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Reinstatement of nicotine self-administration in rats by presentation of nicotine-paired stimuli, but not nicotine priming

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Abstract

The objective of the present study was to determine the relative efficacy of nicotine priming and nicotine-paired stimuli in reinstating extinguished NSA in rats. The relative efficacy of different stimulus conditions in reinstating NSA was also determined. Rats were trained to self-administer nicotine (0.03 mg/kg/inf) under an FR 5 schedule. Onset of a light above the active lever was correlated with nicotine availability, while offset of the light was paired with each nicotine infusion. In Experiment 1, saline extinction was arranged in the presence of these light stimuli. After extinction criteria were met, the effects of priming doses of nicotine (0.01, 0.03. and 0.06 mg/kg/inf, i.v.) on active lever pressing were determined. In Experiment 2, extinction of NSA was arranged in the absence of the light stimuli. After extinction criteria were met, reinstatement sessions were arranged involving either (1) a priming infusion of nicotine (0.03 mg/kg), (2) presentation of the same light stimuli as during NSA training, (3) constant illumination of the cue light, or (4) a combination of a nicotine priming infusion with one of the stimulus-light conditions. In Experiment 1, nicotine generally failed to reinstate NSA at any priming dose. In Experiment 2, both stimulus conditions reinstated NSA, with the stimulus condition identical to training producing a greater effect. Nicotine priming alone failed to significantly reinstate NSA. Nicotine priming combined with either stimulus condition was no more effective than each stimulus condition alone in reinstating NSA. These findings suggest that nicotine-paired cues are more effective than nicotine alone in reinstating extinguished NSA and are consistent with other studies showing that nicotine-paired stimuli play an important role in the reacquisition of NSA.

Keywords: Nicotine; Self-administration; Reinstatement; Rats; Nicotine-paired stimuli

1. Introduction

High rates of relapse are common in people trying to abstain from tobacco use (Fiore, 2000). Several factors have been shown to be associated with relapse, including exposure to smoking cues, stress, negative affect, and withdrawal symptoms (Brigham et al., 1990; Kassel et al., 2003). Research has also shown that, regardless of the circumstances surrounding relapse, 85–100% of smokers that ever experience a smoking lapse will eventually relapse to regular smoking (Brandon et al., 1990; Chornock et al., 1992; Kenford et al., 1994). Human and animal models that help elucidate the variables controlling the lapse and relapse to smoking may be helpful in developing better relapse prevention techniques to achieve long-term smoking abstinence.

One animal model considered suitable for studying relapse phenomena is the reinstatement of drug self-administration (Shaham et al., 2003). In this assay, non-contingent administration of drug (i.e., priming) or re-exposure to drug-paired stimuli during extinction of drug

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self-administration produces an increase in the frequency of responses (e.g., lever presses) that previously produced drug infusions. Studies using the reinstatement model in animals may be relevant to understanding relapse in humans insofar as variables reported to reinstate drug seeking in animals also provoke relapse in humans (Shaham et al., 2003).

Although the reinstatement model has been used extensively to examine variables potentially involved in relapse to abuse of other psychostimulants (e.g., cocaine, amphetamine), relatively few studies have examined reinstatement of nicotine self-administration. Studies in rats have shown that non-contingent administration of nicotine during extinction of nicotine self-administration (NSA) reinstates responding previously reinforced by nicotine (Chiamulera et al., 1996; Lindblom et al., 2002; Shaham et al., 1997). However, the magnitude of the reinstatement effect has been weak in some cases compared to that with other drugs of abuse, such as cocaine and heroin (Erb et al., 1996; Shaham and Stewart, 1995; Shaham et al., 1996). As such, the ability of a given nicotine priming dose to reinstate responding has varied across these studies. For example, one study demonstrated reinstatement induced by doses equal to or greater than the NSA training dose (0.03 and 0.06 mg/kg, (Shaham et al., 1997), while others demonstrated reinstatement only with doses much lower than the training dose (Chiamulera et al., 1996; Lindblom et al., 2002). These studies differed in the strain of rat used, duration of extinction, and stimulus conditions during extinction. Any one of these factors, or a combination, could account for the disparate results.

In a related assay, it has been shown that nicotine-paired stimuli facilitate the reacquisition of NSA in rats. Caggiula et al. (2001) found that after a period of extinction in the absence of NSA training stimuli, reacquisition of NSA was obtained when responding produced both nicotine infusions and the training stimuli but not when responding produced nicotine infusions alone. This finding demonstrates that nicotine-paired stimuli are important determinants of the effects of response-contingent nicotine. Studies examining the influence of nicotine-paired stimuli on the ability of non-contingent nicotine priming to reinstate extinguished NSA have not been reported.

The purpose of the present study was to (a) examine the relative efficacy of noncontingent nicotine priming and presentation of nicotine-paired stimuli in reinstating extinguished NSA, (b) examine the interaction between nicotine priming and nicotine-paired stimuli in reinstating extinguished NSA, and (c) examine the relative efficacy of nicotine-paired stimuli that are identical to or vary from those during NSA training in reinstating extinguished NSA. Regarding this latter purpose, it was hypothesized that reinstatement would be weaker if the nicotine-paired stimuli during reinstatement testing varied from those used during NSA training.

2. Materials and methods

2.1. Animals

Experimentally naive male Holtzman rats weighing 300–400 g were maintained under a restricted feeding regimen (approx. 20 g/day rat chow) to maintain stable body weight during the experiment. Each rat was individually housed in a temperature- and humidity-controlled colony room with unlimited access to water under a reversed 12 h light/dark cycle (lights off at 10:00 am). Animal husbandry and experimental protocols were approved by the Institutional Animal Care and Use Committee of the Minneapolis Medical Research Foundation are were in accordance with the 1996 NIH Guide for the Care and Use of Laboratory Animals.

2.2. Apparatus

Subjects were tested in operant-conditioning chambers (Coulbourn Instruments, Allentown, PA), measuring 29 cm long, 33 cm high, and 26 cm wide. Two response levers were located on the front wall 10 cm above the chamber floor on either side of a food aperture located 2 cm above the floor. Stimulus lights were located 2 cm above each response lever. Each chamber was placed inside a sound-attenuating cubicle equipped with an exhaust fan that provided masking noise. Infusion pumps (Model RHSY, Fluid Metering, Syosset, NY) were placed outside each cubicle and delivered infusions through PE 90 tubing connected to a fluid swivel mounted above the chamber, and from the swivel through a spring leash connected to the guide cannula mounted in the harness assembly on the back of the rat. A computer with MED-PC IV software (Med Associates, St. Albans, VT) was used for operating the apparatus and recording data.

2.3. Drugs

Nicotine bitartrate (Sigma, St. Louis, MO) was dissolved in sterile saline containing 25 units/ml heparin. The pH of the solution was adjusted to 7.4 with dilute NaOH. Nicotine doses are expressed as the base.

2.4. Surgery

Each rat was implanted with a chronic indwelling jugular catheter under intramuscular droperidol (2.0 mg/kg) and fentanyl (0.04 mg/kg) anesthesia. A silicon catheter (0.51 mm I.D.×0.94 mm O.D.) was inserted into the right jugular vein and advanced to the junction of the vena cava and the right atrium and sutured to tissue surrounding the vein. The catheter was tunneled subcutaneously to the back where it exited between the scapulae and attached to a guide cannula mounted in a harness assembly on the back of the rat. A stainless steel spring tether attached to the guide cannula allowed connection to a fluid swivel for nicotine admin-

istration. Rats were allowed to recover for at least 4 days after surgery, during which each rat received daily intravenous (i.v.) infusions of heparinized saline (25 units/ml) and antibiotic (enrofloxacin, 1.1 mg) into the jugular catheter. Catheters were also flushed with streptokinase (0.67 mg/ml of heparinized saline) once per day on weekends to help maintain patency. Infusions of pentobarbital (0.1 ml, 50 mg/ml, i.v.) were administered occasionally to confirm catheter patency (production of ataxia) if catheter malfunction was suspected.

2.5. Self-administration training

Twenty-one rats were trained to self-administer nicotine during 1-h sessions using a unit nicotine dose of 0.03 mg/kg/inf. Sessions were run during the dark phase of the rat's light cycle. Procedures were similar to those previously reported (LeSage et al., 2002; Shaham et al., 1997). Briefly, sessions began with onset of the stimulus light above the active (right) response lever. When the response requirement for nicotine was met on the active lever, the stimulus light was extinguished during the nicotine infusion and a subsequent 15-s timeout during which responses had no programmed consequence. Following the timeout, the stimulus light was illuminated indicating availability of the next nicotine infusion. All rats were initially given access to nicotine, but some rats exhibited little or no lever pressing in the first five sessions, which required baiting the active lever with food for two to three sessions or lever-press training under an FR 1 schedule of food delivery for two to three sessions to establish lever pressing. After substantial responding for nicotine developed under the FR 1 schedule of nicotine delivery (at least eight infusions per session), the response requirement was gradually increased to FR 5 across several sessions. Rats were considered to have acquired NSA when, under the FR 5 schedule, at least eight infusions were earned per session and the ratio of active to inactive lever presses was at least 2:1 for three consecutive sessions. Once acquisition criteria were met, rats were assigned to one of two experiments in which extinction and reinstatement of NSA was observed. In both experiments, all rats were given access to nicotine following completion of reinstatement testing in order to examine reacquisition of NSA and confirm catheter patency. Rats that failed to reacquire NSA were excluded from the study.

2.6. Experiment 1: Effects of nicotine priming during extinction of NSA in the presence of nicotine-paired stimuli

For eight rats, extinction of NSA was arranged in the presence of the nicotine-paired stimuli used during training. Immediately prior to each session, an i.v. saline priming infusion was delivered via computer-controlled operation of the infusion pump. Priming infusions were not signaled. During each extinction session, responding under an FR 5 schedule produced the same stimulus changes as during training, but no infusion was delivered. NSA was considered extinguished when, after at least 10 sessions, responding on the active lever had decreased by at least 50% for three consecutive sessions and no trend was apparent across these three sessions. After extinction criteria were met, reinstatement tests were conducted in which one of three nicotine priming doses (0.01, 0.03, or 0.06 mg/kg) was substituted for the saline priming infusion prior to a 1-h extinction session. Infusion volume accounted for the dead space in the catheter (approximately 25 μl). Each rat received all doses in a random order, and extinction criteria had to be met before each priming dose was tested (i.e., at least three sessions intervened between reinstatement tests). Reinstatement tests were never conducted on Mondays, since spontaneous recovery of NSA has been previously reported after suspending NSA sessions for 21 days (Shaham et al., 1997). In the present experiments however, spontaneous recovery after suspending sessions over the weekend was very rare. Typically, rats received one reinstatement test per week. Each priming dose was administered once to each rat.

2.7. Experiment 2: Effects of nicotine-paired stimuli alone and in combination with nicotine priming during extinction of NSA in the absence of nicotine-paired stimuli

Twelve rats underwent extinction in the absence of the training stimuli. Procedures were identical to Experiment 1, except that the stimulus light above the active lever remained off for the entire session. After extinction criteria were met, reinstatement conditions were arranged consisting of (a) a nicotine priming infusion (0.03 mg/kg), (b) constant illumination of the stimulus light (S^C), (c) onset and offset of the stimulus light under the FR 5 schedule as during training (S^T), or (d) a nicotine priming infusion (0.03 mg/kg) in combination with one of the stimulus-light conditions (b or c). The visual stimulus conditions for training and reinstatement sessions were chosen in order to replicate the stimulus conditions of Experiment 1 and avoid confounds when comparing data from the two experiments. Extinction criteria were the same as in Experiment 1. Each rat was tested under all reinstatement conditions, arranged in random order. Extinction criteria had to be met before each reinstatement test, resulting in rats typically receiving one reinstatement test per week (never on Mondays). Each reinstatement condition was examined once in each rat and reinstatement sessions were one hour in duration.

2.8. Data analysis

An alpha level of 0.05 was used to determine significance in all statistical analyses. The baseline level of responding was calculated for each rat as the mean number of active-lever responses during the last five sessions prior to extinction. The level of responding during saline priming sessions for each rat was calculated as the mean number of active-lever

responses across sessions immediately prior to each reinstatement test session (i.e., across three sessions for Experiment 1 and five sessions for Experiment 2). For Experiment 1, a repeated measures ANOVA with Tukey post hoc tests was conducted comparing the mean number of active-lever responses during saline priming and nicotine priming sessions. To determine whether the level of responding decreased across repeated testing, a separate ANOVA was conducted comparing levels of responding during the first, second, and third nicotine priming tests (ignoring priming dose). For Experiment 2, a two-factor repeated measures ANOVA was conducted, with priming dose (0.0 and 0.03 mg/kg) and stimulus condition (no cues, S^T cues, and S^C cues) as factors. Following a significant main effect or interaction, multiple pairwise comparisons between treatment conditions were conducted using Bonferroni's adjustment. The level of responding between the five successive reinstatement tests (regardless of nicotine or cue condition) was compared using ANOVA to determine whether the reinstatement effect waned across successive tests.

3. Results

3.1. Experiment 1: Effects of nicotine priming on extinguished NSA

The mean number of infusions earned during baseline was 15.6±3.5 SD. The mean number of responses on the active lever during baseline was 78±17.6 SD. Fig. 1 (upper left panel) shows the mean number of responses during extinction (saline priming) and nicotine priming sessions for all rats. The number of responses during extinction was significantly decreased relative to baseline (t=12.44, p<0.001). For subjects as a group, none of the nicotine priming doses produced a significant increase in responding relative to saline priming (F=0.052, p=0.984). To illustrate the individual variability observed, Fig. 1 also shows data for five rats in which one of the nicotine priming doses increased the number of responses above the range of responses during saline priming sessions. These increases were small in three rats and the priming dose that produced an effect varied across rats. In four of these rats, the effect was seen on the first nicotine priming test, while no effect was seen on the second and third test. In the other rat, the effect was only seen on the third test session. In other words, 50%, 0%, and 13% of all rats showed some evidence of reinstatement on the first, second, and third, priming test, respectively. An ANOVA comparing levels of responding in all rats across successive nicotine priming test sessions (regardless of dose) was not significant (F=3.31, p=0.07). The mean number of responses on the inactive lever remained low during all phases of the experiment (3.6, 1.0, 0.6, 1.3, and 0.4 responses during baseline, saline priming, and 0.01, 0.03. and 0.06 mg/kg nicotine priming, respectively). All rats reacquired NSA after completion of reinstatement testing (data not shown).

3.2. Experiment 2: Effects of nicotine-paired stimuli alone and in combination with nicotine priming on extinguished NSA

The mean number of infusions earned during baseline was 14.28±4.5 SD. The mean number of responses on the

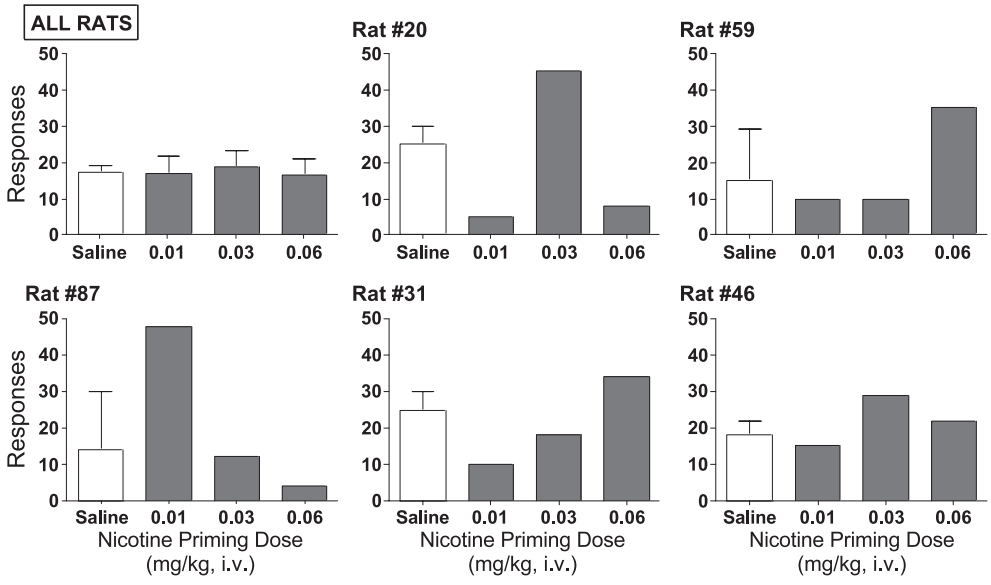

Fig. 1. Effects of nicotine priming infusions on extinguished nicotine self-administration in the presence of nicotine-paired stimuli (Experiment 1). In the upper left panel, each bar represents the mean (±SEM) number of responses on the active lever for eight rats during sessions immediately preceded by a saline or nicotine priming infusion. Other panels show data for five of eight rats that exhibited an increase in responding above the range of responding during extinction sessions. In these panels, bars above saline indicate the mean and range of responses across the three saline priming sessions preceding nicotine priming sessions. Bars above each nicotine priming dose indicate the number of responses during a single session.

active lever during baseline was 72.4±22 SD. The number of responses during extinction was significantly decreased relative to baseline (t=13.67, p<0.001). Two-factor ANOVA indicated a significant main effect of nicotine-paired stimuli (i.e., significant differences between responding during cue conditions regardless of nicotine priming condition, F=13.58, p<0.001), no main effect of nicotine priming (i.e., no significant difference between nicotine priming conditions regardless of cue condition, F=0.14, p=0.708), but a significant interaction between nicotine priming and nicotine-paired stimuli (F=3.17, p=0.049). Pairwise comparison of the marginal means for each stimulus condition indicated that the main effect of the S^T condition was significantly greater than that of the S^C condition (t=2.41, p=0.02). Fig. 2 shows the mean number of responses during extinction and each reinstatement condition. Although the mean number of responses during nicotine priming alone was greater than during saline-priming sessions, this increase was not statistically significant (t=−1.84, p=0.071). Only five of the 12 rats exhibited increased responding during nicotine priming sessions above the range of responding during saline priming sessions. When presented alone, both types of nicotine-paired stimuli produced a significant increase in responding relative to saline priming sessions (S^T condition t=−5.24, p<0.001; S^C condition t=−3.5, p<0.001). The combination of nicotine priming with each nicotine-paired stimulus condition produced a significant increase in responding (S^T+N condition t=4.1, p<0.01; S^C+N condition t=3.3, p<0.05), but this effect was not different from that produced by each stimulus condition alone. An ANOVA comparing levels of responding across successive reinstatement test sessions (regardless of nicotine or cue condition) was not significant (F=0.82, p=0.52). The mean number of responses on the inactive lever remained low during all phases of the experiment (1.9, 0.8, 1.0, 1.0, 1.3, 1.2, and 0.9 responses during baseline, saline priming, nicotine priming, S^T, S^C, S^T+N, and S^C+N conditions, respectively). All rats reacquired NSA after completion of reinstatement testing (data not shown).

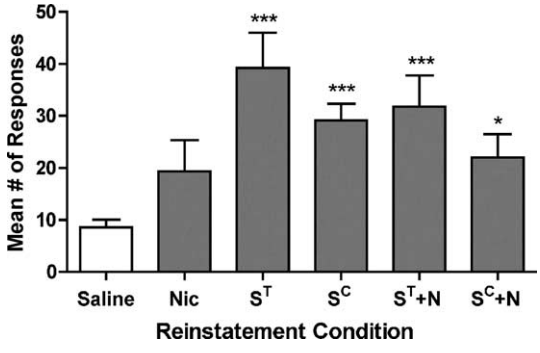

Fig. 2. Effects of nicotine-paired stimuli and nicotine priming alone and in combination after extinction of nicotine self-administration in the absence of nicotine-paired stimuli (Experiment 2). Each bar represents the mean (±SEM) number of responses on the active lever for 12 rats. "Sal" indicates responses during sessions when a saline priming infusion was delivered alone, "Nic" when a nicotine (0.03 mg/kg) priming infusion was delivered alone, S^T when nicotine-paired stimuli identical to those during training were presented alone, S^C when nicotine-paired stimuli that varied from training stimuli (i.e., constant cue light) were presented alone, S^T+N and S^C+N when nicotine priming was combined with each stimulus condition. Asterisks indicate a statistically significant difference from "Sal" sessions, ***p<0.001, *p<0.05.

4. Discussion

The main findings of the present study are that (1) nicotine generally failed to reinstate extinguished NSA at any priming dose regardless of whether or not nicotine-paired stimuli were present during extinction, (2) presentation of nicotine-paired stimuli reinstated extinguished NSA, (3) nicotine priming combined with either nicotine-paired stimulus condition was no more effective than each stimulus condition alone in reinstating NSA, and (4) a nicotine-paired stimulus condition that only partially replicated the stimulus conditions during training (the S^C condition) was less effective in reinstating responding as a stimulus condition that was identical to that used during training (the S^T condition).

The lack of a statistically significant effect of nicotine priming in the present study contrasts with other studies demonstrating nicotine-induced reinstatement of extinguished NSA in the presence (Shaham et al., 1997) and absence (Chiamulera et al., 1996; Lindblom et al., 2002) of nicotine-paired stimuli. This was somewhat surprising, since the priming doses and stimulus conditions used during extinction in the present study were similar to previous studies. On the other hand, the present findings are not entirely inconsistent with previous studies for several reasons. First, increases in responding during nicotine priming sessions were observed in some rats in Experiment 1, and the effect of nicotine priming alone in Experiment 2 approached significance. Second, robust reinstatement at a given priming dose (e.g. 0.03 mg/kg) and a clear priming dose–response relationship has not been consistently demonstrated in previous studies. Third, nicotine-induced reinstatement of NSA has been less robust in some studies compared to the reinstatement effect with other drugs of abuse (e.g., cocaine and heroin). Finally, the present findings are entirely consistent with those of Caggiula et al. (2001) showing that reacquisition of NSA was not obtained with response-contingent nicotine infusions in the absence of the nicotine-paired stimuli used during training. Thus, the present and previous studies taken together suggest that nicotine-induced reinstatement of extinguished NSA is a weak phenomenon and that variability in the effect is likely to be seen within and between studies that employ procedures similar to the present and previous studies. It is not known whether more robust reinstatement would be observed using other well-established procedures for studying reinstatement (for review, see (Shaham et al., 2003).

In light of the lack of significant effects of nicotine priming, use of a within-subjects design in the present study raises the concern that reinstatement effects could be attenuated as a result of repeated testing. Indeed, four of the five rats that showed some reinstatement exhibited the effect on the 1st priming test, but not subsequent tests. However, there were no significant differences between the level of responding across successive tests in either experiment. It is also important to note that prior studies reporting nicotine-induced reinstatement used a within-subjects design similar to that used in the present study (Chiamulera et al., 1996; Shaham et al., 1997). Therefore, the lack of a significant reinstatement effect in the present study with nicotine priming cannot be attributed to the use of a within-subjects design.

One difference between the present and previous studies is the level of responding obtained during extinction. In the present study, a mean of 17.3 responses was obtained during saline priming sessions in Experiment 1, which was somewhat higher than that in previous studies (<10 responses). Since the level of responding during nicotine priming sessions was as high or higher than in previous studies, a significant priming effect might have been obtained if lower levels of responding in extinction were achieved. The nearly significant effect of nicotine priming in Experiment 2 is consistent with this analysis, since the level of extinction was lower than in Experiment 1. However, the level of responding during extinction in rats that exhibited a reinstatement effect in Experiments 1 and 2 was no lower than that of other rats. Thus, extinction levels probably do not entirely account for the lack of nicotine-induced reinstatement in the present study.

One factor that may account for the discrepancy between the present study and previous studies of nicotine-induced reinstatement is the use of a different rat stain. The Holtzman strain used in this study has been shown to acquire NSA less readily than the Lewis strain (Brower et al., 2002). To the extent that this indicates Holtzman rats may be less sensitive to nicotine's reinforcing effects, this strain may also be less sensitive to the reinstating effects of nicotine priming. Given the variety of strains used in previous studies (Sprague-Dawley, Long Evans, Wistar) and the discrepant findings between these reports, strain differences could play a role in the ability of nicotine priming to reinstate extinguished NSA.

The effects of nicotine-paired stimuli observed in the present study are consistent with previous studies showing that (a) nicotine-paired stimuli play an important role in the acquisition and reacquisition of NSA (Caggiula et al., 2001, 2002b), (b) re-exposure to the environmental context previously paired with NSA after suspending NSA sessions for 21 days can produce spontaneous recovery of extinguished NSA (Shaham et al., 1997), and (c) stimuli paired with delivery of other drugs of abuse can also reinstate extinguished drug self-administration (for a review see Shaham et al., 2003). The present study is the first to directly compare the efficacy of different stimulus conditions in reinstating extinguished NSA. It was found that a stimulus condition that varied from that during NSA training (constant exposure to the drug availability cue, S^C) was less effective in reinstating NSA than a stimulus condition identical to that during training. To our knowledge, no other study of cue-induced reinstatement of drug self-administration has examined the effects of varying the stimulus conditions during reinstatement tests.

The S^C stimulus involved the noncontingent presentation of a constant cue light. The lower efficacy of this stimulus in reinstating NSA, compared to the response-contingent S^T stimulus, suggests that a contingency between responding and the inducing event facilitates the reinstatement effect. As such, nicotine priming may have been more effective in the present study if the priming infusion was response contingent, rather than noncontingent.

The mechanisms responsible for the reinstating effects of nicotine-paired stimuli cannot be ascertained from the present study. Although the pairing of visual stimuli with nicotine infusions during training may have established these stimuli with discriminative and conditioned reinforcing functions, recent studies have shown that visual stimuli alone like those used in the present study have relatively weak primary reinforcing effects and that noncontingent administration of nicotine can enhance the reinforcing effects of such stimuli through a nonassociative mechanism (Donny et al., 2003). Therefore, it is possible that the cue-induced reinstatement effect in the present study was a consequence of any one or a combination of these behavioral mechanisms.

In the present study, exposure to nicotine-paired stimuli was more effective in reinstating extinguished NSA than nicotine priming. This finding lends support to the suggestion that interventions for smoking cessation should increase attention toward reducing the impact of smoking-related cues in provoking relapse (Caggiula et al., 2001, 2002a; Shiffman, 1993). Cue-induced reinstatement of NSA provides a potential animal model for studying interventions aimed at reducing cue-induced relapse in human smokers.

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