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BRIEF COMMUNICATIONS

Renewal of Drug Seeking by Contextual Cues After Prolonged Extinction in Rats

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Contextual stimuli associated with drug exposure can modulate various effects of drugs, but little is known about their role in relapse to drug seeking. Using a renewal procedure, the authors report that drug-associated contextual stimuli play a critical role in relapse to drug-seeking previously maintained by a heroin–cocaine mixture (speedball). Rats were trained to self-administer speedball, after which drug-reinforced behavior was extinguished over 20 days in the self-administration context or in a different context. On the test day, rats exposed to the drug-associated context, after extinction in a different context, reliably renewed drug seeking. The authors suggest that the renewal procedure can be used to study mechanisms underlying relapse to drug seeking elicited by drug-associated contextual stimuli.

In humans, environmental cues associated with the rewarding effects of heroin or cocaine are thought to play an important role in relapse to drug use after prolonged abstinence (Childress, Ehrman, Rohsenow, Robbins, & O'Brien, 1992; Jaffe, 1990). In laboratory animals, discrete conditioned stimuli (CSs) that are paired with heroin or cocaine injections or stimuli that signal the availability of these drugs (discriminative stimuli) provoke relapse to drug seeking when they are reintroduced after the operant behavior is extinguished in the absence of these cues (Davis & Smith, 1976; Ettenberg, MacConell, & Geist, 1996; Grimm & See, 2000; McFarland & Ettenberg, 1995, 1997; Weiss et al., 2000). Although there is now considerable evidence that discrete drug-contingent stimuli and discriminative stimuli can provoke relapse to drug seeking, little is known about the role of contextual stimuli such as the physical characteristics of the test environment and the time of day in drug relapse. This issue is important because studies using nondrug reinforcers demonstrate that the environmental context plays an important role in extinction and reinstatement of learned behaviors (Balsam & Tomie, 1985; Bouton & Swartzentruber, 1991). In addition, there is now an abundance of evidence that contextual stimuli can modulate various behavioral effects of drugs of abuse (Anagnostaras & Robinson, 1996; Robinson, Browman, Crombag, & Badiani, 1998; Siegel, 1989; Stewart, 1992).

Here we characterized the role of contextual stimuli in relapse to drug seeking using a *renewal* procedure (Bouton & Bolles, 1979) in rats trained to self-administer a heroin–cocaine mixture (speedball), a potent reinforcer in rats (Hemby, Co, Dworkin, & Smith, 1999), monkeys (Mello et al., 1995), and humans (Schottenfeld, Pakes, Oliveto, Zeidonis, & Kosten, 1997). In the renewal procedure, conditioned responses to discrete CSs are recovered when they are reintroduced in the original conditioning context (in which they were paired with the primary reinforcer) after extinction in a different context (Bouton & Bolles, 1979).

Method

Subjects and Surgery

Male Long–Evans (Charles River, Raleigh, NC) rats (325–375 g) were housed individually in a climate-controlled animal colony (lights on from 8 p.m. to 8 a.m.) with food and water freely available. All training and testing took place during the dark phase of the light–dark cycle. Rats were anesthetized with a ketamine + xylazine mixture (100 + 10 mg/kg ip), and intravenous catheters were implanted using procedures described previously (Shalev, Highfield, Yap, & Shaham, 2000). After catheter implantation, rats were allowed to recover for at least 5 days. The catheters were flushed daily with sterile saline containing the antibiotic Gentamicin (0.08 mg/ml). The procedures used followed guidelines established by the National Institutes of Health (1986).

Procedure

Rats were trained and tested in standard operant chambers (27 cm long × 25 cm wide × 30 cm high) located inside sound-attenuating cabinets (MED Associates, Georgia Center, VT). The ceiling, back wall, and hinged front door of the operant chambers were constructed of clear acrylic plastic, and the side walls were made of aluminum. Each chamber was equipped with two levers located 9 cm above the grid floor. Presses on one lever (an active, retractable lever) resulted in the illumination of a 7.5-V white cue light located above the lever and activated the infusion pump (Razel Scientific Instruments, Stamford, CT). Presses on the other lever (an inactive, nonretractable lever), located on the opposite wall of the chamber, were recorded but had no programmed consequences. A house-

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light provided low-level illumination during the sessions, and a fan was located in the sound-attenuating cabinets.

Two different contexts were provided by two sets of operant chambers that were located in nearby rooms. In one context, white vertical stripes were mounted on the hinged front door, the doors of the sound-attenuating cabinet were closed during the session, a white houselight provided illumination, the ventilation fan was turned on, and the waste trays underneath the grid floor were filled with water containing a small amount of Vicks Vaporub. In the second context, the hinged front doors were clear, the doors of the sound-attenuating cabinet remained open during the session, illumination was provided by a red houselight, the ventilation fan was turned off, and the waste tray underneath the grid floor contained a 1% acetic acid solution. Thus the two contexts differed in their tactile, visual, auditory, and olfactory properties. The contexts are referred to as A and B, where A is the context in which drug self-administration occurred and B is the alternative context. The physical environments that provided Contexts A and B were counterbalanced within each group.

The experiment was conducted over 31 days and consisted of three phases: speedball self-administration training (10 days), extinction training (20 days), and a test for renewal (1 day). Rats were assigned to one of three groups: *renewal* ($n = 13$), *control* ($n = 12$), or *novel* ($n = 8$). Rats assigned to the renewal group were trained to self-administer speedball in Context A, responding was then extinguished in Context B, and on the test day these rats were returned to Context A. Rats assigned to the novel group were trained to self-administer speedball in Context A, responding was extinguished in Context A, and on the test day these rats were exposed to Context B. Finally, for rats assigned to the control group, half were trained to self-administer speedball in Context A, responding was extinguished in Context A, and these rats were tested in Context A, whereas the other half were trained to self-administer speedball in Context A, responding was extinguished in Context B, and on the test day these rats remained in Context B. Table 1 summarizes for each group the contextual setting in which drug self-administration, extinction, and the test for renewal were conducted.

Speedball self-administration phase. Rats were trained on a fixed-ratio 1 (each leverpress is reinforced) schedule of reinforcement to self-administer speedball, a heroin (diacetylmorphine HCL, infusion of 0.025 mg/kg) plus cocaine HCl (infusion of 0.25 mg/kg) mixture (drugs were obtained from the National Institute on Drug Abuse). This dose of speedball is based on our previous work (Highfield, Yap, Grimm, Shalev, & Shaham, 2001). During the first 7 days, rats were trained for 3 hr/day, and for the last 3 days they were trained for 2 hr/day. Each day, the rats were transported from the animal colony to the testing rooms, where they were placed in the operant chambers. Each session began with the illumination of the houselight and the introduction of the active lever into the chamber. Also, the white cue light located above this lever was turned on for 30 s. Responding on the active lever resulted in an infusion of speedball, delivered at a volume of 0.13 ml. At the same time, the cue light was turned on for 20 s after each infusion, and during this time leverpresses were not reinforced (a timeout period). At the end of each session, the houselight was turned off, the active lever was retracted, and the rats were returned to the animal colony.

Table 1
Summary of the Experimental Groups

Group	Acquisition	Extinction	Test	*n*
Renewal	A	B	A	13
Control	A	A	A	6
	A	B	B	6
Novel	A	A	B	8

Note. Letters represent Context A and Context B. Data from the AAA and ABB groups were pooled to yield a single control group.

Extinction phase. During the extinction phase, all procedures were identical to those described before, except that the drug syringes were removed from the infusion pumps. Thus responding on the previously active lever resulted in the presentation of the discrete CSs (the 20-s cue light and the sound of the syringe pump) but not in drug delivery. For rats in the novel group (AAB) and half of the rats in the control group (AAA), extinction training occurred in the same context as where drug self-administration had occurred. For rats in the renewal group (ABA) and the other half of the rats in the control group (ABB), extinction occurred in a context that was different from the drug-taking context (see Table 1). A total of 20 daily 2-hr extinction sessions were conducted, and the total number of responses on the active lever and inactive lever were recorded.

Test for renewal. On the test day, all of the rats were tested for renewal of speedball seeking after exposure to the context previously paired with drug self-administration (renewal group), the context previously paired with extinction (control group), or a novel context (novel group).The total number of active and inactive lever responses were recorded during a 2-hr test session.

Statistical Analysis

Data were analyzed separately for the training, extinction, and test phases of the experiment. For the training phase, the dependent measures were speedball infusions, total active lever responses (infusions + timeout responses), and inactive lever responses. Because of the change in session duration on Day 8, data were analyzed separately for Days 1–7 and Days 8–10 of training. For the extinction and test phases, the dependent measures were the total (nonreinforced) responses on the previously active lever and inactive lever responses. Differences between groups (renewal, control, and novel) in these measures during training and extinction were analyzed using two-way analyses of variance (ANOVAs), with repeated measures for one variable (session). Differences between groups on the test for renewal were analyzed by a one-way ANOVA, followed by Fisher's protected least significant difference (PLSD) tests.

Results

The data from the two control groups (Groups AAA and ABB) did not differ during any phase of the experiment and were pooled to yield a single control group.

Speedball Self-Administration

Rats rapidly acquired speedball self-administration, and no group differences were observed during the training phase. The statistical analyses for Days 1–7 of training (3-hr sessions/day) revealed effects of session for number of infusions and total responses on the active lever, $F(6, 180) = 11.4$ and 2.7, respectively ($ps < .01$). The effects of group or Group × Session interaction were not significant ($Fs < 1.1$, $ps > .05$). During Days 8–10 (2-hr sessions/day), responding on the active lever remained stable, and there were no group differences for the number of infusions and total active lever responses ($Fs < 1.2$, $ps > .05$, for effects of session; $Fs < 1.0$, $ps > .05$, for effects of group; and $Fs < 0.3$, $ps > .05$, for Group × Session effects). The mean ($\pm SEM$) number of infusions, total responses, and inactive lever responses per 2 hr on the last day of training for the 33 experimental rats were 17.8 ± 1.5, 31.9 ± 8.5, and 0.4 ± 0.3, respectively. No significant effects were observed for responses on the inactive lever ($Fs < 0.8$, $ps > .05$).

Extinction

The left panels of Figures 1A and 1B show the mean ($\pm$ *SEM*) number of responses on the previously active lever and on the

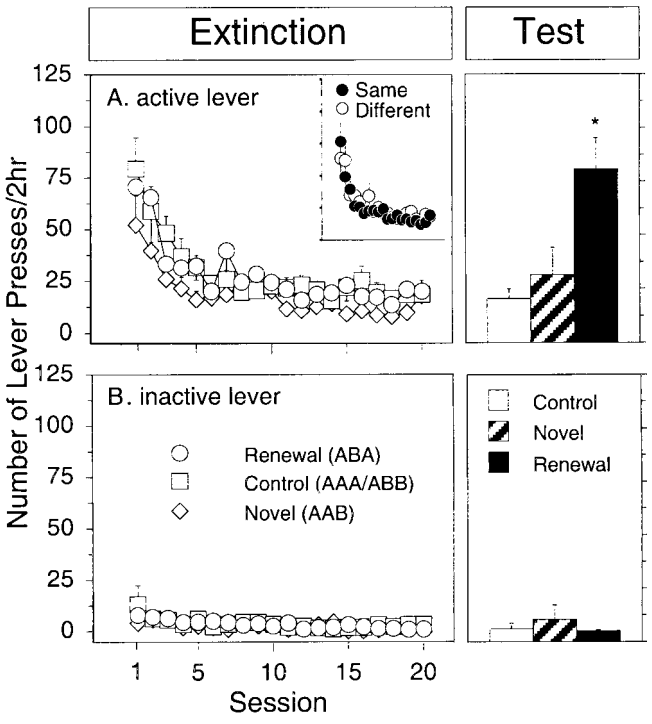

Figure 1. Mean (± *SEM*) number of responses on the previously active lever (A) or the inactive lever (B) during the extinction phase of the experiment and during the test for renewal. There were no differences between groups (renewal, control, or novel) in extinction behavior, but when rats from the renewal group returned to the drug-associated context, drug seeking was renewed to preextinction levels. The inset shows that there were no differences in lever-pressing behavior between rats undergoing extinction in the same context where drug self-administration occurred (AAA and AAB) and rats undergoing extinction in a different context (ABA and ABB).

inactive lever during the extinction phase. Half of the rats in the control group (AAA) and the novel group underwent extinction training in the context previously associated with speedball self-administration, whereas the renewal group and the remaining rats in the control group (ABB) underwent extinction training in a different context. Regardless of the extinction context (see Figure 1A, inset), all of the groups showed similar extinction behavior that was characterized by initial high rates of responding (i.e., an extinction burst) that progressively decreased over time. Statistical analysis for active lever responses revealed an effect of session, $F(38, 570) = 14.4$, $p < .01$, but not of group, $F(2, 30) = 1.3$, $p > .05$, or Session × Group, $F(38, 570) = 0.5$, $p > .05$. Responses on the inactive lever also decreased over time; there was an effect of session, $F(38, 570) = 3.2$, $p < .01$, but there was no effect of group, $F(2, 30) = 0.6$, $p > .05$, or Group × Session interaction, $F(38, 570) = 1.0$, $p > .05$.

Test for Renewal

The right panels of Figures 1A and 1B show the mean (±*SEM*) number of responses on the previously active lever and on the inactive lever during the test for renewal of speedball seeking. Statistical analysis indicated that there was an effect of group, $F(2, 30) = 8.7$, $p < .01$, for active lever responses but not for inactive lever responses $F(2, 30) = 0.5$, $p > .05$. Post hoc analyses (Fisher's PLSD tests) revealed that responses on the previously active lever (but not the inactive lever) in the renewal group were higher than those of the control or the novel groups ($ps < .05$), and the latter groups were not different from one another.

Discussion

Extinction training, during which speedball-contingent discrete stimuli were presented in the absence of the drug, produced a progressive loss of drug-seeking behavior, irrespective of whether extinction occurred in the drug-taking environment or in a different environment. However, when on the test day rats were returned to the drug-paired environment, drug seeking was recovered to preextinction levels (i.e., drug seeking was renewed). This context-dependent effect cannot easily be attributed to a nonspecific effect of switching rats to a different environment because rats that were exposed to a novel environment (novel group) did not resume lever-pressing behavior. Taken together, the present data extend previous reports demonstrating contextual renewal with various aversive and appetitive (nondrug) reinforcers using classical and operant conditioning procedures (Bouton & Swartzentruber, 1991; Goddard, 1999; Nakajima, Tanaka, Urushihara, & Imada, 2000; Welker & McAuly, 1978). Furthermore, renewal of responding is achieved when rats are exposed to the two contexts concurrently prior to renewal testing, as is typically the case in discrimination procedures (Wilson, Brooks, & Bouton, 1995), or serially (Bouton & King, 1983), as was the case here.

It is not immediately clear how context renews drug seeking despite extensive extinction training, during which drug-contingent CSs were presented in the absence of the drug. One possibility is that contextual stimuli, because they reliably signal drug availability, acquire excitatory conditioned stimulus (CS+) properties (Gracy, Dankiewicz, Weiss, & Koob, 2000). Because in the present experiment extinction occurred in a different environment, contextual cues would have retained their CS+ properties, and subsequently reexposing rats to the context elicited drug seeking. For example, Weiss et al. (2000) reported that discriminative cues that signaled cocaine or heroin availability evoked drug seeking following prolonged extinction of the lever-pressing behavior in the absence of these cues. It should be pointed out that in these studies neither discriminative cues nor drug-contingent CSs were extinguished, making it difficult to determine their relative importance in the resumption of drug seeking. However, to the extent that drug seeking is critically dependent on the CS+ properties of contextual stimuli, lever-pressing behavior should have been altered when extinction training occurred in a context different from the drug-taking context. Consistent with previous reports (Bouton & King, 1983; Goddard, 1999; Nakajima et al., 2000; but see Bouton & Ricker, 1994; Welker & McAuly, 1978), however, changing the environment following acquisition of drug self-administration did not affect extinction behavior (see inset Figure 1).

It is also possible that drug seeking was renewed because contextual stimuli acquired conditioned inhibitory (CS–) properties (Rescorla, Durlach, & Grau, 1985). In the renewal group, Context B was explicitly paired with nonreinforcement, and it is possible that contextual stimuli acquired CS– properties, which

actively inhibited drug seeking. On the test day, when rats were removed from the inhibitory extinction context but not when rats remained in the extinction context, drug seeking resumed. Consistent with this inhibitory conditioning notion, renewal of responding can occur when conditioning occurs in A, extinction in B, and testing in a novel context, suggesting that removal from the extinction context, rather then return to the conditioning context, is critical for renewed responding to occur (Bouton & Bolles, 1979; Gunther, Denniston, & Miller, 1998). However, to the extent that drug seeking is modulated by conditioned inhibitory properties of the extinction (B) context, one would expect increased resistance to extinction in rats in which training and extinction were conducted in the same context (AAA or AAB groups), which was not the case here. Furthermore, Bouton and colleagues (Bouton, 1993; Bouton & King, 1983), using summation and retardation procedures (Rescorla, 1967), have consistently been unable to demonstrate that the extinction context functions as a conditioned inhibitor.

Recent developments in the field of learning and memory provide yet another explanation for the present findings. That is, contexts often come to control the expression of behavior by functioning as occasion setters (Holland, 1992) or modulators (Rescorla et al., 1985). According to this view, contexts function as retrieval cues in cases in which the meaning of the discrete CSs is ambiguous because they have been paired with both reinforcement and nonreinforcement (Bouton, 1993). In the present experiment, the discrete CSs (the cue light and the sound of the pump) were paired at one time with speedball taking (acquisition phase) and at a different time with nonreinforcement (extinction phase). As such, these cues would have acquired ambiguous meanings. Because the occurrence of reinforcement versus nonreinforcement was reliably signaled by contextual stimuli, performance to the cues would have been determined by whether the contextual stimuli in the background retrieved the conditioning or the extinction experience. It is important to note that occasion setters are fundamentally different from traditional CSs in that they do not elicit behavior themselves but rather modulate the ability of other stimuli to elicit behavior (Bouton, 1993). This explains, for example, why switching contexts following conditioning did not affect extinction responding.

In conclusion, the present results demonstrate that contextual stimuli can renew drug seeking after prolonged extinction and withdrawal periods. On the basis of the robust effect observed here, it is likely that the renewal phenomenon will generalize to rats trained with other drugs of abuse. Indeed, we recently found using similar experimental procedures that rats trained to lever-press for cocaine (infusion of 0.75 mg/kg) reliably renew drug seeking (Crombag, Grimm, & Shaham, 2002; see also Rauhut, Castle, Fenton, & Bardo, 2000). Thus the present renewal procedure may provide a promising method to elucidate the mechanisms underlying relapse to drug seeking induced by environmental stimuli. Finally, our findings may have implications for behavioral treatment strategies for relapse prevention in humans. It has been reported that high rates of relapse occur after successful extinction of the physiological and psychological responses to the drug-associated cues in the clinic when drug addicts return to their home environment (Childress et al., 1993). On the basis of the present data and previous studies using nondrug reinforcers (for review, see Bouton & Swartzentruber, 1991), it appears that, for cue exposure behavioral interventions to succeed, it is critical that contextual stimuli are considered.

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