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Renewal of sucrose-seeking behavior in rats: Role of D_2 dopamine receptors

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ABSTRACT

The present study characterized renewal of sucrose-seeking behavior in rats (Experiment 1). The role of the dopamine subtype-2 (D_2) receptors in mediating renewal of sucrose-seeking behavior also was examined (Experiment 2). Rats were trained to respond for sucrose pellets (45 mg each) on a fixed-ratio 25 (Experiments 1 and 2) schedule of reinforcement in Context A. Following acquisition, rats underwent extinction and 4 renewal tests in Contexts B and A, respectively. In Experiment 2, rats were pretreated with vehicle or the D_2 dopamine receptor antagonist eticlopride (5, 10, 20, or 40 μg/kg) 30 min prior to the first renewal test session. A follow-up experiment (Experiment 3) examined the effect of a high eticlopride dose (40 μg/kg) on locomotor activity. Renewal of sucrose-seeking behavior persisted for 3 sessions. Eticlopride dose-dependently blocked renewal of sucrose-seeking behavior without suppressing locomotor activity, implicating a role of D_2 dopamine receptors in mediating renewal of sucrose-seeking behavior.

1. Introduction

The renewal effect has been studied extensively in aversive (fear conditioning; Bouton and Bolles, 1979; Bouton and King, 1983; Rauhut et al., 2001; Thomas et al., 2003) or appetitive (Goddard, 1999) Pavlovian conditioning paradigms. Recently, the renewal effect also has been studied in an operant, drug-seeking paradigm and conceptualized as an animal model of drug relapse (see Bossert et al., 2005, for a recent review). For example, Crombag and Shaham (2002) showed that renewal of drug-seeking behavior can be produced when a mixture of cocaine + heroin (speedball) is used as a reinforcer during the acquisition phase. In this experiment, rats were trained to self-administer cocaine + heroin on a fixed-ratio 1 (FR 1) schedule of reinforcement in Context A. Following the acquisition phase, rats underwent extinction in Context B where responses were no longer followed by drug infusions. For the renewal test, rats were returned to Context A and the number of responses was recorded, although responses were still not followed by drug infusions. Control rats received a similar training regimen, except that they underwent an AAB or an ABB training procedure. Crombag and Shaham (2002) found that a return to Context A, following extinction in Context B, increased the rate of responding (i.e., renewal) compared with control rats. Since this original demonstration of renewal in a drug-seeking paradigm, several other researchers have reported that other drugs of abuse such as cocaine (Crombag et al., 2002; Fuchs et al., 2005), alcohol (Burattini et al., 2006; Hamlin et al., 2007), or heroin (Bossert et al., 2005; Bossert et al., 2004; Bossert et al, 2007) can engender renewal.

Both glutamatergic and dopaminergic systems have been implicated in mediating renewal of drug-seeking behavior. For example, the $mGluR_{2/3}$ agonist LY379268, a negative modulator of glutamatergic transmission, decreases renewal of heroin-seeking behavior (Bossert et al., 2004). Bossert et al. (2004) also found that LY379268 microinjected into the ventral tegmental area, but not the substantia nigra, decreases renewal of heroin-seeking behavior. It has been reported that systemic injections of the dopamine D_1 antagonist SCH 23390 or D_2 antagonist raclopride attenuate renewal of cocaine-seeking behavior (Crombag et al., 2002); SCH 23390 also attenuates alcohol- (Hamlin et al., 2007) or heroin- (Bossert et al., 2007) seeking behavior. Furthermore, systemic injections of SCH 23390 have been found to decrease renewal-induced increases in c-Fos expression in the nucleus accumbens shell (Hamlin et al., 2007), and Bossert et al. (2007) found that microinjections of SCH 23390 into the medial or lateral accumbens shell decreased renewal of heroin-seeking behavior. Collectively, these observations suggest that glutamatergic transmission modulates mesolimbic D_1 and D_2 dopamine receptors in mediating renewal of drug-seeking behavior.

Evidence indicates that the renewal effect is not specific to drug-seeking behavior, but that it generalizes to non-drug reinforcers. Studies have shown that renewal of food-seeking behavior can be produced when food pellets (Nakajima et al., 2002; Welker and McAuley, 1978) or liquid sucrose presentations (Hamlin et al., 2006) are used as reinforcers during the acquisition phase in an ABA renewal paradigm. Similar to renewal of drug-seeking behavior, both glutamatergic and dopaminergic processes have been implicated in mediating renewal of food-seeking behavior. Bossert et al. (2006)

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found that systemic injections of LY379268 attenuated renewal of sucrose-seeking behavior. Hamlin et al. (2006) also found that systemic injections of SCH 23390 decreased renewal of sucrose-seeking behavior, decreased renewal-induced increases in c-Fos expression throughout the nucleus accumbens, and selectively decreased renewal-induced c-Fos expression in the lateral hypothalamus. These results suggest that food-seeking behavior is similar to drug-seeking behavior based on its involvement of glutamatergic modulation of mesolimbic D_1 dopamine receptors.

D_2 dopamine receptors also have been shown to underlie other conditioned incentive-motivated behaviors; however, their role is less clear. For example, haloperidol failed to attenuate the ability of an odor discriminative stimulus paired with heroin to reinstate drug-seeking behavior in an operant runway task (McFarland and Ettenberg, 1997) and See et al. (2001) found that microinjections of the D_2 dopamine antagonist raclopride into the basolateral amygdala failed to alter reinstatement induced by a punctate cue. However, Katner and Weiss (1999) found that an odor discriminative stimulus paired with alcohol self-administration effectively reinstated drug-seeking responding and concurrently increased dopamine overflow in the nucleus accumbens. Weiss et al. (2001) also found that the D_2 dopamine antagonist raclopride attenuated reinstatement induced by an auditory discriminative stimulus.

Given that studies supporting a role of D_2 dopamine receptors in cue-induced reinstatement have used discriminative stimuli associated with a drug, rather than punctate cues, it appears that D_2 dopamine receptors may be involved primarily in reinstatement induced by discriminative stimuli. Indeed, Crombag and Shaham (2002) have suggested that renewal stems from contextual cues serving as either occasion setters or conditioned modulators of drug- or food-seeking behavior. Consistent with this idea, Crombag et al. (2002) found that the D_2 dopamine antagonist raclopride attenuated renewal of cocaine-seeking behavior. However, because raclopride also decreased locomotor activity in that study, the attenuation of renewal of cocaine-seeking behavior may have been, at least in part, an artifact of drug-induced motor impairment. Thus, the role of the D_2 dopamine receptors in mediating renewal of cocaine-seeking behavior is unclear. Moreover, no studies to date have examined the role of D_2 dopamine receptors in mediating renewal of sucrose-seeking behavior.

Therefore, in the present study, we first characterized the robustness and persistence of renewal of sucrose-seeking behavior using two different dependent measures: 1) number of responses and 2) latency to complete the first FR schedule of reinforcement (Experiment 1). We next examined the ability of the D_2 dopamine antagonist eticlopride to attenuate renewal of sucrose-seeking behavior (Experiment 2). If D_2 dopamine receptors mediate the discriminative stimulus effects of contextual stimuli, similar to D_1 dopamine receptors, then eticlopride was predicted to dose-dependently block renewal of sucrose-seeking behavior. In order to determine if eticlopride altered renewal of sucrose-seeking behavior by disrupting behavior nonspecifically, we examined whether eticlopride decreased locomotor activity (Experiment 3). Assessment of general locomotor activity has been shown to be sensitive to dopamine antagonist-induced disruption in operant performance (Murray and Bevins, 2007).

2. Methods

2.1. Animals

For Experiments 1 and 2, the subjects were male Sprague–Dawley rats, approximately 200–225 g, obtained from Harlan Industries (Indianapolis, IN). Rats were housed individually in Plexiglas cages with pine chip bedding and wire lids. Rats were given 3–5 g of rat chow daily for 7 days prior to the start of the experiment in order to reduce the rats to 80% of their free-feeding body weights. Rats were given 10–20 g of rat chow after each daily operant conditioning session in order to maintain the rats at approximately 80% of their free-feeding body weights throughout the duration of the experiment. The animal colony was kept on a 12 h/light:12 h/dark cycle. All experimental procedures were conducted during the light phase of the cycle. Upon arrival, the rats were acclimated to the animal colony for at least 5 days. The Institutional Animal Care and Use Committee of the University of Kentucky approved the experiments.

For Experiment 3, subjects were male experimentally naïve Sprague–Dawley rats (Charles River Laboratories, Raleigh, NC). The rats ranged in weight from 136–164 g at the start of the experiment. Rats had ad libitum access to food and water for the duration of the experiment. Rats were housed individually in opaque, polypropylene tubs that measured $8 \times 12 \times 6$ in (L×W×H) and contained wire lids. The rats were kept on a 12 h/light: 12 h/dark cycle. Upon arrival, the rats were acclimated to the animal colony for a 7-day period and handled daily for 1 min during this period. This experiment was approved by the Dickinson College Animal Care and Use Committee. All experiments conform to the guidelines established by the *NIH Guide for the Care and Use of Laboratory Animals* (1996 Edition) and the *APA Ethical Principles of Psychologists and Code of Conduct*.

2.2. Apparatus

For Experiments 1 and 2, twelve operant conditioning chambers (ENV-001, Med Associates, St Albans, VT), housed in sound-attenuating cubicles, were used. Six of these operant chambers constituted one distinct context and the other six chambers constituted a second distinct context. For one context, the end walls of these chambers were aluminum and the front and back walls were clear Plexiglas, covered by black cardboard that impeded the rat's view directly in front of and behind the chamber. Located in the bottom center of one of the end walls was an opening to a recessed food tray (5×4.2 cm). Located on either side of the recessed food tray was a response lever. The floor consisted of 18 stainless steel rods, with newspaper underneath the floor of these chambers. The second context differed from the first context as follows: (1) a white piece of Plexiglas was inserted into the operant chamber and truncated the chamber; (2) white cardboard was placed on the front and back walls of the chamber, which impeded the rat's view directly in the front and rear of the chamber; (3) one cup of pine bedding (P.J. Murphy, New Jersey) was poured on top of the newspaper that lined the floor; and (4) a square piece of hardwire cloth was placed over the stainless steel rods. In both of the distinct contexts, a 28-V cue light was located 6 cm above each response lever. At the beginning of the session, both cue lights were illuminated and remained on for the duration of the session. All stimulus and response events were controlled by a personal computer (MED-PC software).

For Experiment 3, eight open-field activity chambers (MED-OFA-510; Med-associates, St Albans ,VT) were used. The walls of the compartments were constructed of Plexiglas and the overall inside dimensions were 27.9 cm × 27.9 cm (L×W). Locomotor activity was determined by three, 16-beam infrared arrays and recorded by an IBM personal computer (MED-PC Activity Software) located in the same room. A speaker provided an ambient white noise (70 dB) background.

2.3. Drugs

S(-)-eticlopride HCl (Sigma, MO) was prepared in physiological saline (0.9% NaCl) and given subcutaneously (s.c.) in a volume of 1 ml/kg body weight. Doses of eticlopride were based on salt weight.

2.4. Procedures and statistical analyses

2.4.1. Experiment 1. Demonstrating renewal of sucrose-seeking behavior

Following the weight-reduction period, the experiment consisted of 3 phases: acquisition, extinction, and renewal tests. For acquisition, rats were first shaped to lever press for sucrose pellets (45 mg each)

in one of the two distinct contexts (counterbalanced across rats), which was designated as Context A. Following shaping, the rats were trained on an FR 1 schedule of reinforcement for a 15-min period in which responses on one lever (active) were reinforced. Responses on the other lever (inactive) had no programmed consequence. Active and inactive levers were counterbalanced. Rats were required to earn 10 reinforcers in the 15-min period. The FR 1 schedule was then increased to an FR 2, followed by an FR 3, 6, 12, and 25 using 30-min daily sessions. On the terminal FR 25 schedule of reinforcement, rats ($n=8$) were trained to respond for sucrose pellets on an FR 25 schedule of reinforcement in Context A. The rats were required to earn greater than 10 pellets for 10 consecutive daily sessions during the acquisition phase. Following the acquisition phase, the extinction phase began in the alternate context (designated as Context B), where responses were recorded but not followed by sucrose pellets. Extinction continued for 10 consecutive daily sessions. This extinction procedure resulted in the rats making less than 25 responses by the last session of extinction training (see results); however, rats were not explicitly matched to groups based on rate of responding during acquisition or extinction. The criteria for acquisition and extinction were selected in order to ensure a well-trained response during the acquisition phase and complete behavioral extinction during the extinction phase; similar extinction criteria have been adopted for studying renewal of cocaine-seeking behavior in rats (Fuchs et al., 2005). For the renewal test phase, rats were returned to Context A for 4 consecutive daily 30-min sessions (Test Sessions 1–4). Similar to the extinction phase, responses were recorded but not followed by sucrose pellets. A control group of rats ($n=4$) underwent a similar training procedure except that acquisition, extinction and renewal test phases all occurred in Context A (i.e., AAA training procedure). The number of responses and the latency to complete the first FR schedule of reinforcement served as dependent measures.

Data were analyzed using the statistical software package, SPSS (version 15.0 for Windows). Response data were subjected to analyses of variance (ANOVAs). Group (Renewal vs. Control) served as a between-subject factor and Session and Lever (Active vs. Inactive) served as within-subject factors. Post hoc contrasts of interest involved paired-samples and unpaired-samples *t*-tests for between- and within-subject comparisons, respectively. Because the latency data violated the assumption of homogeneity of variance, nonparametric Mann–Whitney *U* and Wilcoxon signed-rank tests were used for analyses involving between- and within-subject factors, respectively. The results of these latter tests are reported as standard scores (*z* values). All statistical decisions were made with α set at 0.05 (two-tailed).

2.4.2. Experiment 2. Effect of eticlopride on renewal of sucrose-seeking behavior

The procedures for the acquisition and extinction phases of Experiment 2 were similar to Experiment 1. As in Experiment 1, rats were not explicitly matched to groups based on their rate of responding during acquisition or extinction. Following extinction, on Test Session 1, rats ($n=6$ per dose) received vehicle (physiological saline) or eticlopride (5, 10, 20, or 40 μg/kg) 30 min prior to the start of the session. The eticlopride doses and injection parameters (time and route of administration) chosen were based on a previous study that found that eticlopride dose-dependently decreased responding maintained by food under an FR 15 [120 s Time-Out (TO)] multiple schedule of reinforcement (Caine and Koob, 1994). Because the AAA control group failed to provide any evidence for renewal in Experiment 1 (see Results), this control group was omitted from this experiment. Instead, in Experiment 2, renewal was defined by a within-session comparison of the last day of extinction and the renewal tests. Such within-session comparisons to define renewal have been used in renewal studies employing either aversive, Pavlovian fear conditioning paradigms (Rauhut et al., 2001) or operant conditioning paradigms involving a pharmacological manipulation (Bossert et al., 2007). On Test Session 2, rats did not receive any pretreatment prior to the start of the session; this session sought to determine if eticlopride-pretreated rats on Test Session 1 would demonstrate renewal in the absence of the drug.

For response data, ANOVAs were conducted, with Day and Lever serving as within-subject factors and Dose serving as a between-subject factor. In order to control for experiment-wide α error associated with multiple between-group contrasts, and because several eticlopride doses (5, 10, 20 and 40 μg/kg) were compared with a single control group (vehicle), between-subject post hoc contrasts of interest involved Dunnett's tests. The latency data were subjected to Kruskal–Wallis *H* and Wilcoxon signed-ranked tests for between- and within-subject comparisons, respectively.

2.4.3. Experiment 3. Effect of eticlopride on locomotor activity

Rats ($n=5$ per group) received vehicle (saline) or eticlopride (40 μg/kg) and were placed immediately into the activity chamber for 60 min. The distance travelled (cm) served as the dependent measure of locomotor activity. Locomotor activity data were collected for the entire 60-min session. However, in order to compare to the timeframe of operant conditioning experiment (Experiment 2), only the first 30 min of the session were plotted and analyzed using an independent-samples *t*-test.

3. Results

3.1. Experiment 1. Demonstrating renewal of sucrose-seeking behavior

In order to examine group differences in the rate of acquisition and extinction, separate Group (Renewal vs. Control) × Session (1–10) ANOVAs were conducted on the number of responses on the active lever (or previously active lever when tested in extinction) and multiple Mann−Whitney *U* tests were conducted on the latency measure. For active lever press responses, only a significant main effect of Session for the acquisition data was found, $F(9, 90)=17.1$. Neither the main effect of Group nor the Group × Session interaction was significant on these acquisition data (Fig. 1, Panel A, far left). In addition, across both groups, the number of inactive lever presses was consistently less than 25 per session (results not shown). Multiple Mann–Whitney *U* tests conducted on the latency data of the acquisition phase revealed no significant group differences on any acquisition session (Fig. 1, Panel B, far left). Taken together, these results indicate that groups did not differ with respect to their rates of acquisition.

During extinction, a significant main effect of Session, $F(9, 90)=71.6$, and Group, $F(1, 10)=24.7$, as well as a significant Group × Session interaction, $F(9, 90)=17.3$, was detected on the response measure. Post hoc contrasts involving unpaired-samples *t*-tests revealed that responding was lower for renewal rats compared with control rats on Extinction Sessions 1, 2, 3 and 5, $ts\ (10)>2.4$, $ps<0.05$, and did not differ on the remaining extinction sessions (Fig. 1, Panel A, far right). Multiple Mann–Whitney *U* tests conducted on the latency data of the extinction phase revealed that the latency to complete the first FR was longer in renewal rats compared with control rats on Extinction Sessions 1, 2 and 3, $zs>2.3$, and did not differ on the remaining sessions (Fig. 1, Panel B, far right). Collectively, these results indicate that renewal rats extinguished at a faster rate compared with control rats.

3.1.1. Renewal tests

Three-way Group (Renewal vs. Control) × Session (Last Session of Extinction vs. Test Sessions 1–4) × Lever (Active vs. Inactive) ANOVA conducted on the response data revealed significant main effects of Lever, $F(1, 10)=11.4$, Session, $F(4, 40)=17.3$, and Group, $F(1, 10)=18.3$; all two- and three-way interactions also were significant, $Fs>11.4$ (Fig. 2, Panel A, far right). Post hoc contrasts involving unpaired-samples *t*-tests found that renewal rats responded more than control rats on the active lever on Test Sessions 1, 2 and 3, $ts\ (10)>2.6$, $ps<0.05$. On Test

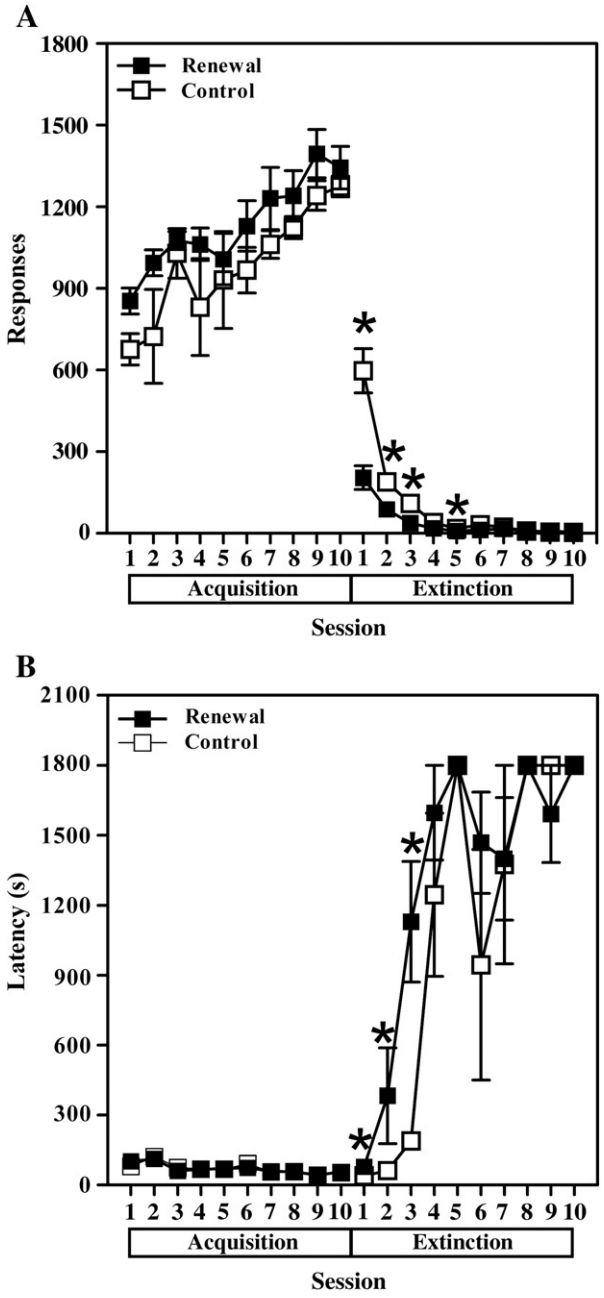

Fig. 1. Mean (± SEM) number of responses emitted on the active lever during the acquisition sessions (1–10) and extinction sessions (1–10) for renewal (ABA) and control (AAA) rats of Experiment 1 (Panel A). Mean (± SEM) latency to complete the first FR requirement during the acquisition sessions (1–10) and extinction sessions (1–10) for renewal (ABA) and control (AAA) rats of Experiment 1 (Panel B). The asterisk (*) symbol denotes a significant difference from control rats at a particular session, *ps*<0.05.

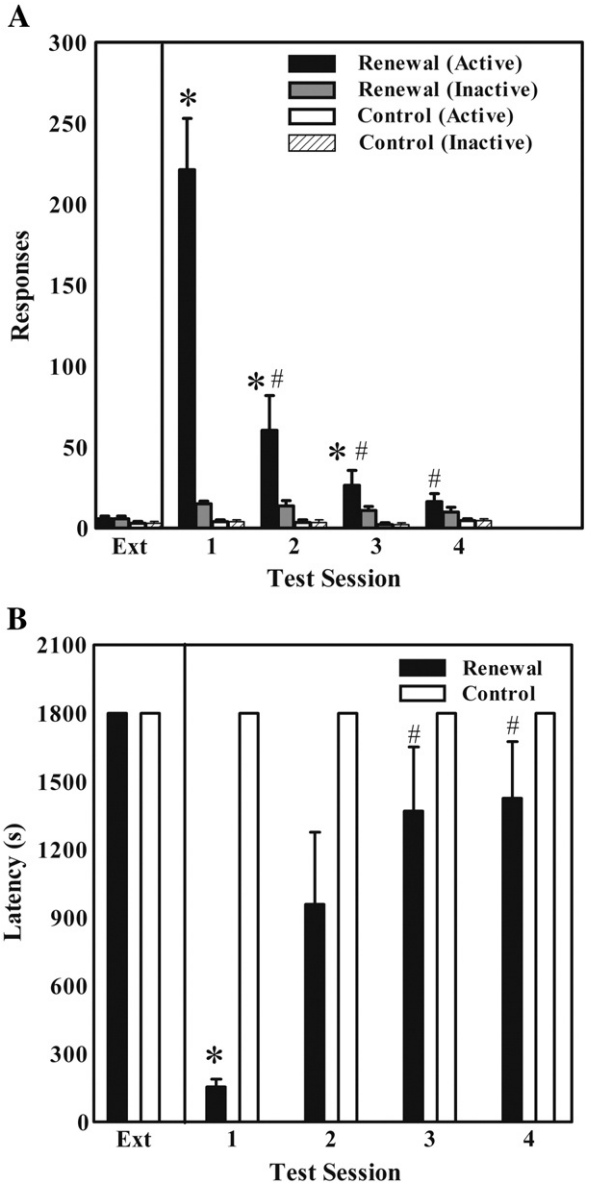

Fig. 2. Mean (+ SEM) number of responses emitted on the active (i.e., previously active) and inactive levers during the last session of extinction (Ext; Panel A, far left) and the test sessions (Panel A, far right) for renewal (ABA) and control (AAA) rats of Experiment 1. Mean (+ SEM) latency to complete the first FR requirement during the last session of extinction (Ext; Panel B, far left) and the test sessions (Panel B, far right) for renewal (ABA) and control (AAA) rats of Experiment 1. The asterisk (*) and pound (#) symbols denote a significant difference from the last session of extinction and Test Session 1, respectively, *ps*<0.05.

Session 4, responding tended to be higher in renewal rats compared with control rats, but this difference was not significant, $p = 0.06$. Responding on Test Sessions 2, 3 and 4 also differed from Test Session 1 for renewal rats, *t*s (7)>6.1, suggesting that renewal decreased with repeated testing.

Mann–Whitney *U* tests conducted on the latency data of Test Sessions 1–4 found that the latency to complete the first FR was shorter for renewal rats compared with control rats only on Test Session 1, $z = 2.8$ (Fig. 2, Panel B, far right). Furthermore, Wilcoxon signed-ranked tests found that the latency to complete the first FR was longer by Test Sessions 3 and 4 compared with Test Session 1 for renewal rats, *z*s>2.1, suggesting that renewal decreased with repeated testing.

3.2. Experiment 2. Effect of eticlopride on renewal of sucrose-seeking behavior

3.2.1. Renewal tests

Three-way Dose (0–40 μg/kg) × Session (Last Session of Extinction vs. Test 1 vs. Test 2) × Lever (Active vs. Inactive) repeated-measures ANOVA conducted on the response data revealed main effects for Session, $F(2, 50) = 35.7$, and Lever, $F(1, 25) = 56.4$, *ps*<0.001. With the exception of the Group × Lever interaction, all two- and three-way interactions were significant, *F*s>4.9. Post hoc paired-samples *t*-tests revealed that on Test Session 1 responding on the active lever (i.e., previously active lever) was higher following vehicle, 5 or 10 μg/kg of eticlopride compared with the last day of extinction, *t*s (5)>2.7, indicating that renewal was obtained in each of these pretreatment groups (Fig. 3, Panel A). Responding on the active lever also tended to

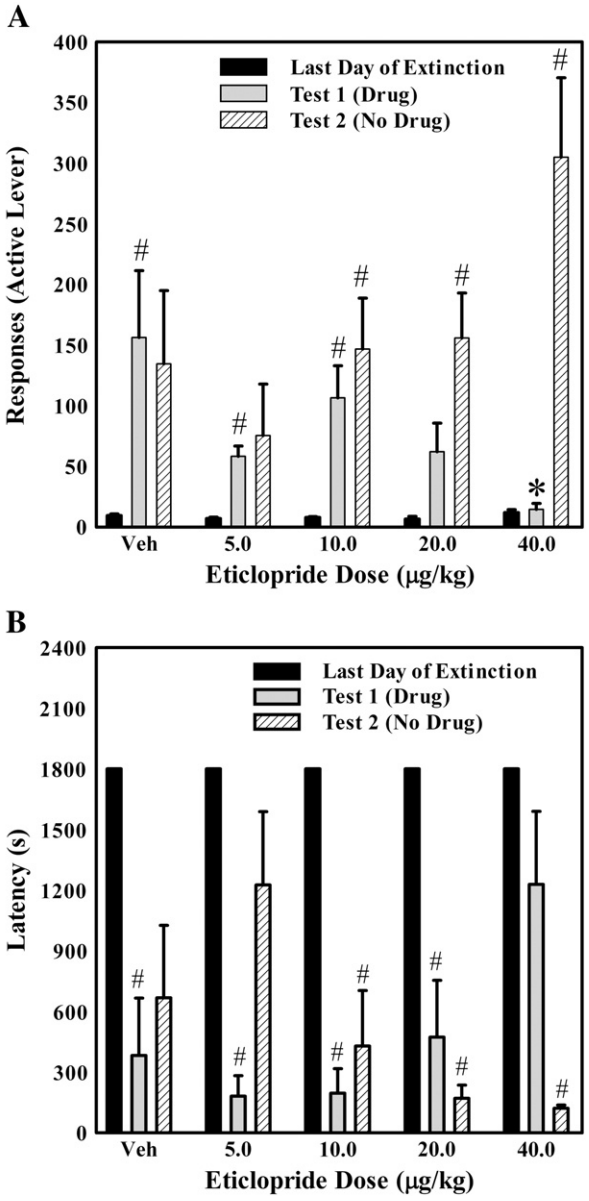

Fig. 3. Mean (+ SEM) number of responses emitted on the previously active lever (Panel A) as a function of eticlopride dose during the last session of extinction or Test Sessions 1 and 2 of Experiment 2. Mean (+ SEM) latency to complete the first FR requirement (Panel B) as a function of eticlopride dose during the last session of extinction or Test Sessions 1 and 2 of Experiment 2. The asterisk (*) and pound (#) symbols denote a significant difference from the last session of extinction and vehicle (Veh), respectively, $ps < 0.05$.

be higher on Test Session 1 for the moderate eticlopride dose (20 μg/kg) relative to the last day of extinction, but this tendency toward renewal failed to reach significance, $p = 0.06$. Importantly, responding on the active lever following the highest eticlopride dose (40 μg/kg) did not differ from the last day of extinction.

Post hoc Dunnett's tests found no significant difference in active lever responding between rats pretreated with 5, 10 or 20 μg/kg of eticlopride compared with vehicle on Test Session 1. However, rats pretreated with 40 μg/kg of eticlopride decreased responding on the active lever compared with vehicle on Test Session 1, $p < 0.01$, indicating that this dose blocked renewal. On Test Session 2, when no pretreatment was administered, responding on the active lever increased in rats pretreated previously with 10, 20 or 40 μg/kg of eticlopride relative to the last day of extinction, $ts\ (5) > 3.2$. Responding on the active lever also tended to be higher in rats pretreated previously with vehicle or 5 μg/kg of eticlopride compared with the last day of extinction, but these differences failed to reach significance, $ps > 0.08$. Rats previously pretreated with 5, 10 or 20 μg/kg did not differ in active lever responding from rats pretreated with vehicle on Test Session 2. At the highest eticlopride dose (40 μg/kg) responding on the active lever tended to be higher than rats pretreated with vehicle, but this difference too was not significant, $p = 0.08$.

As can be seen in Fig. 4, the highest dose of eticlopride (40 μg/kg) tended to suppress responding on the inactive lever on Test Session 1. However, analyses of inactive lever responding, involving several one-way ANOVAs conducted on the different sessions (Last Day of Extinction, Test Session 1 and Test Session 2), revealed no reliable group differences, during any of the sessions, $Fs < 1.8$. These results suggest that group differences noted with respect to active lever responding were not complicated by general changes in activity. In particular, the absence of reliable group differences in responding on the inactive lever on Test Session 1 suggests that none of the eticlopride doses suppressed responding nonspecifically.

Post hoc contrasts found that on Test Session 1 the latency to complete the first FR requirement was shorter than the last day of extinction for rats pretreated with vehicle, 5, 10 or 20 μg/kg of eticlopride, $zs > 2.0$, but not for rats pretreated with the highest eticlopride dose (40 μg/kg; Fig. 3, Panel B). The latency to complete the first FR requirement was not different between any of the eticlopride doses and vehicle on Test Session 1. The finding that the latency to complete the first FR requirement following 20 μg/kg of eticlopride was shorter than the last day of extinction and the latency in this group did not differ from vehicle, suggests that the attenuated renewal effect (based on the response measure) was not due merely to motor impairment produced by eticlopride. However, because there was no significant change in the latency to complete the first FR requirement following the highest eticlopride dose (40 μg/kg) compared with the last day of extinction, the blockade of renewal at this dose may have been due to motor deficits produced by eticlopride. On Test Session 2, when no pretreatment was administered, the latency to complete the first FR requirement was significantly shorter for rats pretreated previously with 10, 20 or 40 μg/kg of eticlopride, $zs > 2.0$, but not for the vehicle ($p = 0.06$) or the lowest eticlopride dose (5 μg/kg), relative to the last day of extinction. None of the eticlopride doses differed from

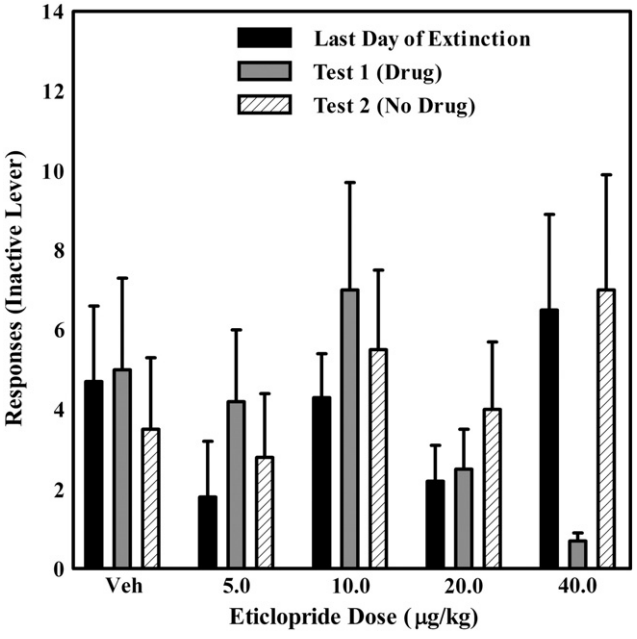

Fig. 4. Mean (+ SEM) number of responses emitted on the inactive lever as a function of eticlopride dose during the last session of extinction or Test Sessions 1 and 2 of Experiment 2.

vehicle on Test Session 2. Importantly, consistent with the evidence from the response measure (Fig. 3, Panel A), the latency to complete the first FR requirement was shorter for the highest eticlopride dose (40 μg/kg) compared with the last day of extinction, suggesting that the blockade of renewal with this dose on Test Session 1 was reversed after eticlopride pretreatment was omitted on Test Session 2.

3.2.2. Experiment 3. Effect of eticlopride on locomotor activity

Although eticlopride decreased locomotor activity slightly relative to vehicle (Fig. 5), an independent-samples *t*-test revealed no group differences in the first 30 min of the session, $p > 0.21$. This result suggests that the eticlopride-induced attenuation of renewal of sucrose-seeking behavior reported in Experiment 2 was not simply an artifact of motor impairment.

4. Discussion

As determined by both dependent measures of sucrose-seeking behavior (response and latency), renewal and control rats acquired responding at similar rates, but renewal rats were significantly faster to extinguish than control rats (Experiment 1). These results contrast with other renewal of drug- or food-seeking studies that have compared rates of extinction produced when different reinforcers were suspended and found either no difference (Crombag and Shaham, 2002; Hamlin et al, 2006) or slower rates (Marinelli et al., 2007) of extinction between renewal and control groups . For example, Hamlin et al. (2006; Experiment 1) found that ABA renewal rats did not extinguish at different rates compared with AAA control rats when nose pokes were no longer followed by liquid sucrose presentations (10%) during the acquisition phase. In addition, Crombag and Shaham (2002) found that ABA renewal rats did not extinguish at different rates compared with either AAA or AAB control rats when lever presses were no longer followed by cocaine during the acquisition phase. Finally, Bossert et al. (2004) found that ABA and ABB rats did not extinguish at different rates compared with AAA and AAB control rats when lever presses were no longer followed by heroin during the acquisition phase. In all of these previous studies, responding had been reinforced on an FR 1 schedule during the acquisition phase. Thus, the discrepant findings between the present report and other renewal of drug- or food-seeking behavior studies may stem from differences in reinforcement schedules (partial vs. continuous) used during the acquisition phase. At present, it is unclear as to why a partial schedule of reinforcement would produce a faster rate of extinction compared with a continuous schedule when contexts are changed from acquisition to extinction.

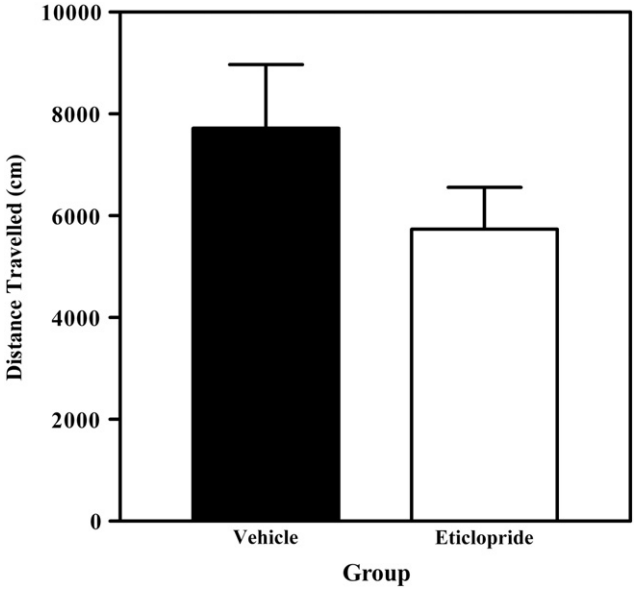

Fig. 5. Mean (+ SEM) distance travelled (cm) following pretreatment with vehicle or eticlopride (40 μg/kg) during the first 30 min of the 60-min locomotor activity session of Experiment 3.

Perhaps the relative novelty of Context B contributed to the faster rate of extinction in renewal rats compared to control rats in Experiment 1. Novelty-induced disruption of responding would be expected to be most evident early during extinction training, when Context B would have been most novel. Indeed, differences between renewal and control rats were observed early in extinction training (e.g., Extinction Days 1, 2 and 3). A novelty interpretation for the faster extinction is consistent with previous work showing that exposure to novel environmental cues reduces operant responding (Klebaur et al., 2001). For example, in Experiment 1 of Klebaur et al (2001), rats were first trained to respond for infusions of amphetamine on an FR 5 schedule of reinforcement. Once responding had stabilized, novel contextual changes (e.g., new floor texture, novel objects) were introduced into the operant conditioning chamber. Klebaur et al (2001) found that novelty disrupted amphetamine self-administration, perhaps by eliciting responses that compete with operant responding for amphetamine. Along similar lines, the switch to Context B from Context A in renewal rats in Experiment 1 in the current report may have elicited competing responses, resulting in a decrease in the operant, lever-pressing response. However, this suggestion is speculative and requires further empirical support.

The current study also found that robust renewal of sucrose-seeking behavior was obtained following acquisition on an FR 25 schedule of reinforcement (Experiment 1). With this high FR requirement, the response engendered during the renewal test phase was greater in the present report when high FR requirements were used during the acquisition phase than in previous reports using lower FR requirements. Specifically, acquisition of sucrose-maintained responding (45 mg pellet; Experiment 1) on an FR 25 schedule produced approximately 220 responses during a 30-min renewal test. In contrast, Hamlin et al. (2006) found that nose pokes for liquid sucrose presentations on an FR 1 schedule produced approximately 50 responses during a 60-min renewal test and Crombag et al. (2002) found that cocaine self-administration (0.75 mg/kg/infusion) on an FR 1 schedule produced approximately 30 responses in a 60-min renewal test. Self-administration of other drugs of abuse such as alcohol (Burattini et al., 2006), heroin + cocaine (speedball; Crombag and Shaham, 2002), or heroin (Bossert et al., 2007) under an FR 1 schedule during the acquisition phase also produced similar rates of responding during the renewal test compared with those reported by Crombag et al. (2002) and Hamlin et al. (2006). While Burattini et al. (2006) did not find any difference in response rates for the renewal effect following training with two different FR requirements, that study only compared FR 1 and FR 3 requirements. The results of the current study suggest that increasing the FR requirement during the acquisition phase produces a more robust renewal effect, a conclusion consistent with a recent report that found that the level of operant responding during training predicts level of drug-induced reinstatement (Keiflin et al., 2008).

A renewal effect also was observed in Experiment 2 (see Fig. 3); however, the magnitude of the effect was not as robust as in Experiment 1 (Experiment 1, Mean of Test Session 1 = 221 vs. Experiment 2, Mean of Test Session 1 = 157). An inspection of individual rats in Group Vehicle revealed that one rat did not show renewal (i.e., the rat only made 3 and 8 responses at the time of the first and second renewal tests, respectively). Most likely, the failure of this one rat to demonstrate renewal at the time of renewal testing, accounts for the less-than-robust renewal effect as was observed in Experiment 1. Moreover, the increase in variability in Group Vehicle, due to the lack of renewal observed in one rat, prevented statistical differences between Group Vehicle and certain groups that received eticlopride doses (e.g., 20 μg/kg) on Test

Session 1. That is, low-to-moderate eticlopride doses (5–20 μg/kg) attenuated responding on the active lever at the time of Test Session 1 (Means of Active Lever Responding = 58–107); however, none of these doses reliably differed from the vehicle control condition. Indeed, only the high eticlopride dose (40 μg/kg) reliably differed from the vehicle control condition. Thus, while it appeared that eticlopride doses below 40 μg/kg attenuated renewal, due to the lack of statistical differences, we cannot firmly make this conclusion.

In the present studies, renewal tests immediately followed extinction training. Such an approach has been widely adopted by many laboratories studying renewal (Crombag and Shaham, 2002; Rauhut et al., 2001; Thomas et al., 2003). In situations in which renewal testing immediately follows extinction training, the reappearance of the response could have stemmed from spontaneous recovery (Graham and Gagne, 1940). Indeed, researchers have interspersed extinction trials between renewal tests in order to lessen spontaneous recovery (e.g., Crombag et al., 2002). However, in the present studies, it seems unlikely that the reappearance of the response in the renewal groups stemmed from spontaneous recovery. In both studies, renewal testing occurred following 10 extinction sessions. By the end of extinction training, there was little evidence of spontaneous recovery (see Fig. 1). Moreover, if spontaneous recovery accounted for the reappearance of the response at the time of renewal testing, then elevated responding should have occurred in the AAA control group in Experiment 1. However, neither elevated responding nor a decrease in latency to complete the first FR schedule was noted in this group during any of the renewal tests (See Fig. 2), suggesting that the reappearance of the response stemmed from the contextual change (i.e., renewal) as opposed to spontaneous recovery.

While renewal of sucrose-seeking behavior was robust on Test Session 1, the renewal effect dissipated with repeated testing. That is, on Test Session 1, rats in the renewal group emitted 221 responses, whereas 61 and 27 responses were emitted on Test Sessions 2 and 3, respectively. Though responding on Test Sessions 2 and 3 still reliably differed from the last day of extinction, suggesting a renewed response, the magnitude of the renewal was not as great as on Test Session 1. By Test Session 4, no reliable differences were detected between Test Session 4 and the last day of extinction, suggesting that the renewal effect dissipated completely. Moreover, the response and latency measures were differentially sensitive in detecting renewal on subsequent test sessions. That is, the response measure detected renewal on Test Sessions 1, 2 and 3, whereas the latency measure detected renewal only on Test Session 1. Such differential results suggest that the response measure is more sensitive in detecting renewal and underscore the importance of using multiple dependent measures when assessing context conditioned effects (Bevins et al., 1997). Moreover, these results are consistent with studies that have shown that partial, as compared with continuous, schedules of reinforcement produce more persistence in responding once an extinction procedure is instituted (Bacon, 1962; Traupmann et al., 1971).

A potential limitation of the present report is that Experiment 1 did not include a "no-extinction" control group, i.e., a group that did not undergo extinction in either Context A or B. A "no extinction" group has been used to control for forgetting due to the passage of time (see Rauhut et al., 2001). Furthermore, Experiment 1 did not include control groups that underwent ABB and/or AAB training procedure(s). Different laboratories have elected to use different control groups in studying renewal of drug- or food-seeking behavior. For example, several laboratories have used ABB training (Bossert et al., 2004; Crombag and Shaham, 2002; Crombag et al., 2002; Hamlin et al., 2006; 2007), AAB training (Bossert et al., 2004; Crombag and Shaham, 2002), or both (Bossert et al., 2004; Crombag and Shaham, 2002) in studying renewal of drug- or food-seeking behavior. It should be noted that the AAB training procedure has been shown to produce less renewal than the ABA training procedure (Thomas et al., 2003). This result suggests that the AAB training procedure is not the ideal control group, as it produces renewal. Instead, the use of the AAA control group, as in the present report, is more common in studies examining renewal in either an aversive Pavlovian conditioning paradigm (Thomas et al., 2003) or appetitive, operant conditioning paradigm involving drug- or food-reinforcement (Bossert et al., 2004; Crombag and Shaham, 2002; Hamlin et al., 2006; Hamlin et al., 2007). Moreover, Crombag and Shaham (2002) found no differences between AAA and ABB control groups during any phase of the experiment. Thus, the AAA control group is an appropriate control group to assess renewal.

The finding that eticlopride dose-dependently attenuated the renewal of sucrose-seeking behavior implicates D_2 dopamine receptors in mediating this effect (Experiment 2). Specifically, low-to-moderate eticlopride doses (5–20 μg/kg) failed to attenuate renewal of sucrose-seeking behavior, whereas the highest eticlopride dose (40 μg/kg) blocked it. However, in Experiment 2, rats that underwent an AAA training procedure, and received different eticlopride doses on the renewal test, were not included. Moreover, eticlopride has been shown previously to produce locomotor sedation (Ferrari and Giuliani, 1995; see Smith et al., 2000, for a recent discussion of the issue), decrease responding for food reinforcement under an FR 15 (120 s TO) schedule (Caine and Koob, 1994; Hemby et al., 1996), and suppress oral intake of food (Pawloski et al., 2001). Indeed, it has been suggested that the effects of dopamine antagonists on conditioned motivated behaviors may be simply due to drug-induced motor impairments instead of decreases in the motivational value of the stimulus (Mason et al., 1980). These observations suggest that the eticlopride-induced attenuation of renewal of sucrose-seeking behavior may have been an artifact of eticlopride-induced motor problems. However, at least two findings make this idea unlikely. First, while the eticlopride dose of 40 μg/kg has been found to decrease responding for food reinforcement under an FR 15 (120 s TO) schedule, this dose does not decrease responding for cocaine reinforcement under an FR 5 (20 s TO) schedule (Caine and Koob, 1994). Second, in the current report, neither responding on the inactive lever nor general, locomotor activity was altered in rats that received 40 μg/kg of eticlopride (Experiments 2 and 3, respectively). These latter observations suggest that the eticlopride-induced attenuation of renewal of sucrose-seeking behavior was not due simply to a nonspecific motoric impairment.

Test Session 2 of Experiment 2 was conducted in order to examine the effects of pretreatment with eticlopride the previous day (Test Day 1) on renewal of sucrose-seeking behavior. It was found that rats pretreated the previous day with moderate (10 and 20 μg/kg) or high (40 μg/kg) eticlopride doses showed elevated responding on Test 2 Day relative to the last day of extinction (i.e., renewal). The lowest eticlopride dose (5 μg/kg) also tended to show elevated responding; however, this difference was not statistically significant. These results suggest that renewal of sucrose-seeking behavior was observed in rats for whom responding was suppressed previously by the presence of eticlopride. Most likely, the renewal of sucrose-seeking behavior observed in these rats on Test Day 2 stems from a release of inhibition or a change in motivational valence of sucrose-associated cues as a result of the absence of eticlopride.

There is strong support for the involvement of D_1 dopamine receptors in mediating another extinction-related phenomenon, cue-induced reinstatement (see Shaham et al., 2003, for a review), and renewal of drug- or food-seeking behavior (see Bossert et al., 2005, for a review). D_1 dopamine antagonists have been shown to attenuate reinstatement induced by a punctate cue (See et al., 2001) or discriminative stimuli (Alleweireldt et al., 2001; Ciccocioppo et al., 2001; Weiss et al., 2001). D_1 dopamine antagonists also have been shown to attenuate renewal of drug- (Crombag et al., 2002; Hamlin et al., 2007; Bossert et al., 2007) or food-seeking (Bossert et al., 2006; Hamlin et al., 2006) behavior. Collectively, these studies provide results consistent with incentive motivational theories of dopaminergic functioning (see Berridge, 2007, for a recent elaboration; Robinson

and Berridge, 1993), especially among theories that place special emphasis on D_1 dopamine receptors as part of an integral signaling pathway (Beninger and Miller, 1998; see Sutton and Beninger, 1999, for a review and discussion of this issue).

In contrast, studies examining the role of D_2 dopamine receptors in mediating cue-induced reinstatement have produced equivocal results. The D_2 dopamine antagonists haloperidol and raclopride failed to attenuate reinstate of drug-seeking behavior when either discriminative stimuli or punctate cues were used, respectively (McFarland and Ettenberg, 1997; See et al., 2001). Other researchers, however, have found that raclopride attenuates reinstatement induced by a discriminative stimulus (Weiss et al., 2001) and that discriminative stimuli reinstate drug-seeking behavior and concurrently increase dopamine overflow in the nucleus accumbens (Katner and Weiss, 1999). Given that studies supporting a role of D_2 dopamine receptors in cue-induced reinstatement have used discriminative stimuli associated with a drug, rather than punctate cues, it appears that D_2 dopamine receptor activation may be involved primarily in reinstatement induced by discriminative stimuli. The present finding showing that eticlopride attenuated renewal of sucrose-seeking behavior induced by discriminative stimuli (i.e., contextual cues) bolsters this idea. However, it should be noted that the effects of eticlopride on renewal of sucrose-seeking behavior may not be unique to renewal per se, but rather similar effects of eticlopride on sucrose responding on an FR 25 schedule of reinforcement and/or sucrose-induced reinstatement also may be observed.

Finally, the finding that D_2 dopamine receptors mediate renewal of sucrose-seeking behavior is consistent with suggestions concerning dopamine's involvement in mediating the occasion-setting or conditioned modulatory effects of contextual stimuli (Crombag et al., 2002). That is, as applied to renewal of sucrose-seeking behavior, a return of the renewal rats to Context A following extinction in Context B reactivates a response-sucrose association and motivates sucrose-seeking behavior. In this conceptual framework, eticlopride decreases the motivational value of the anticipated sucrose reinforcement. This interpretation is consistent with incentive motivational theories of dopaminergic functioning (Berridge, 2007; Robinson and Berridge, 1993) and Bouton's explanatory framework of renewal (Bouton, 1988).

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