory increase in methamphetamine self-administration at the last time point (Harrod et al., 2001). These findings suggest that lobelane has a shorter duration of action than does lobeline for decreasing methamphetamine self-administration. In the current report, acute pretreatment with lobelane (5.6 mg/kg) also resulted in a specific decrease in methamphetamine self-administration, i.e., without altering sucrose-maintained responding or locomotor activity.

In locomotor activity experiments, lobelane (0.1 – 10 mg/kg) did not significantly alter activity when analyzed across the entire 60-min session. However, analysis of the 15–30 min interval revealed a decrease in activity following the highest dose tested (10 mg/kg), which coincides with the time interval of interest in the methamphetamine self-administration and sucrose maintained responding experiments. Importantly, no effect on locomotor activity was observed following administration of a dose (5.6 mg/kg) of lobelane that decreased methamphetamine self-administration, demonstrating further that lobelane administration results in a behaviorally specific decrease in methamphetamine self-administration.

In the current study, tolerance developed to the effect of lobelane on methamphetamine self-administration across repeated pretreatments. These results contrast with those obtained previously with lobeline using similar procedures. Specifically, while Harrod et al. (2001) found that acute lobeline decreased both methamphetamine self-administration and sucrose

reinforced responding, tolerance developed to the lobeline-induced decrease in sucrose reinforced responding, but did not develop to the decrease in methamphetamine self-administration. In this respect, lobelane lacks affinity for $\alpha 4\beta 2^*$ and $\alpha 6$ -containing nicotinic acetylcholine receptors, in contrast to lobeline (Miller et al., 2004). Thus, it is possible that tolerance does not develop to the effect of lobeline due to its action as an antagonist at these nicotinic acetylcholine receptor subtypes, suggesting that specific differences in pharmacodynamics between these two alkaloids may be responsible for the different behavioral effects observed. Significant differences in affinity between lobeline and lobelane have also been reported at the dopamine transporter and serotonin transporter (Miller et al., 2004), suggesting that these targets may also be implicated in the differential behavioral effects of these alkaloids. Since lobeline and lobelane have similar affinities for $\alpha 7^*$ nicotinic acetylcholine receptors and for the norepinephrine transporter (Miller et al., 2004), these targets are not likely responsible for the observed differential behavioral effects between these alkaloids. These results are intriguing and suggest the possibility that more than one target is required to produce the desired behavioral outcome, i.e., a potent decrease in methamphetamine self-administration in the absence of the development of tolerance. Future studies will need to investigate the relationship between tolerance and the ability to decrease methamphetamine self-administration using a small library of lobeline analogs with different activities at the relevant pharmacological targets.

An alternative explanation for the development of tolerance with lobelane, but not with lobeline, may involve pharmacokinetic differences because the *des*-oxy lobelane molecule is likely a better substrate for hepatic metabolic oxidation reactions compared to lobeline, which already has two oxygen containing functionalities. These metabolic differences may also lead to differential distribution and elimination of these two drugs with repeated treatment. In this respect, a more rapid metabolism and elimination of lobelane compared with lobeline would suggest a shorter duration of action. Consistent with this, lobeline has been shown previously to decrease methamphetamine self-administration during the first 25 min of the session (Harrod et al., 2001), whereas the current report showed that lobelane decreased methamphetamine self-administration only during the first 15 min of the session.

In summary, the current results demonstrate that lobelane, a molecule formed from deoxygenation of the lobeline molecule, selectively decreases operant responding for methamphetamine compared to sucrose-maintained responding, and has a shorter duration of action compared to lobeline. However, this deoxygenation of the lobeline molecule also resulted in an unexpected emergence of tolerance, suggesting that in addition to the critical interaction with the vesicular monoamine transporter, another pharmacodynamic or pharmacokinetic component(s) of lobeline's action may be important for maintaining the decrease in methamphetamine self-administration upon repeated treatment.

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Figure 1. Chemical Structures of Lobeline and Lobelane

Figure 2. Dose and Time Course Effects of Acute Lobelane Pretreatment on Methamphetamine Self-Administration

Data represent the mean number of infusions ($\pm$ S.E.M.) obtained during each 5-min interval of the methamphetamine self-administration session following lobelane (5.6 or 10 mg/kg) or saline. * indicates a significant difference of both doses from saline control at the time point indicated ($P < 0.05$)

Figure 3. Dose Effect of Acute Lobelane on Methamphetamine Self-Administration and Sucrose-Maintained Responding

Data represent the mean number of sucrose pellets or methamphetamine infusions ($\pm$ S.E.M.) earned during the first 15 min of the 60-min operant session following pretreatment with lobelane (0.1–10 mg/kg) or saline. *indicates a significant difference from saline control ($P < 0.05$)

Figure 4. Dose Effect of Acute Lobelane on Locomotor Activity

Data represent the mean total distance traveled ($\pm$ S.E.M.) during the 15–30 min time interval, which corresponded to the first 15 min of the operant session in the operant conditioning experiments. *indicates a significant difference from saline control ($P < 0.05$, one-tailed).

Figure 5. Dose Effect of Repeated Lobelane (5.6 or 10 mg/kg) on Methamphetamine Self-Administration

Data represent the mean number of methamphetamine infusions ($\pm$ S.E.M.) earned during the first 15 min of the session following repeated administration of lobelane (5.6 or 10 mg/kg) across 7 sessions. *indicates a significant difference from baseline infusions ($P < 0.05$).