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Ketanserin, a 5-HT$_2$ receptor antagonist, decreases nicotine self-administration in rats

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Abstract

Nicotine intake constitutes a principal mechanism for tobacco addiction. In addition to primary effects on nicotinic acetylcholine receptors, nicotine has cascading effects, which may underlie its neurobehavioral actions. Nicotine induces serotonin (5-HT) release, which has not classically been thought to be involved in tobacco addiction. However, addiction can be characterized more as a disorder of compulsion than a disorder of enjoyment. 5-HT mechanisms play key roles in compulsive disorders. Nicotine-induced 5-HT release may be a key to tobacco addiction. Ketanserin, a 5-HT2a and 2c receptor antagonist, significantly attenuates nicotine effects on attention and memory. These studies were conducted to determine if ketanserin would reduce nicotine self-administration in rats. Male Sprague- Dawley rats (N=12) were given initial food pellet training and then 10 sessions of nicotine self-administration training (0.03 mg/kg/infusion, i.v.). Then the rats were administered ketanserin (1 or 2 mg/kg, s.c.) or the saline vehicle. Ketanserin (2 mg/kg) significantly decreased nicotine self-administration. This did not seem to be due to sedative or amnestic effects of ketanserin. In a second study, the effects of repeated administration of 2 mg/kg ketanserin (N=11) vs. saline injections (N=10) were examined. In the initial phase, the acute effectiveness of ketanserin in significantly reducing nicotine self-administration was replicated. The effect became attenuated during the following several sessions, but the significant effect became re-established during the final phases of this two-week study. 5-HT mechanisms play critical roles in the maintenance of nicotine self-administration. Better understanding of those roles may help lead to new 5-HT-based treatments for tobacco addiction.

Index Words

Nicotine; Self-administration; Serotonin; 5-HT$_2$; Ketanserin; Rat

1. Introduction

Nicotine self-administration and by extension tobacco addiction has been linked to the neural effect of nicotine-induced dopamine release, particularly via activation of dopamine projections from the ventral tegmental area to the nucleus accumbens, but the this projection is just part of a complex circuit underlying motivated behavior in general and addiction in particular (Corrigall, 1991; Di Chiara, 2000; Di Chiara et al., 2004; Koob, 1999; Mansvelder

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and McGehee, 2002; Picciotto and Corrigall, 2002). A wide variety of neurotransmitter systems are involved in these neural circuits involving the midbrain, limbic system, basal ganglia and frontal cortex. In addition, dopamine is not the only neurotransmitter system affected by nicotine. Nicotine also induces the release of serotonin, norepinephrine, histamine, GABA, glutamate, and acetylcholine, the endogeneous ligand for nicotinic receptors (Kenny et al., 2000; Li et al., 1998; Wonnacott et al., 1989). The roles of other transmitter systems, in addition to dopamine and acetylcholine, in the neural bases of nicotine reinforcement are important areas of investigation. Discovering their involvement in the neural basis of nicotine self-administration will not only provide a more comprehensive understanding of the neural bases of tobacco addiction, but could lead to the development of new approaches to help people quit smoking.

Often in drug development research, clues to new therapeutic avenues can come from serendipitous findings from people taking medications for other reasons. Antipsychotic drugs taken by people with schizophrenia may provide important clues for new types of smoking cessation treatment. People with schizophrenia have some of the highest smoking rates in our society, double to triple the general population rate (Barnes et al., 2006; Dalack et al., 1998; Hughes et al., 1986). Interestingly, lower smoking is seen with patients with schizophrenia who are taking atypical antipsychotic drugs (Barnes et al., 2006), in particular clozapine (McEvoy et al., 1995). Clozapine is a complex drug with actions on a variety of different neurotransmitter receptors. There may be a subcomponent of clozapine actions that underlies its efficacy in reducing smoking. We have found that clozapine's serotonin 5-HT_2 receptor antagonist effects are particularly relevant to blocking nicotine-induced cognitive enhancement (Levin and Rezvani, 2007).

Nicotine actions on cognitive function have been found in our studies to be reduced by ketanserin, which is an antagonist at 5-HT_{2A} and 5-HT_{2C} receptors. Nicotine-induced improvements in spatial working memory in the radial-arm maze (Levin et al., 2005) and sustained attention in a signal detection operant task (Rezvani et al., 2005) are reversed by ketanserin. The role of 5-HT_2 receptors in mediating nicotine actions are clearly seen with cognitive and reinforcing effects, but this action does not seem to extend to all of nicotine's effects. Damaj et al. did not find ketanserin to attenuate the reduction in activity or antinociceptive effects of nicotine in mice (Damaj et al., 1994).

There has been some work on a possible neural effect that could underlie ketanserin blockade of nicotine effects. Ketanserin blocked nicotine effects of reducing thalamo-cortical high voltage spindles (Jakala et al., 1997). There is evidence that serotonin and serotonergic receptor acting drugs such as ketanserin can act directly on nicotinic receptors. Ketanserin and other serotonergic ligands as well as serotonin itself have been found to block and enhance desensitization of the muscle nicotinic receptor (Garcia-Colunga and Miledi, 1999). It would be interesting to see if this direct action of ketanserin occurs on neuronal nicotinic receptors as well.

The current study examined the interactive role of 5-HT_{2A} and 5-HT $_{2C}$ receptor systems with nicotine self-administration. Serotonergic systems have been found to play an important role in nicotine dependence (Olausson et al., 2002). In addition to stimulating the release of serotonin (Li et al., 1998),, nicotine may also have direct effects on presynaptic re-uptake of serotonin. There is *in vitro* evidence that nicotine can increase the activity of the serotonin transporter in frontal cortical neurons (Awtry et al., 2006). Serotonergic projections from the raphe to the VTA inhibit dopaminergic neuronal activity. Serotonin 5-HT_{2C} receptor antagonists enhance mesocorticolimbic dopamine activity and 5-HT_{2C} receptor agonists suppress it and in contrast 5-HT_{2A} receptors appear to play the opposite role with 5-HT_{2A}

receptor agonist treatment potentiating nicotine-induced dopamine release (Di Matteo et al., 2002).

Serotonergic and nicotinic systems interact in a variety of ways important for neurobehavioral activity (Seth et al., 2002). Behavioral pharmacology studies have found important roles for 5-HT_2 receptor systems in the expression of nicotine effects. The discriminative stimulus effects of nicotine have been found to be reduced by 5-HT_{2A} and/or 5-HT_{2C} receptor agonists (Batman et al., 2005; Zaniewska et al., 2007). The effect of the 5-$HT_{2A/2C}$ receptor agonist DOI in reducing nicotine discrimination was reversed by administration of the 5-$HT_{2A/2C}$ receptor antagonist ketanserin (Batman et al., 2005). The effects of more selective 5-HT_{2A} or 5-HT_{2C} receptor agonists in reducing nicotine discrimination were reversed by the respective receptor antagonists for these receptors (Zaniewska et al., 2007). In addition, the effects of nicotine on locomotion were also Levin et al., 2008 attenuated by 5-$HT_{2A/2C}$ receptor agonist treatment (Batman et al., 2005). The 5-HT_{2C} receptor agonist R0-60-0175 significantly reduced nicotine self-administration, an effect, which was reversed by the 5-HT_{2C} receptor antagonist SB 242,084 (Grottick et al., 2001). In addition, R0-60-0175 also reduced food motivated responding, reduced chronic nicotine-induced sensitization of locomotor hyperactivity and attenuated nicotine-induced improvement of attentional function in the 5-choice serial reaction time task (Quarta et al., 2007).

In the current study we assessed the involvement of serotonergic mechanisms in one of nicotine's effect, reinforcement as measured by nicotine self-administration. Ketanserin was chosen for investigation because it provides 5-HT_{2A} and 5-HT_{2C} receptor antagonist activity. Individually 5-HT_{2A} and 5-HT2C ligands have both been found to be important for nicotinic action. Combined 5-HT_{2A} and 5-HT_{2C} antagonism with ketanserin has been found to block nicotine-induced cognitive improvement. However, it is not clear what combined 5-HT_{2A} and 5-HT_{2C} receptor blockade would have on nicotine reinforcement. The current study was conducted to determine whether 5-HT_{2A} and 5-HT_{2C} or as well as 5-HT_{1D} blockade with ketanserin may be helpful in reducing nicotine self-administration.

2. Methods

2.1. Subjects

The procedures used in this study were approved by the Duke University Animal Care and Use Committee and conform to the 1996 edition of the Animal Care Guide. Young adult male Sprague-Dawley albino rats (Taconic Farms, Germantown, N.Y., USA) were singly housed in approved standard laboratory conditions in a Duke University vivarium facility near the testing room to minimize any stress- induced by transporting the rats. The day-night cycle was reversed cycle (lights on 18:00-6:00) so that they were in their active phase during behavioral testing. All rats had *ad lib* access to water and were fed the same type of rat chow once daily throughout the study to keep them at approximately 85% *ad lib* weight with food amounts adjusted from 8–16 g per day as they grew to provide a lean healthy growth curve.

2.2. Nicotine Preparation and Administration

Solutions of nicotine ditartrate were prepared weekly in pyrogen-free glassware in sterilized isotonic saline. The doses used were 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 0.22 •m filter (Millipore Corp, Billerica, MA, USA). All solutions were kept refrigerated in the dark between experiments.

2.3. Nicotine Self-Administration

Chronically indwelling intravenous jugular catheters were implanted i.v. under ketamine anesthesia and were flushed daily with a 0.3 ml solution containing 100U/ml heparinized saline (Baxter Health Corporation, Deerfield, IL, USA), and after sessions the nicotine remaining in each port was drawn out and a sterile lock was infused, consisting of heparinized saline 500U/ml with 0.4 mg Gentamicin as an antibiotic. (American Pharmaceutical Partners, Schaumburg, IL, USA). Phenobarbitol injection tests through the catheter were used to verify patency.

For behavioral training, rats were placed in dual lever test chambers (Med-Associates, VT, USA). Each chamber was equipped with a tone generator, house light, cue light above each lever, and a metal tether to cover the drug delivery line. A Pentium 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), and tethers made of polyethylene tubing with huber needles for access to ports and catheters (Instech-Solomon, Plymouth Meeting, PA, USA). During each session, the rats wore Covance infusion harnesses to connect them to the tethers.

Initially, the rats were trained daily with 3 tutor sessions, lasting 15 min., to press the levers for food pellet reinforcers. Half the animals were rewarded for responding on the right lever and half for responding on the left. The cue light over the correct lever was illuminated while the light over the incorrect lever was covered (under the tutor program, both cue lights are turned on, but only one cue light is uncovered, to show which lever is correct.) Responses on the correct lever were rewarded by pressing a button, connected to the control panel, which caused immediate delivery of one 45-mg food pellet and activation of the feedback tone for 0.5 sec. There was no timeout in the tutor sessions. These tutor sessions were followed by 3 daily pellet sessions on a FR-1 schedule, with feedback tone, lasting 45 min. This program activated the correct lever and only the cue light above that lever was illuminated. The training procedure was just before the surgery for catheter implantation, which was just before the onset of nicotine access. This has been added to the methods section.

After the pellet sessions, animals had catheters surgically implanted under ketamine anesthesia to provide access for nicotine self-administration by infusion. A plastic SoloPort was attached intraoperatively to a heparin-coated polyurethane catheter and inserted into a subcutaneous interscapular pocket and sutured to underlying fascia. (Instech-Solomon, PA, USA) The following day, the rats began self-administration sessions with nicotine (0.03mg/kg/infusion, i.v.) as the reinforcer.

A lever press on the active side resulted in the activation of the feedback tone for 0.5 sec, the immediate delivery of one 50 μl infusion of nicotine in less than 1 sec. Each infusion was immediately followed by a one-min. timeout in which the house and cue lights went out and responses were recorded but not reinforced. Two levers were available to be pressed in every session of nicotine self-administration. Only one caused the delivery of nicotine the other did not and served as a control. The benchmark infusion dose of nicotine was (0.03 mg/kg/infusion, i.v.).

In study 1, acute doses of ketanserin (1 and 2 mg/kg, s.c.) and the control saline vehicle solution were given in a repeated measures counterbalanced order twice (N=12). The injections were given ten min. before the onset of the session. Consecutive injections were at least 2 days apart. In study 2, in a separate set of rats, after a pretraining of five sessions the rats were randomly assigned to ketanserin and saline control treatment groups based on the average number of nicotine infusions in the presessions. The effective ketanserin dose from the first study (2 mg/kg, s.c.) was given repeatedly before testing for ten days over the course of two weeks (5 days/

week). Saline vehicle-treated controls (N=10) and ketanserin-treated rats (N=11) matched for preketanserin nicotine self-administration were administered injections on the same schedule.

2.4. Statistical Analysis

The self-administration data were assessed by analysis of variance. In study 1, a repeated measures design was used with each rat receiving both of the ketanserin doses and the saline vehicle. The baseline for each animal under the saline treatment condition is used as the control as is standard for repeated measures analysis of variance. In study 2, there was a mixed design with a between subjects factor of ketanserin administration (0 vs. 2 mg/kg) and a repeated measures within subject factor of repeated dosing and testing. A blocking factor of pretest infusion rate (above or below the pretest median) was used in the analysis of the ketanserin effect. An alpha level of $P<0.05$ (two-tailed) was used as a cutoff for statistical significance.

3. Results

3.1. Study 1

The average number of food pellets earned per session was 60.1±5.4 (mean±S.E.M.). During the 10 sessions of training with nicotine reinforcement the rats averaged 6.09±0.84 infusions per session. The main effect of ketanserin on nicotine self-administration was significant ($F(2,22)=5.45$, $P<0.025$). As shown in Fig. 1, comparisons of each dose with control showed that the lower 1 mg/kg ketanserin did not quite cause a significant ($P=0.08$) decrease in nicotine self-administration, a decrease of 25.5%. The higher 2 mg/kg ketanserin dose did cause a clearly significant ($P<0.005$) reduction in nicotine self-administration, a decrease of 46.5%. The mean±S.E.M. for the rats with the different ketanserin doses were: Saline=3.58±0.87, Ketanserin 1 mg/kg=2.67±0.87, and Ketanserin 2 mg/kg=1.92±0.95.

Two-thirds of the subjects showed reductions in nicotine self-administration with 2 mg/kg of ketanserin (Fig. 2). The ketanserin effect seemed to be specific to nicotine self-administration inasmuch as the number of responses on the incorrect lever was not significantly affected by ketanserin.

3.2. Study 2

The effect of repeated ketanserin administration on nicotine was assessed. There was a significant interaction of ketanserin treatment × session block ($F(4,76)=3.07$, $P<0.025$). Fig. 3 depicts the effect of ketanserin over the course of administration. The analysis of the simple main effects showed that during the first session block (sessions 1–2) there was a significant ($P<0.005$) ketanserin-induced reduction in nicotine self-administration. This effect was not seen during the middle sessions of the study (sessions 3–6) until it was reestablished during the later stages of testing. During sessions 7–8 there was not quite significant ($P=0.054$) ketanserin-induced decrease relative to control. During sessions 9–10, the final phase of the study, there was a clearly significant ($F(1,17)=5.62$, $P<0.05$) ketanserin-induced reduction in nicotine selfadministration. The controls showed some indication of variation of infusion number through ten-session injection period but this was not significant ($P=0.40$). In contrast, the ketanserin-treated subjects did show a significant ($F(4,40)=3.46$, $P<0.025$) effect of session block with a significant ($P<0.025$) quadratic trend across sessions reflecting the lessening of the effect in the middle sessions and its re-establishment during the later sessions.

4. Discussion

The serotonin 5-HT_2 receptor antagonist ketanserin significantly reduced nicotine self-administration in rats. The first study identified an acute dose of 2 mg/kg of ketanserin that significantly reduced nicotine self-administration. This dose has not been seen previously to

cause sedative effects or to cause cognitive impairment. However, it has been shown to significantly attenuate nicotine-induced improvements in working memory and attentional performance (Levin et al., 2005; Rezvani et al., 2005). The second study in a separate set of rats replicated the finding that acute ketanserin significantly reduces nicotine self-administration. In addition, it extended this finding with tests of the effectiveness of chronic ketanserin administration. Interestingly, there was a biphasic effect of chronic ketanserin. After the initial suppression of nicotine self-administration, ketanserin was not found to be effective for several sessions. Finally, during the final phase of the ten-session test series the effectiveness of ketanserin in significantly reducing nicotine self-administration was re-established.

Other studies have found serotonergic interactions with nicotine self-administration. It is interesting that other studies have found that the discriminative stimulus effects of nicotine were reduced by 5-HT_{2A} and/or 5-HT_{2C} receptor agonists (Batman et al., 2005; Zaniewska et al., 2007), that the effect of the 5-$HT_{2A/2C}$ receptor agonist DOI in reducing nicotine discrimination was reversed by administration of the 5-$HT_{2A/2C}$ receptor antagonist ketanserin (Batman et al., 2005) and that 5-HT_{2C} receptor agonist treatment reduced nicotine self-administration (Grottick et al., 2001). It may be that an optimal serotonergic tone is needed to support nicotine self-administration and that either increases or decreases from this tone can effectively reduce nicotine self-administration.

Principally, research on mechanisms of nicotine reinforcement and tobacco smoking addiction have focused on nicotinic acetylcholinergic receptors as the immediate target of nicotine and dopaminergic projections from the ventral tegmental area to the nucleus accumbens as the reward pathway critical for the action of a variety of abused drugs. However, abused drugs in general and nicotine in particular engage a variety of interconnected neural systems, which may be critical substrates for their abuse potential. Serotonergic mechanisms, particularly 5-HT_{2C} receptors, are key in controlling the activity of dopamine neurons of the ventral tegmental area (Di Matteo et al., 2002). Manipulations of serotonergic systems may provide a way to reduce drug-taking behavior.

Other actions of ketanserin may also underlie the effectiveness of ketanserin in reducing nicotine self-administration. In addition to ketanserin effects on 5-HT_{2A} and 5-HT_{2C} receptors ketanserin also binds to 5-HT_{1D} receptors (Varnas et al., 2001; Wurch et al., 1998), which may also be relevant to nicotine self-administration given their presence in the nucleus accumbens (Bonaventure et al., 1997). Ketanserin also has effects at α-1 adrenergic receptors (Marwood, 1994). This action may also contribute to ketanserin-induced reduction in nicotine self-administration. Prazocin, an α-1 adrenergic receptor antagonist has been found to reduce nicotine self-administration (Villegier et al., 2007).

Ketanserin and similar 5-HT_2 antagonists may have broader use in combating drug abuse. Filip et al found that ketanserin significantly attenuates cocaine-induced locomotor activation (Filip et al., 2001). Ketanserin reduces MDMA-induced dopamine release (Nash, 1990). Ketanserin attenuates the discriminative stimulus effects of methamphetamine (Munzar et al., 1999). Ketanserin and similar drugs may be useful in attenuating psychotomimetic effects of lysergic acid diethylamide (LSD) given that it blocks the 5-HT_2 receptor site of action of LSD (Munzar et al., 1999).

In conclusion, the results of this study show that the 5-HT_2 receptor antagonist ketanserin significantly reduces nicotine self-administration in rats. Previously, we found that ketanserin blocks nicotine effects of memory and attentional improvement (Levin et al., 2005; Rezvani et al., 2005). Drugs acting on 5-HT_2 or possibly 5-HT_{1D} receptors may be a new effective means for smoking cessation.

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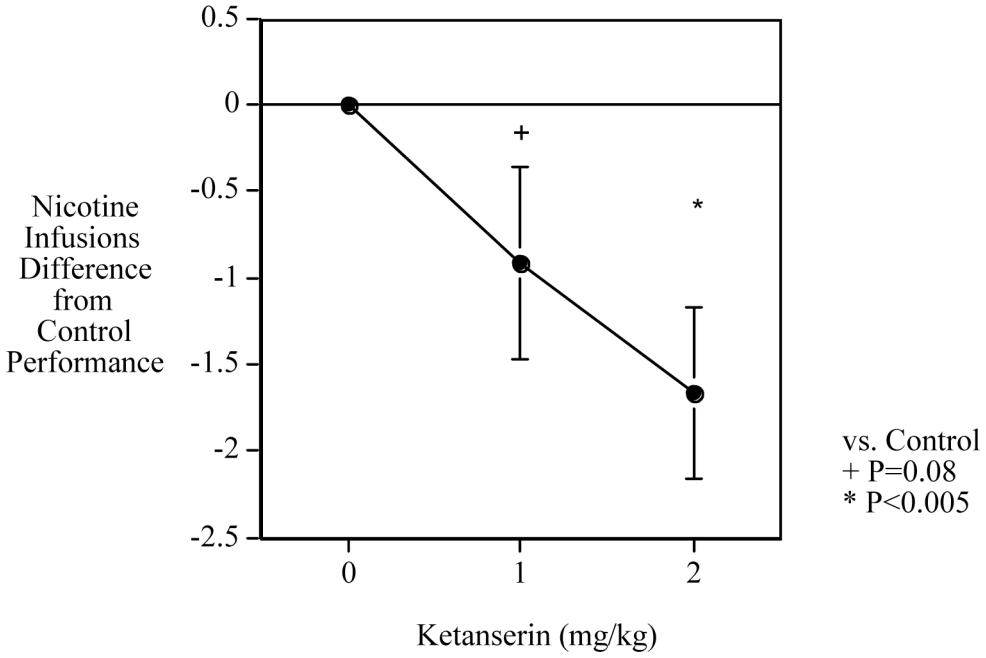

Fig. 1. Acute Ketanserin Effects on Nicotine Self-Administration

Dose-effect function of acute ketanserin attenuating nicotine self-administration in rats (mean ± S.E.) difference in performance after ketanserin injection vs. performance of each rat after control saline injection (N=12).

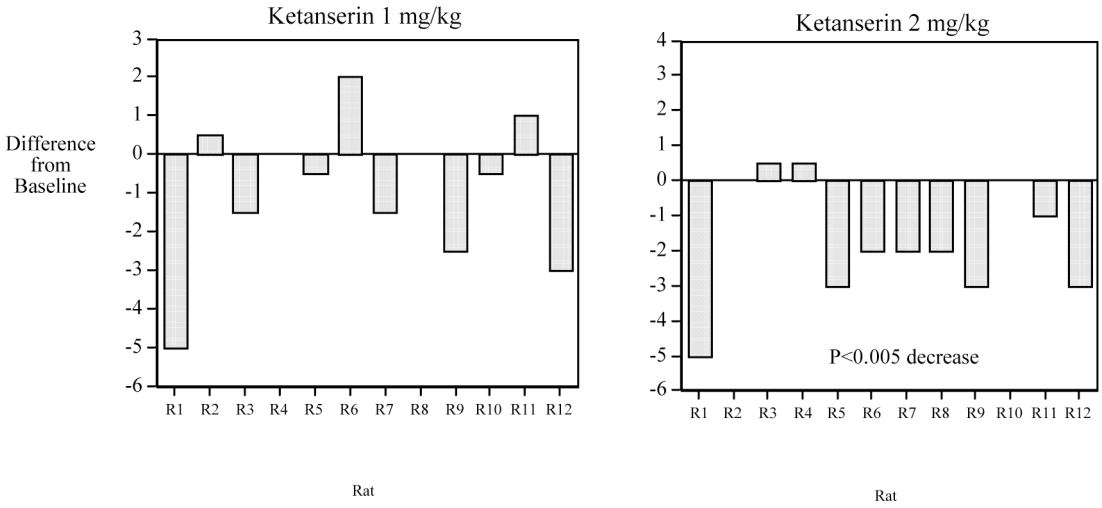

Fig. 2. Ketanserin Effects on Nicotine Self-Administration in Rats

Individual animal data for acute ketanserin effects on nicotine self-administration (N=12). Two-thirds of the subjects showed reductions in nicotine self-administration with 2 mg/kg of ketanserin vs. their performance after control saline injections.

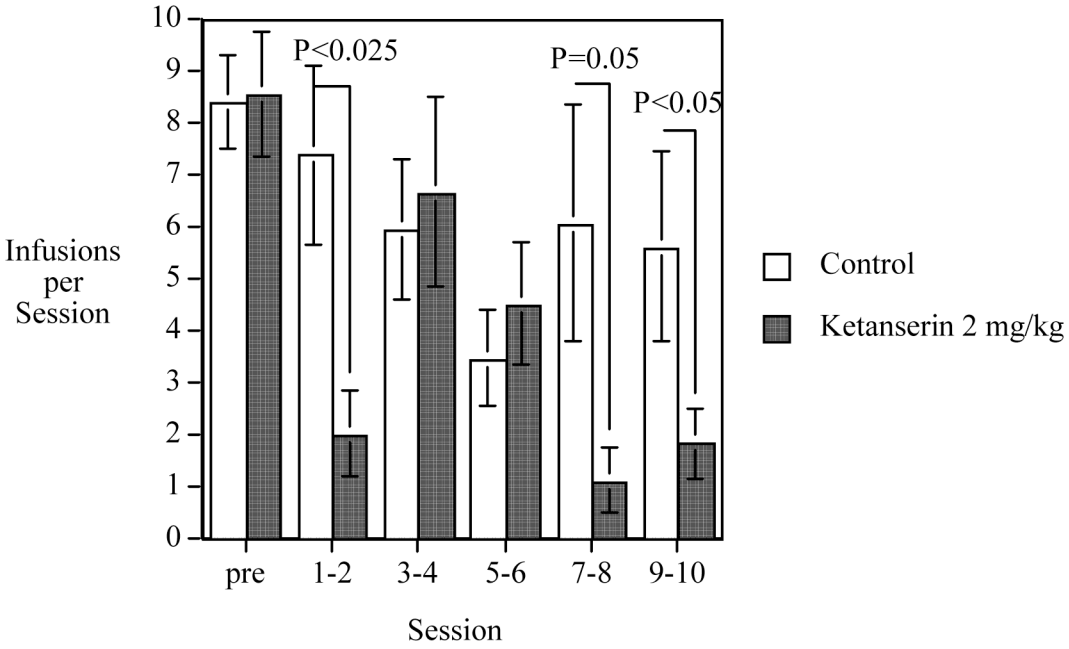

Fig. 3. Chronic Ketanserin Effects on Nicotine Self-Administration

Chronic ketanserin effects on nicotine self-administration (mean± S.E.) Controls (N=10) and Ketanserin 2 mg/kg (N=11). The pre session average is the mean for the five sessions of training on nicotine self-administration before the randomization of the rats into matched treatment groups.