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IV Nicotine Self-Administration in Rats Using a Consummatory Operant Licking Response: Sensitivity to Serotonergic, Glutaminergic and Histaminergic Drugs

Vanessa Cousins, **Jed E. Rose**, and **Edward D. Levin**
Department of Psychiatry and Behavioral Sciences, Duke University Medical Center

Abstract

Tobacco smoking is characterized by repeated self-administration of nicotine by placing the cigarette in the mouth. The repeated hand-to-mouth self-administration is essentially a consummatory act. We recently developed a paradigm in which rats lick one of two spouts to trigger intravenous (IV) delivery of nicotine, which combines a consummatory act with rapid delivery of nicotine to model the act of tobacco smoking. We have found that rats will lick hundreds of times per nicotine infusion. In the current study, using the operant licking nicotine self-administration model with young adult Sprague-Dawley rats (0.03 mg/kg/infusion of nicotine), we tested the effect of antagonists of H_1 histamine receptors pyrilamine, serotonin (5HT) type 2 receptors ketanserin and lorcaserin and N-methyl-D-aspartate (NMDA) glutamate receptors with D-cycloserine in dose ranges that we have found in previous studies to significantly reduce IV nicotine self-administration with the operant lever press operand. The H_1 antagonist pyrilamine significantly reduced operant licking for nicotine self-administration. Pyrilamine caused significant reductions in the operant licking paradigm at lower doses (10 and 20 mg/kg) than those we previously observed to affect responding in the operant lever press paradigm. In contrast, the $5HT_{2A\text{ and }C}$ antagonist ketanserin did not show an effect of reducing nicotine self-administration in the same dose range we had found in a previous study to significantly reduce operant lever press nicotine self-administration. The $5HT_{2C}$ agonist lorcaserin significantly decreased nicotine self-administration in the licking paradigm at the same dose threshold as with lever press responding. The NMDA glutamate partial agonist D-cycloserine did not produce any change in nicotine self-administration with the licking operand, in contrast to its effect on the classic lever-pressing task. The rat model incorporating consummatory aspects of tobacco addiction can provide distinct and potentially more relevant information concerning possible new avenues of treatment to combat tobacco addiction.

Address Correspondence to: Edward D. Levin, Ph.D., Department of Psychiatry and Behavioral Sciences, Box 104790 DUMC, Duke University Medical Center, Durham, NC 27710, USA, Phone: 1-919-681-6273, Fax: 1-919-681-3416, edlevin@duke.edu.

Keywords

Nicotine Self-administration; Operant Licking; Pyrilamine; Lorcaserin; D-cycloserine

1. Introduction

The act of self-administering tobacco by smoking involves the repetitive hand-to-mouth and oral acts of consumption, even though the tobacco smoke is inhaled rather than swallowed. This consummatory behavior is associated with rapid delivery of nicotine. Rat models of nicotine self-administration have repeatedly shown the reinforcing properties of nicotine (Corrigall, 1992), but the tenacity of nicotine self-administration in the rat model is quite modest compared with the very addictive properties of tobacco smoking in humans. The important role of conditioned sensory cues in human tobacco smoking investigated and characterized by Rose and colleagues (Rose and Levin, 1991) has also been shown by Caggiula and colleagues (Caggiula et al., 2001, Caggiula et al., 2002, Chaudhri et al., 2006) to be essential for maintenance of nicotine self-administration. The importance of the repeated motor acts of self-administration for nicotine reinforcement has until recently received little attention. The hand-to-mouth and oral aspects of tobacco smoking have not generally been included in rat models of nicotine self-administration.

To capture the motor consummatory aspect of tobacco addiction in the rat model of nicotine self-administration, we recently developed a method of using a licking response instead of a lever press to self-administer IV nicotine. IV delivery was used to avoid first-pass liver metabolism, which is substantial for nicotine. Including the consummatory motor act with nicotine self-administration and the high number of consummatory responses per infusion may better model compulsive addiction than classic lever responding. We have modeled the consumptive act of licking a waterspout as the operant response to produce rapid IV nicotine self-administration. This method engaged an overt consumptive oral act to trigger nicotine self-administration as is the case with smoking. By this method we aimed to encompass more completely the behavioral processes of smoking addiction. IV delivery of nicotine also enabled direct comparisons with the classic lever press operant for IV nicotine self-administration. Using the operant licking paradigm we showed that rats would preferentially respond to the spout on the active side, which would cause the delivery of nicotine. Over the course of 25 sessions of testing, the rats self-administered a steady level of nicotine but continually increased their number of licks per nicotine infusion to an average level of over 100 licks per infusion (Levin et al., 2010).

The operant licking response has a long history of use in operant conditioning studies (Miller and Debold, 1965, Hulse, 1967, Sprott et al., 1970). Operant licking can be easily conditioned to trigger rewarding contingencies (Buxton and Allison, 1990, Sclafani and Ackroff, 2003). Conditioned operant licking is sensitive to the dopamine actions in the nucleus accumbens (Robbins et al., 1983). The operant licking response for heroin infusions has been shown to result in hundreds of licks per session (Kuntz et al., 2008). We have found the same to occur with operant licking for nicotine self-administration (Levin et al., 2010). The operant licking response for IV nicotine self-administration in rodents provides both the oral consummatory aspects of smoking as well as the rapid nicotine delivery. This

may provide a more complete model of smoking than either the standard lever press operant response -which does not require a consummatory response- or drinking of nicotine, which does not result in rapid nicotine delivery.

In the current set of studies, we used the operant licking model for IV nicotine self-administration to determine the effects of pharmacological treatments that we have previously found to cause a significant reduction in nicotine self-administration in the classic operant lever press paradigm for IV nicotine self-administration. This comparison of drug effects on IV nicotine self-administration with the operant lever pressing and licking was conducted to help determine which neural systems are more or less involved in the consummatory aspects of nicotine self-administration. In recent studies with the operant lever press method, we have found that the serotonin $5HT_{2A\ and\ C}$ antagonist ketanserin (Levin et al., 2008) and the histamine H_1 antagonist pyrilamine (Levin et al., 2011c) were effective in reducing nicotine self-administration. We studied these antagonists of $5HT_{2A\ and\ C}$ and H_1 receptors because these receptor subtypes are two of the more prominent actions of the antipsychotic drug clozapine, which has been found to reduce smoking significantly in people with schizophrenia (McEvoy et al., 1995, McEvoy et al., 1999). We also assessed the $5HT_{2C}$ agonist lorcaserin and the NMDA glutamate partial agonist D-cycloserine because we have previously found these drugs to reduce nicotine self-administration in the classic lever press operant task (Levin et al., 2011a, Levin et al., 2011b). The current study examined the efficacy of these different agents in reducing operant licking for IV nicotine self-administration. The procedures used in the current licking operant and our earlier lever press studies were the same, including the sex, strain, age and supplier of the rats, configuration of the operant test station and the behavioral contingencies and the doses of nicotine and the test drugs so that comparisons of drug effects on nicotine self-administration could more easily be made.

2. Methods

2.1. Subjects

The experiments were carried out in accordance with protocols approved by the Institutional Animal Care and Use Committee and in accordance with federal and state guidelines. Young adult female Sprague-Dawley rats were housed individually on a reverse day: night light cycle (lights on 18:00-6:00). Animals were given *ad lib* access to water at all times except during the three hours prior to the experimental sessions, and were fed daily after the completion of their experimental session in an amount to keep the rats at a lean healthy weight.

2.2. Behavioral Procedures

For behavioral training and self-administration, rats were placed in dual lickometer test chambers (Med Associates, Georgia, VT, USA). Each chamber was equipped with a tone generator, house light, cue light in between the licking spouts, and a stainless steel tether to cover the drug delivery line. A computer programmed with MED-PC software controlled experimental events and data collection. Each catheter was connected to a High Speed Micro-Liter Syringe Pump (Med Associates), with polyethylene tubing and a Huber needle

to access the port (Instech-Solomon, Plymouth Meeting, PA, USA). During each session, the rats wore Covance infusion harnesses (Instech-Solomon) that were connected to the stainless steel tethers that protected the drug delivery lines.

2.3. Nicotine Self-Administration

Solutions of nicotine bitartrate were prepared biweekly in pyrogen-free glassware in sterilized isotonic saline. The dose used for self-administration (0.03 mg/kg/infusion) was calculated as a function of the nicotine base weight. The pH of the solutions was adjusted to 7.0 using NaOH and then the solutions were passed through a Nalgene filter (Nalgene Nunc International, Rochester, NY, USA) for sterilization. Between sessions, all solutions were kept refrigerated in the dark to prevent the decomposition of nicotine.

Rats had catheters surgically implanted into the jugular vein to enable them to receive nicotine infusions. Aseptic surgery was performed with the rat under general anesthesia (ketamine and medetomidine 70/0.3 mg/kg, i.p.). The jugular vein was tied off distal to the place of cannula insertion and a small V-shaped incision was made in the jugular. A catheter of silicon rubber tubing (Silastic Medical Grade Tubing, Dow-Corning Co., USA) was secured into the right jugular vein with cyanoacrylate adhesive so that the tip was just outside the heart. The portion of the cannula external to the vein was sutured to deep muscle and placed subdermally such that it exited the body of the dorsal surface between the scapulae. Surgical mesh under the skin in this area anchored the catheter. Catheters were flushed before the sessions began, with a 0.3 ml solution containing 100U/ml heparinized saline (Baxter Health Corporation, Deerfield, IL, USA). When sessions were over, the nicotine remaining in the ports was drawn out and replaced by a 0.25 ml sterile lock consisting of heparinized saline 500U/ml with 8-mg/ml gentamicin (American Pharmaceutical Partners, Schaumburg, IL, USA).

Two spouts were available to be licked and only one caused the delivery of nicotine on an Fixed Ratio-1 (FR1) schedule throughout testing. The capacitance change when the rats licked a spout registered the licks. Licking the spout on the active side resulted in the activation of the feedback tone for 0.5 sec and the immediate delivery of one 50 μl infusion of nicotine containing 0.03 mg/kg of nicotine in less than 1 sec. The schedule of reinforcement was FR1 and each infusion was immediately followed by a one-minute period in which the cue lights went out and responses were recorded but not reinforced. A light cue was used to signal delivery of nicotine. Each session lasted for 45-minutes. The rats had ten sessions of training for nicotine self-administration prior to the drug treatment studies.

2.4. Drug Treatments

The drug treatments were administered subcutaneously (SC) 10 minutes before the beginning of the test session in a volume of 1 ml/kg with normal saline as a vehicle with injections given in counterbalanced order twice with at least two days between successive doses.

For pyrilamine and ketanserin, half of the subjects were tested for pyrilamine effects first followed by ketanserin and the other half were tested in the reverse order (N=12). The H_1 histamine antagonist pyrilamine HCl (Sigma, St. Louis, MO, USA) was administered

acutely by SC injection in doses of 10, 20 and 40 mg/kg with a saline vehicle as the control. The $5HT_2$ antagonist ketanserin HCl (Sigma, St. Louis, MO, USA) was administered subcutaneously (SC) in doses of 0.5, 1 and 2 mg/kg with saline as the control.

The lorcaserin study was conducted in another set of young adult female Sprague-Dawley rats (N=11). Lorcaserin was purchased from Trylead Chemical Co., Inc. (Hangzhou, China) by the National Institute on Drug Abuse and identity was confirmed by Nuclear Magnetic Resonance (NMR) and liquid chromatography/mass spectrometry. Liquid chromatography/mass spectrometry confirmed that the masses of protonated parent ions found in all test solutions were consistent with the known structure of the compound. (Levin et al., 2011a). The dose range of 0, 0.3125, 0.625, 1.25 and 2.5 mg/kg was given in a repeated measures counterbalanced design two times.

The D-cycloserine study was conducted in another set of young adult female Sprague-Dawley rats (N=20). For analysis the rats in this study were divided into low and high responders based on a median split of nicotine self-administration during the four sessions of pretraining sessions. This was done because of the findings of differential response to D-cycloserine in low and high responders in the classic lever press operand for IV nicotine self-administration (Levin et al., 2011b). There were 10 low responders and 10 high responders in the four baseline sessions prior to the drug tests. Acute doses of 0, 10, 20 and 40 mg/kg were injected sc 10 minutes before testing in a repeated measures counterbalanced design.

2.5. Data Analysis

The dependent measures were nicotine infusions per session as well as active and inactive side licks per session. These were assessed by analysis of variance across the dose levels of drug treatment. Within the factor of drug treatment planned comparisons using Fisher's Least Significant Difference (LSD) tests were conducted of each dose level with control to determine the threshold and extent of the dose effect. A p-value of 0.05 (two-tailed) was used as the threshold for significance.

3. Results

3.1. Pyrilamine

The H_1 antagonist pyrilamine significantly ($F(3,33)=18.56$, pitalic>0.0005) reduced nicotine self-administration by operant licking (Fig. 1A). The effective doses were lower in the operant licking paradigm than were previously seen in the operant lever press paradigm with a similar sample size (Levin et al., 2011c). All three of the pyrilamine doses caused significant reduction in nicotine self-administration in Fisher's LSD tests of pair-wise means comparisons (10 mg/kg $F(1,33)=5.76$, pbold>0.025; 20 mg/kg $F(1,33)=21.12$, $p<0.005$; 40 mg/kg $F(1,33)=50.84$, $p<0.0005$).

Pyrilamine had selective effects on licking of the active spout. As shown in figure 1B, pyrilamine caused significant decreases in active spout licking at doses of 10 mg/kg ($F(1,33)=5.48$, $p<0.05$), 20 mg/kg ($F(1,33)=10.89$, $p<0.005$) and 40 mg/kg ($F(1,33)=21.98$, $p<0.0005$). None of the pyrilamine doses caused significant decreases in responses on the

inactive spout. There was a trend toward decreased responding on the inactive spout with the highest dose of 40 mg/kg ($F(1,33)=3.26$, $p=0.08$), but the lower pyrilamine doses did not show any hint of an effect with 10 mg/kg ($F(1,33)=0.02$, $p=0.88$) and 20 mg/kg ($F(1,33)=0.96$, $p=0.33$).

3.2. Ketanserin

In contrast to the dramatic pyrilamine effects, the $5HT_2$ antagonist ketanserin was ineffective in reducing nicotine self-administration within the same dose range (Fig. 2A),. No significant ketanserin effects on nicotine self-administration were seen in the lick operand paradigm ($F(3,33)=0.30$, $p=0.83$). There were also no significant effects of ketanserin on the numbers of licks of the active ($F(3,33)=0.82$, $p=0.49$) and inactive spouts ($F(3,33)=2.36$, $p=0.09$) (Fig. 2B). We had earlier found ketanserin to effectively reduce operant lever press nicotine self-administration with a similar sample size (Levin et al., 2008).

3.3. Lorcaserin

The serotonin $5HT_{2c}$ agonist lorcaserin caused a significant ($F(4,40)=32.58$, $p<0.0001$) decrease in nicotine self-administration (Fig. 3A). Comparisons of the treatment conditions vs. control showed significant decreases in nicotine self-administration caused by 0.625 mg/kg ($F(1,40)=6.34$, $p<0.025$), 1.25 mg/kg ($F(1,40)=67.98$, $p<0.0001$) and 2.5 mg/kg ($F(1,40)=67.98$, $p<0.0001$) of lorcaserin. Active side licks were significantly affected ($F(4,40)=4.57$, $p<0.005$). Comparisons of the treatment conditions vs. control showed that the 2.5 mg/kg lorcaserin dose ($F(1,40)=8.59$, $p<0.01$) significantly reduced licks on the active side. Lorcaserin did not produce a significant main effect on inactive side licking ($F(4,40)=1.87$, $p=0.13$).

3.4. D-cycloserine

The partial agonist of NMDA glutamate receptors D-cycloserine did not produce any significant ($F(3,54)=0.10$, $p=0.96$) change in nicotine self-administration with the lick operand task. As shown in figure 4A, neither the high nor low responders for nicotine self-administration showed significant effects of acute D-cycloserine. Neither licking on the active ($F(3,54)=0.93$, $p=0.43$) or inactive sides ($F(3,54)=0.39$, $p=0.76$) were significantly affected by D-cycloserine (Fig. 4B). This contrasts with the finding with the classic lever press task that D-cycloserine decreases nicotine self-administration in rats with low baseline levels of nicotine self-administration and increases nicotine self-administration in rats with high levels of baseline responding with similar sample sizes as the current study (Levin et al., 2011b).

4. Discussion

The operant licking for IV nicotine self-administration was found to produce very large numbers of responses and a steady number of nicotine infusions. For example, with control treatment in the pyrilamine study, the rats averaged 145 correct side licks per infusion, replicating our earlier finding of robust responding (Levin et al., 2010). Pyrilamine was even more effective in reducing operant licking for IV nicotine self-administration than we have

previously seen for reducing lever pressing for IV nicotine self-administration (Levin et al., 2011c). Lorcaserin effectively reduced nicotine self-administration in the same dose effect function as we have previously seen with the classic lever press operand (Levin et al., 2011a). Inasmuch as the lorcaserin effect is robust with both the operant licking and lever pressing paradigms for IV nicotine self-administration suggests that this drug, and by extension $5HT_{2C}$ agonists generally, hold promise for further investigation to determine if they may be effective aids for promoting smoking cessation. In contrast, the $5HT_{2A\ and\ C}$ antagonist ketanserin did not show any efficacy in reducing IV nicotine self-administration with the licking operant even though we had previously seen the 2 mg/kg dose to significantly reduce nicotine self-administration with the classic lever press operant response (Levin et al., 2008). D-cycloserine was not found to significantly affect nicotine self-administration, with either an increase or decrease. With the classic lever press operand for nicotine self-administration we previously showed that at this dose range, rats with low baseline rates of nicotine self-administration showed reduced responding, although in that study the mean levels of nicotine infusion were higher than in the current study. These contrasting drug effects may lend insight into differential control over the behavioral responses to self-administer nicotine. Nicotine acts primarily to enhance the rewarding effects of stimuli or responses. Even though the IV nicotine is constant across paradigms, the different responses of licking vs. lever pressing appear to cause differential sensitivity to pharmacologic agents it appears that the consummatory oral response for nicotine is more clearly under control of H_1 histaminergic systems than the more neutral lever press response. Activating the $5HT_{2C}$ serotonergic system appears to be equally potent with controlling the consummatory oral response for nicotine as with lever pressing. Inasmuch as nicotine self-administration in humans by smoking or oral tobacco use engages consummatory responses, it may be the case that H_1 antagonist and $5HT_{2C}$ agonist treatment may hold particular promise for combating human tobacco use.

There were some differences between the earlier studies using the lever press operand and the current studies using the licking operand, which could limit the comparability between the studies. For example, with the lever press task to train the rats to lever press, the subjects were initially trained to self-administer food. This pretraining was not necessary and was not used in the operant licking studies. In addition, all of the current studies used female rats. Most of the cited lever press studies also used females but one study (Levin et al., 2008), the one, which tested the effects of ketanserin used male rats. Another difference include the fact that the rats in the current study has a modest three hour water restriction prior to testing whereas the rats in the lever press studies did not.

The average nicotine self-administration rates in the current series of studies was lower than some other studies. There is a wide spectrum of smoking levels of concern in the human population. The same is the case with rats. Some rats self-administer considerable amounts of nicotine while others self-administer relatively little. Some studies only evaluate the subjects who maintain high levels of nicotine self-administration and omit the lower responding subjects. Therefore the nicotine self-administration reported apply to higher, but not lower level nicotine self-administration. We have chosen to study both the higher and lower levels of nicotine self-administration to include a broader range of smokers, heavy and light.

The operant licking response for IV nicotine self-administration may provide a more complete model of the consummatory actions people actually use to self-administer nicotine via cigarette smoking and may be key in determining the role of conditioned consummatory acts in the basis of tobacco addiction (Levin et al., 2010). This paradigm will help determine if different therapies are needed to combat this type of nicotine self-administration. The process of drug addiction appears to co-opt normal neurobehavioral processes in service of continuing the addictive behavior. Motor acts of consumption which are normally engaged in the basis of feeding can become critical parts of the basis of addiction, especially in the form of tobacco smoking, which uses oral acts to self-administer nicotine. Sensory cues are known to become conditioned reinforcers of smoking behavior and become essential in the maintenance of smoking addiction (Caggiula et al., 2001, Rose, 2006). Both the classic lever press IV nicotine self-administration paradigm and the lick operand IV self-administration paradigm involve a distal visual cue as a conditioned reinforcer. There is also a distal auditory cue from the operation of the syringe pump in both paradigms, however since the pump is located outside the sound attenuating operant test chamber, the auditory cue is minimal. Also possibly important in the neurobehavioral basis of tobacco smoking addiction is the consumptive motor act. The neural systems normally controlling food consumption may be drafted into service of drug self-administration in the process of addiction. Including the consumptive motor act in the rat model of IV nicotine self-administration could more completely capture the entire context in which people self-administer nicotine by smoking cigarettes, providing a way to determine the interactions of consumptive motor stereotypies and nicotine in the basis of tobacco addiction.

Acknowledgments

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List of Abbreviations

5HT	Serotonin
IV	Intravenous
NMDA	N-methyl-D-aspartate
FR1	Fixed Ratio-1
NMR	Nuclear Magnetic Resonance
SC	subcutaneously
LSD	Least Significant Difference

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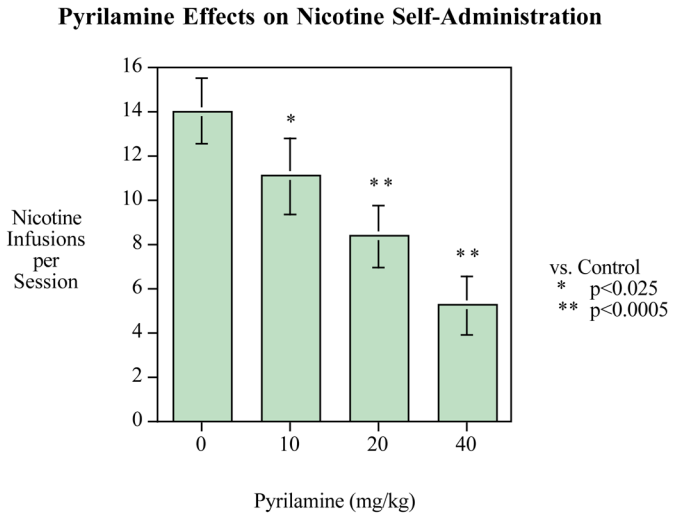
Research Highlights

- Operant licking will support steady rates of IV nicotine self-administration (SA)
- H1 blockade reduced nicotine SA at lower doses than needed with lever pressing
- 5HT2c stimulation reduced nicotine SA at the same doses needed with lever pressing
- 5HT2 blockade did not affect nicotine SA at a dose effective with lever pressing
- D-cycloserine did not affect nicotine SA at doses effective with lever pressing

A.



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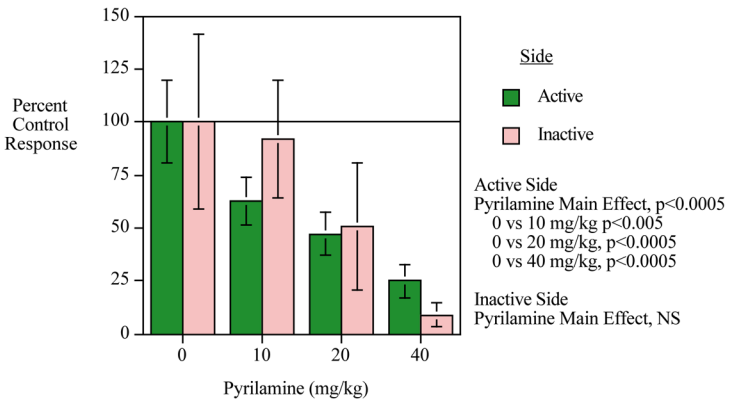
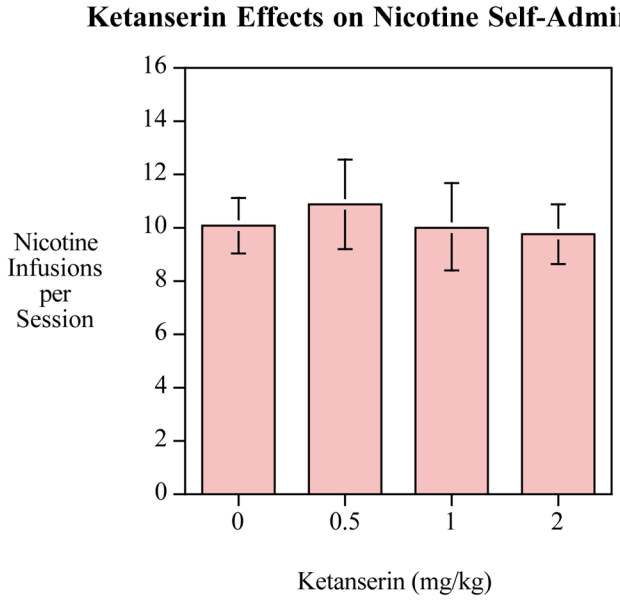


Figure 1.

A. Acute pyrilamine significantly (10 mg/kg. p<0.025; 20 mg/kg, p<0.0005 and 40 mg/kg, p<0.0005) reduced IV nicotine self-administration in the operant licking paradigm (mean ±sem)

B. Acute pyrilamine significantly (10 mg/kg, p<0.005; 20 mg/kg, p<0.0005 and 40 mg/kg, p<0.0005) reduced operant licking on the active side, whereas no significant pyrilamine effect was seen with licks on the inactive side (mean±sem) (N=12).

A.



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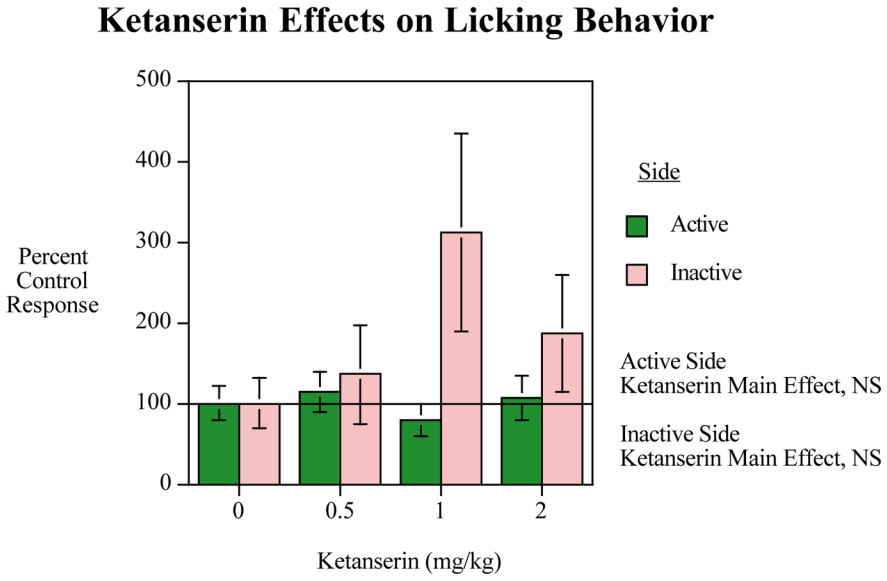
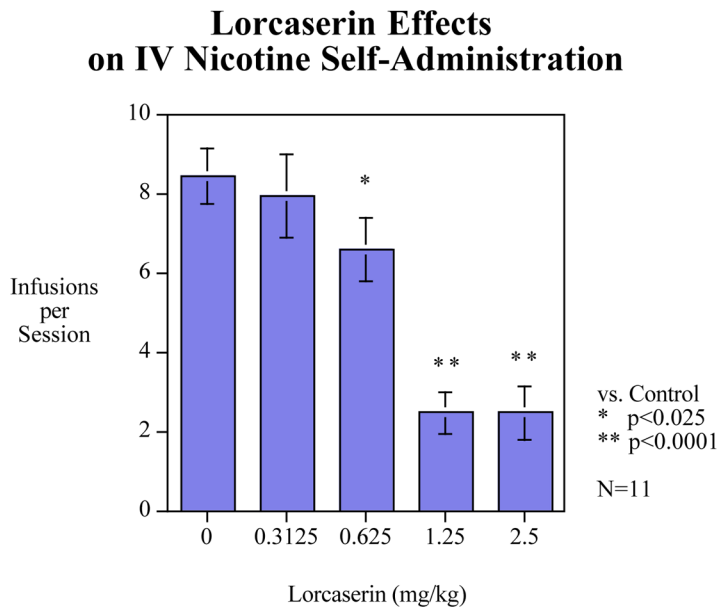


Figure 2.

A. Acute ketanserin (0.5, 1 and 2 mg/kg) treatment produced no significant effects on IV nicotine self-administration in the operant licking paradigm (mean±sem)

B. Acute ketanserin produced no significant effects on licking behavior (N=12).

A.



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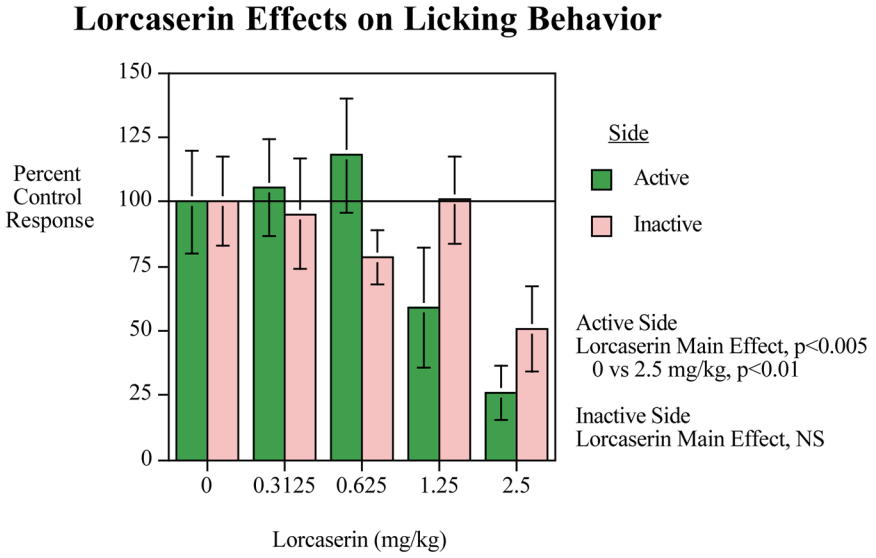
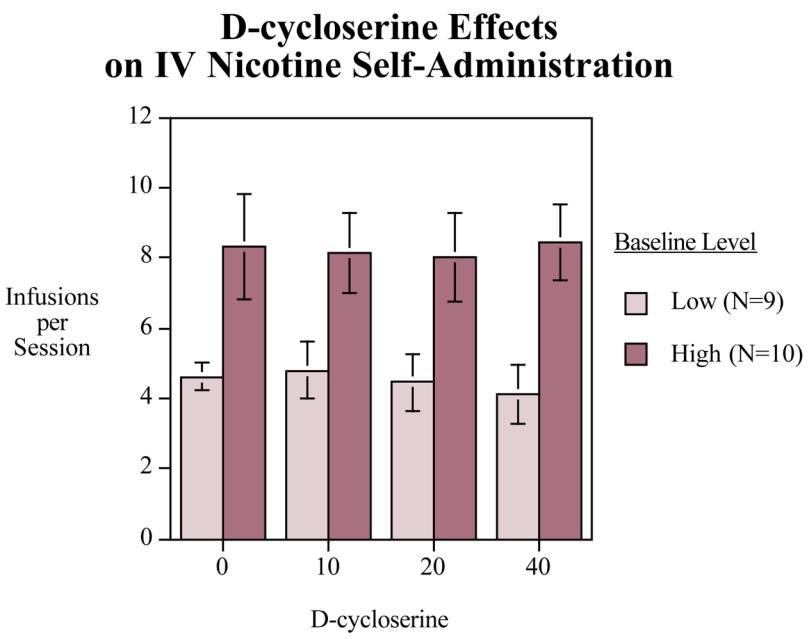


Figure 3.

A. Acute lorcaserin (0.3125, 0.625, 1.25 and 2.5 mg/kg) treatment. Significant reduction in IV nicotine self-administration in the operant licking paradigm was seen with 0.625, 1.25 and 2.5 mg/kg (mean±sem)

B. B. Acute lorcaserin significantly (2.5 mg/kg, $p<0.01$) reduced operant licking on the active side, whereas no significant pyrilamine effect was seen with licks on the inactive side (mean±sem) (N=11).

A.



B.

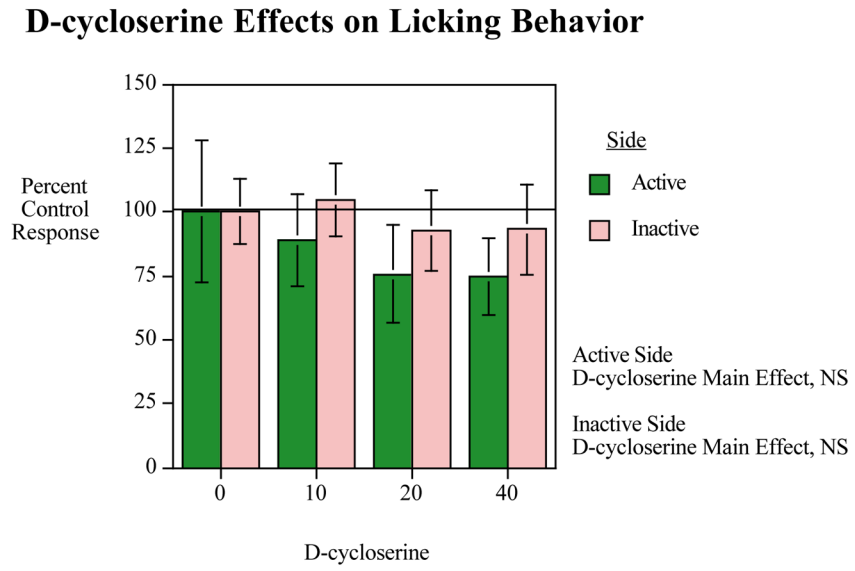


Figure 4.

A. D-cycloserine effects on nicotine self-administration (mean±sem). No significant effects on nicotine self-administration were seen.

B. Acute D-cycloserine produced no significant effects on licking behavior (Baseline low responders N=9, Baseline high responders N=10).