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Effects of dopamine antagonists on drug cue-induced reinstatement of nicotine-seeking behavior in rats

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Abstract

Dopaminergic neurotransmission has been implicated in associative learning processes related to drugs of abuse. However, it is not clear whether blockade of activation of dopamine receptors alters conditioned incentive properties of nicotine-associated cues. Using a response-reinstatement procedure, this study examined the effects of antagonists selective for the D1 and the D2 subtypes of dopamine receptors on cue-induced reinstatement of nicotine-seeking behavior. Male Sprague-Dawley rats were trained in 30 daily 1 h sessions to intravenously self-administer nicotine (0.03 mg/kg/infusion) on a FR5 schedule and associate a conditioned stimulus (cue) with each nicotine delivery. After extinction of responding by withholding nicotine (saline substitution) and its cue, the reinstatement tests were conducted following subcutaneous administration of a D1 antagonist SCH23390 (0, 5, 10, 30 µg/kg) or a D2 antagonist eticlopride (0, 5, 10, 30 µg/kg) in different groups of animals. Both SCH23390 and eticlopride significantly attenuated the magnitude of cue-elicited reinstatement of nicotine-seeking responding. These results indicate that activation of dopaminergic D1 and D2 receptors may play a role in mediating the conditioned motivational effects of nicotine-associated cues as measured in the response-reinstatement procedure. These findings suggest that manipulation of dopaminergic neurotransmission at the D1 and/or D2 receptors may prove to be a potential target for the development of pharmacotherapy for prevention of environmental nicotine cue-triggered smoking relapse.

Keywords

Antagonists; conditioned stimuli; dopamine receptors; eticlopride; nicotine-seeking; reinstatement; SCH23390; self-administration; rat

Introduction

Cigarette smoking and nicotine dependence is a chronic relapsing disorder. The high rates of relapse in abstinent smokers present a formidable challenge for long-term success of smoking cessation treatments. One important factor critically contributing to the resumption of drug use in abstinent addicts is exposure to environmental stimuli previously associated with drug intake (Carter and Tiffany 1999; Childress et al. 1993; Drummond et al. 1995; Niaura et al. 1989;

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O'Brien et al. 1998; Stewart et al. 1984). Indeed, presentation of cigarette cues such as the visual stimuli that were previously associated with nicotine self-administration via cigarette smoking has been shown to reliably elicit strong craving for smoking along with physiological responses (Carter and Tiffany 1999; LaRowe et al. 2007; Miranda et al. 2008; Niaura et al. 1988; Sayette et al. 2001). Recently, using an operant response-reinstatement procedure in laboratory animals it has been demonstrated that cues conditioned to intravenous nicotine self-administration effectively reinstate nicotine-seeking behavior after extinction (Cohen et al. 2005; LeSage et al. 2004; Liu et al. 2006, 2007, 2008; Paterson et al. 2005). These animal studies not only provide experimental support for the significance of environmental cues in triggering relapse to smoking in abstinent smokers but also validate the procedure as a reliable animal model for elucidation of the mechanisms of nicotine-seeking behavior and for medication development.

Corticoesolimbic dopaminergic neurotransmission has been implicated in mediation of the reinforcing actions of nicotine (Balfour et al. 1998; Clarke 1990; Di Chiara 2000; Picciotto and Corrigall 2002; Watkins et al. 2000). For instance, acute nicotine administration increases in vivo dopamine release in the nucleus accumbens, a terminal field of the dopamine circuitry (Balfour et al. 1998; Brazell et al. 1990; Damsma et al. 1989; Di Chiara and Imperato 1988; Ferrari et al. 2002; Maisonneuve et al. 1997; Marshall et al. 1997; Mifsud et al. 1989; Nisell et al. 1994). Neuroadaptive changes in the corticoesolimbic dopamine system have been observed after chronic nicotine exposure via either active self-administration or passive administration by experimenters (Benwell et al. 1995; Carboni et al. 2000; Rahman et al. 2004). In nicotine self-administration studies, 6-hydroxydopamine-induced lesion of the nucleus accumbens (Corrigall et al. 1992) and blockade of activation of the D1 and D2 receptors (Corrigall and Coen 1991) significantly reduced nicotine intake.

Recently, increasing human studies using functional magnetic resonance imaging and positron emission tomography indicate that activation of the corticoesolimbic dopamine circuitry may also be implicated in mediation of the conditioned responses to smoking/nicotine cues. In both clinical and preclinical settings, exposure to environmental stimuli previously associated with cigarette smoking and nicotine intake has been found to activate neurotransmission in the components of corticoesolimbic dopamine circuitry, such as anterior cingulate cortex, amygdale, nucleus accumbens (Brody et al. 2007; David et al. 2005; Franklin et al. 2007; McBride et al. 2006; McClernon et al. 2007b; Schiltz et al. 2005; Schroeder et al. 2001; Smolka et al. 2006). Genetic analysis studies have revealed significant association of smoking cue reactivity including cigarette craving with genetic polymorphism in the components of dopaminergic neurotransmission pathways (Erblich et al. 2005; Franklin et al. 2009; Hutchison et al. 2002; McClernon et al. 2007a; Munafo and Johnstone 2008).

In animal studies, however, little attention has been paid to the issue of whether dopaminergic neurotransmission plays a role in mediation of the conditioned incentive properties of nicotine-associated cues. To address this issue, the present study, by using a response reinstatement procedure in rats, examined whether pharmacological blockade of dopaminergic neurotransmission alters the behavioral motivation by a nicotine-associated cue. Specifically, this study examined the effects of the dopamine D1 antagonist SCH23390 and the D2 antagonist eticlopride on cue-induced reinstatement of extinguished nicotine-seeking behavior.

Methods

Subjects

Male Sprague-Dawley rats (Charles River), weighing 225–250 g at arrival, were used. Animals were individually housed in a humidity- and temperature-controlled (21–22 °C) vivarium on a reversed light/dark cycle (lights on 19:00 h; off 07:00 h) with unlimited access to water. After

the first week of acclimation to the vivarium, rats were placed on a food-restriction (20 g chow/day) regimen throughout the experiments. Training and experimental sessions were conducted during the dark phase at the same time each day (09:00 – 15:00 h). All experimental procedures were carried out in accordance with the *National Institutes of Health Guide for the Care and Use of Laboratory Animals* (1996).

Apparatus

Self-administration training, extinction, and reinstatement test sessions were conducted in operant conditioning chambers located inside sound-attenuating, ventilated cubicles (Med Associates, St. Albans, VT). The chambers were equipped with two retractable response levers on one side panel and with a 28-V white light above each lever as well as a red chamber light on the top of the chambers. Between the two levers was a food pellet trough. Intravenous nicotine injections were delivered by a drug delivery system with a syringe pump (Med Associates, model PHM100-10 rpm). All experimental events and data collection were automatically controlled by an interfaced computer.

Food Training

To facilitate nicotine self-administration training, rats were first trained to press a lever for food reward. These food training sessions began on the second day of food-restriction regimen. Introduction of levers and illumination of the red chamber light signaled the start of the sessions. The right lever was assigned as the active lever, each response on which was rewarded with delivery of a 45 mg food pellet. Sessions lasted 1 hour with a maximum delivery of 45 food pellets. Within 3–5 sessions the reinforcement schedule was increased to a fixed-ratio (FR) 5. Food training finished after rats earned all the 45 food pellets on the FR5 schedule. During these food training sessions, no stimulus other than constant illumination of the red chamber light was presented.

Surgery

After food training, the rats were anesthetized with an isoflurane-oxygen mixture (1–3% isoflurane) and implanted with jugular catheters. Catheters were constructed from a 15 cm piece of Silastic tubing (0.31 mm ID and 0.63 mm OD, Dow Corning) attached to a 22 gauge stainless steel guide cannula. The latter was bent and molded onto a durable polyester mesh (Plastic One) with dental cement and became the catheter base. Through an incision on the rat back, the base was anchored underneath the skin at the level of scapula and the catheter passed subcutaneously to the ventral lower neck region and inserted into the right jugular vein (≈ 3.5 cm). Animals were allowed at least 7 days to recover from surgery. During the recovery period, the catheters were flushed daily with 0.1 ml of sterile saline containing heparin (30 U/ml) and Timentin (66.7 mg/ml) to maintain catheter patency and prevent infection. Thereafter, the catheters were flushed with the heparinized saline prior to and after the experimental sessions throughout the studies. If there was no session on the weekend, the catheter was flushed once/day.

Nicotine self-administration/conditioning

After recovery from surgery, rats were trained to self-administer nicotine intravenously (0.03 mg/kg/infusion, free base) and associate a cue with nicotine delivery. In the training sessions, animals were placed in the operant conditioning chambers and connected to a drug delivery system. The daily 1-h sessions were initiated by introduction of the two levers and illumination of the red chamber light. Once the FR requirement on the active lever was met, an infusion of nicotine was dispensed in a volume of 0.1 ml/kg in approximately 1 s. Each nicotine infusion was paired with a presentation of the cue consisting of a 5 s tone (83 dB) and turn-on of the active lever light for 20 s. The latter signaled a 20 s timeout period during which time responses

were recorded (included in the total number of responses) but not reinforced. Responses on the inactive lever had no consequence. A FR1 schedule was used for days 1–5, a FR2 for days 6–8 and a FR5 for the remainder of the experiments. All rats received 30 daily self-administration/conditioning sessions to equalize their operant experience and nicotine intake.

Extinction

After completion of the self-administration/conditioning phase, rats were subjected to daily extinction sessions, in which the nicotine-maintained lever responding was extinguished by withholding nicotine and its associated cue. Thus, responses on the active lever resulted in the delivery of saline rather than nicotine and the cue was not presented. The FR5 schedule and the 20 s timeout period were still in effect for saline infusions. The criterion for extinction was 3 consecutive sessions in which the number of responses/session was $\leq 20\%$ of that averaged across the last 3 self-administration/conditioning sessions.

Reinstatement test

One day after the final extinction session, reinstatement tests were conducted. As happened in the self-administration/conditioning and extinction phases, the test session started with introduction of the two levers and illumination of the red chamber light. During the sessions, responses on the active lever resulted in presentation of the cue and saline infusion on the FR5 schedule with the 20 s timeout period. As such, there was still no availability of nicotine. Responses on the inactive lever had no consequence. The test sessions lasted 1 hour.

Effect of SCH23390 on cue-induced reinstatement of nicotine-seeking—Rats were designated into four groups ($n=8-10$) in a pseudorandom order so that each group had similar profiles of lever responding and nicotine infusions. Thirty min before the reinstatement test session, SCH23390 (0, 5, 10, 30 $\mu\text{g/kg}$ in a volume of 1 ml/kg, dissolved in sterile saline) was subcutaneously administered to different groups of rats. The test session was performed as described above.

Effect of eticlopride on cue-induced reinstatement of nicotine-seeking—Rats were divided into four groups ($n=8-9$) with a similar rate of lever responding and nicotine infusions in each group. Eticlopride (0, 5, 10, 30 $\mu\text{g/kg}$ in a volume of 1 ml/kg, dissolved in sterile saline) was subcutaneously injected to different groups of rats 30 min before the reinstatement test session, which was performed as described above.

Effect of SCH23390 and eticlopride on food self-administration

Due to the fact that both SCH23390 (highest dose) and eticlopride (all three doses) effectively attenuated lever responding in the reinstatement tests (see results), the effects of these two agents at their respective effective doses on food self-administration were also examined in the respective drug/dose groups of rats. After completion of the drug/reinstatement tests, the rats from highest SCH23390 dose group and three eticlopride dose groups were re-trained to self-administer food pellets. Specifically, responses on the redesignated active lever (inactive lever during nicotine self-administration) were rewarded on a FR10 schedule with 20 s timeout period while responding on the inactive lever was not rewarded. Stable responses for food pellets were established within 7 daily 30 min sessions. Then, in the 8th and 10th sessions (no drug treatment for the 9th session) the effects of drug pretreatment were examined by using a within-subject and counterbalanced design. Individual groups received the same drug/dose treatment respectively as in the reinstatement tests. The saline vehicle control was tested within each individual drug/dose group. That is, half rats of each group received drug injection (SCH23390: 30 $\mu\text{g/kg}$; eticlopride: 5, 10, 30 $\mu\text{g/kg}$ respectively) and the other half received a saline vehicle in the 8th session. The reversed treatment order happened in the 10th session.

Data Analyses

Data are presented as the mean ($\pm$ SEM) number of lever responses and earned nicotine infusions. One-way ANOVA was used to analyze data obtained from the self-administration/conditioning phase averaged across the final three sessions and drug/reinstatement tests, followed by the Fisher's PLSD *post hoc* tests to verify differences among individual means. Because saline vehicle control was performed within each individual drug/dose group, the data obtained from food self-administration tests were analyzed by using a paired *t*-test for each drug/dose group.

Results

Nicotine self-administration/conditioning and extinction

Rats readily acquired stable level of nicotine intake in the 30 daily 1-h self-administration/conditioning training sessions. Averaged across all subjects over the final 3 sessions, animals emitted mean $\pm$ SEM responses of 89.5 ± 6.2 on the active lever and 5.4 ± 1.2 on the inactive lever. Correspondingly, rats earned 15.2 ± 2.2 nicotine infusions in the daily 1-h sessions. In the first extinction session, animals emitted a mean $\pm$ SEM number of responses of 71.6 ± 9.5 on the active lever and 10.1 ± 3.3 on the inactive lever. During subsequent extinction sessions, lever responses gradually decreased. To equalize the number of the extinction sessions and synchronize the reinstatement tests with drug pretreatment, three rats were excluded during the extinction phase because they failed to meet extinction criterion within 10 sessions. Since rats were first divided into the two antagonist testing conditions and then further subdivided into 4 groups for different doses under each drug condition in a pseudorandom (counterbalanced) manner, there was no difference between the two drug conditions and among different dose groups under each individual drug condition in lever responses and nicotine infusions earned during the self-administration/conditioning, or in lever responses during the extinction phases as well as body weights immediately before the reinstatement test session, details of which are shown in Table 1.

Effect of SCH23390 on cue-induced reinstatement of nicotine-seeking

One-way ANOVA on the number of responses on the active lever yielded a near-significant dose effect [$F(3,33)=2.64$, $p=0.06$] and subsequent Fisher's PLSD *post hoc* tests showed a significant ($p<0.05$) difference between the highest dose (30 μ g/kg) versus saline control and the 10 μ g/kg group (Figure 1). However, similar analysis revealed no significant change in the number of responses on the inactive lever. These data indicate that SCH23390 at 30 μ g/kg reduced the magnitude of cue-induced reinstatement of nicotine-seeking behavior.

Effect of eticlopride on cue-induced reinstatement of nicotine-seeking

Pretreatment with eticlopride dose-dependently decreased the magnitude of the cue-induced reinstatement of nicotine-seeking responses. One-way ANOVA on the number of responses on the active lever yielded a significant dose effect [$F(3,30)=12.26$, $p<0.001$]. Further Fisher's PLSD *post hoc* tests verified significant difference among the individual group means, details of which are depicted in Figure 2. Similar analysis on the number of the inactive lever responses did not show a significant dose effect [$F(3,30)=1.72$, *NS*].

Effect of SCH23390 and eticlopride on food self-administration

After completion of the drug/nicotine-seeking tests, rats were successfully re-trained to lever-press for food reward in 7 daily sessions. There was no observable difference among groups (for subsequent drug/dose treatment tests) in the number of both responses and food pellets earned. The detailed numbers of lever responses and food pellets earned in the last pretest session are shown in Table 2.

Figure 3 shows the total number of responses on the active lever rats made for food reinforcement after pretreatment with SCH23390 or eticlopride. There was no difference of responses between SCH23390 (30 µg/kg) and saline control condition ($p>0.5$). Further analysis on the number of responses pooled in 15 min bins of the session revealed no significant change after SCH23390 pretreatment. Similarly, no significant change in the number of active lever responses was observed after pretreatment with eticlopride at the two lower doses (5 and 10 µg/kg). However, there was a significant ($p<0.05$) difference in both the total and the first two 15 min bins in the number of active lever responses between the highest dose (30 µg/kg) of eticlopride and saline control condition, indicating a significant suppression of food self-administering behavior.

In all groups, responses on the inactive lever remained quite low in the food self-administration sessions as shown in Table 2 and no change was observed after pretreatment with these drug/doses (data not shown).

Discussion

This study examined the effects of pharmacological blockade of dopaminergic neurotransmission at the D1 and D2 receptors on conditioned reinstatement of nicotine-seeking behavior after extinction. The finding that both the D1 antagonist SCH23390 and the D2 antagonist eticlopride effectively attenuated the magnitude of nicotine-seeking responding elicited by presentation of a previous nicotine-associated cue indicates a role of dopaminergic neurotransmission via the D1 and D2 receptors in mediation of the conditioned incentive properties of nicotine cues. Therefore, it is suggested that manipulations targeting these receptors may have clinical potential for prevention of drug cue-triggered relapse to tobacco smoking in abstinent smokers.

The first set of data showed that the dopamine D1 antagonist SCH23390 at its highest dose (30 µg/kg) effectively attenuated lever responding for the presentation of the nicotine cue. The lack of effect of this agent on the food self-administering behavior ruled out any nonspecific suppression of operant behavior. This result indicates that SCH23390 selectively decreased the cue-elicited reinstatement of nicotine-seeking responding. It is consistent with a previous report showing that SCH23390 suppressed nicotine cue-maintained lever responding (Cohen et al. 2005). In that study, after training for self-administration of 0.03 mg/kg/infusion nicotine with presentation of a tone/light cue (i.e., 1 s tone + 20 s lever light) lever responding was maintained by presentation of the cue without nicotine injection rather than extinguished by withholding both nicotine and its cue as happened in the present study. SCH23390 dose-dependently suppressed the cue-maintained responding. Although obtained from procedures with some differences, the present results together with the data of Cohen et al. (2005) demonstrate that blockade of dopamine D1 receptor activation decreases the conditioned incentive value of nicotine-associated cues in the animal models of nicotine-seeking. In addition, Bevins et al (2001) reported that SCH23390 blocked a contextual nicotine cue-induced increase in locomotor activity in a passive association procedure, i.e., a particular context was associated with experimenter-administered nicotine. Taken together, these findings indicate that activation of dopamine D1 receptors may play a role in mediation of the conditioned incentive properties of nicotine-associated environmental cues.

The dopamine D2 antagonist eticlopride strongly suppressed the active lever responding during the reinstatement test session. The effect was observed across all the three doses used. However, it should be noted that eticlopride at its highest dose (30 µg/kg) also reduced food self-administration behavior in the same set of rats that had completed nicotine tests and been re-trained for food pellet reward. Thus, it is likely that the highest dose of eticlopride produced nonspecific suppression on operant behavior. This effect is similar to the documentation in the

literature showing that D2 antagonists are in general prone to produce a suppressant effect on locomotor activity, the cataleptogenic properties of D2 blockade (Amalric et al. 1993; Ferrari and Giuliani 1995; Skjoldager and Fowler 1988). An alternative explanation for eticlopride suppression on food responding is that the D2 receptor blockade may attenuate rats' motivation to acquire food reward. For instance, it was previously reported that eticlopride at 30 µg/kg significantly reduced the breaking point in a progressive ratio test for food self-administration (Blokland et al. 2005). As to the two lower doses (5 and 10 µg/kg) of eticlopride, since they did not alter responding in the food self-administration tests, it could be concluded that eticlopride in this dose range specifically attenuated cue-induced reinstatement of nicotine-seeking behavior and this conclusion suggests a selective decrease in conditioned incentive value of the nicotine cue by blockade of dopaminergic neurotransmission at the D2 receptors. This is the first study to demonstrate D2 antagonist attenuation of cue-reinstated nicotine-seeking behavior, so this finding extends the involvement of activation of the D2 receptors in mediation of the incentive value of cues that are conditioned to other drugs of abuse such as alcohol (Liu and Weiss 2002) to the motivational effects of nicotine-associated cues. Further, from a clinical perspective, the present results suggest that the D2 antagonists may prove to be good candidates for smoking cessation treatment, although careful selection of effective doses seems to be critical owing to the fact that these agents are prone to produce extrapyramidal side effects at higher doses.

The implication of dopaminergic neurotransmission via the D1 and D2 receptors in conditioned motivation by nicotine cues is in line with ample evidence demonstrating the important roles of activation of the D1 and D2 receptors in the mediation of conditioned reinforcing properties of the cues that are associated with other drugs of abuse as well as natural rewards such as food and water (Di Chiara and Bassareo 2007; Sutton and Beninger 1999; Wise 2006). Microdialysis and voltametric studies in rodents have demonstrated an increase in dopamine release in the mesolimbic circuitries in response to the presentation of cues that were previously conditioned to food and drugs such as cocaine and alcohol (Bassareo and Di Chiara 1999; Katner and Weiss 1999; McCullough and Salamone 1992; Roitman et al. 2004; Weiss et al. 2000). However, the precise mechanisms underlying a broad spectrum of dopamine antagonism to interfere with the conditioned incentive salience of environmental cues are not quite clear. It is possible that blockade of dopaminergic neurotransmission might reduce motivation to obtain the conditioned reinforcers (cues) and/or dampen perception of the cues. These issues remain to be investigated.

The results of the present study are complementary to reports using discriminative stimulus tests. For instance, both the D1 antagonist SCH23390 and the D2 antagonists haloperidol and spiperone have been found to decrease the discriminative stimulus effects of nicotine (Corrigall and Coen 1994a; b). A D1 agonist SKF82958 could substitute for nicotine in a discriminative stimulus test although the D2/D3 agonists did not (Gasior et al. 1999). However, in a conditioned place preference (CPP) test (Spina et al. 2006), neither the D1 nor the D2 antagonists in nucleus accumbens altered the expression of nicotine-induced CPP although the D1 (but not the D2) antagonist in the shell of the nucleus accumbens impaired the acquisition of the CPP, indicating interference with the primary reinforcement of nicotine. A recent human study using positron emission tomography did not find increased dopamine release in the ventral striatal region when tobacco-dependent smokers smoked a denicotinized cigarette (Brody et al. 2009), suggesting no significant change in dopamine activity in response to exposure to nicotine cues. These conflicting data ask for more investigation on whether and how nicotine cue exposure changes dopaminergic neurotransmission.

In conclusion, this study demonstrates that blockade of activation of the D1 and D2 receptors attenuates the motivational effects of a nicotine-associated cue in the response-reinstatement procedure. This finding suggests that manipulation of dopaminergic neurotransmission at the

D1 and/or D2 receptors may prove to be a potential target for the development of pharmacotherapy for prevention of smoking relapse triggered by exposure to environmental nicotine-associated cues. Therefore, these data lend support for the continued clinical effort to test the effectiveness of antipsychotics for prevention of smoking relapse. For instance, haloperidol has been found to reduce smoking of denicotinized cigarettes, which indicates a decreased reaction to nicotine cue exposure (Brauer et al. 2001; but see Mahler and de Wit 2005), and a D2 receptor antagonist olanzapine to attenuate cue-induced craving for cigarette smoking (Hutchison et al. 2004; Rohsenow et al. 2008).

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Figure 1.

Effect of SCH23390 on lever-pressing responses in the reinstatement tests (n=8–10). Data are expressed as mean±SEM. * $p < 0.05$ different from saline control; + $p < 0.05$ different from 10 µg/kg group.

Figure 2.

Effect of eticlopride on lever-pressing responses in the reinstatement tests (n=8–9). Data are expressed as mean±SEM. * $p < 0.05$, *** $p < 0.001$ different from saline control; + $p < 0.05$, ++ $p < 0.01$, different from 5 µg/kg group.

Figure 3. Effect of SCH23390 (top) and eticlopride (below) on active lever responses for food self-administration. Data are expressed as mean $\pm$ SEM. * $p < 0.05$ different from saline control.

Profiles of mean ($\pm$ S.E.M.) lever responses and corresponding nicotine infusions averaged across the final three sessions of the self-administration/conditioning training phase, responses on the active lever averaged across the last three extinction sessions, and body weights measured before the reinstatement test session.

Table 1

Group (drug/dose)	Nicotine SA responses			Extinction (active lever)	B. W (g)
	Active lever	Inactive lever	Nicotine Infusions		
SCH23390 (μg/kg)					
0	88.9±10.2	7.6±2.3	15.3±2.6	18.3±2.9	398±20
5	95.6±18.2	11.3±5.6	18.1±4.1	19.0±3.2	411±28
10	79.8±15.2	8.6±2.9	14.9±3.1	16.6±2.4	378±25
30	82.1±9.9	6.3±3.5	15.1±1.8	18.6±2.9	376±18
Eticlopride (μg/kg)					
0	76.9±18.3	8.3±2.9	14.3±3.9	17.0±2.9	402±23
5	85.3±12.3	6.9±3.2	15.5±2.8	18.7±2.3	378±16
10	91.3±20.1	14.3±5.2	17.2±4.3	18.5±3.6	386±20
30	89.0±16.5	8.2±3.4	16.8±3.6	17.4±3.0	391±21

Table 2

Mean ($\pm$ S.E.M.) lever responses and food pellets earned in the last session of food self-administration training before drug treatment tests.

Group (drug/dose)	Food SA responses		Food Pellets
	Active lever	Inactive lever	
SCH23390 (μg/kg)			
30	294±36	7±3	28±4
Eticlopride (μg/kg)			
5	283±32	6±2	28±3
10	268±19	5±1	25±2
30	289±27	7±2	27±3