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Heroin-Specific Stimuli Reinstate Operant Heroin-Seeking Behavior in Rats After Prolonged Extinction

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GRACY, K. N., L. A. DANKIEWICZ, F. WEISS AND G. F. KOOB. *Heroin-specific stimuli reinstate operant heroin-seeking behavior in rats after prolonged extinction*. PHARMACOL BIOCHEM BEHAV **65**(3) 489–494, 2000.—The clinical literature suggests that exposure to environmental stimuli previously associated with heroin availability may precipitate relapse. However, experimental studies elucidating the significance of learned associations between drug availability and reinstatement of heroin-seeking behavior in the rat are still scarce. To examine the role of environmental stimuli in reinstatement of heroin-seeking behavior, rats were trained to associate discriminative stimuli (DS+) with intravenous heroin availability vs. nonreward [i.e., availability of intravenous saline (DS−)]. The animals then were subjected to extinction training during which the discriminative stimuli were not presented, and lever pressing did not result in drug or saline infusion. The resistance to extinction varied greatly among animals (2.5–11.4 weeks). When the discriminative stimuli were reintroduced, the DS+ reinstated responding while the DS− did not. The average number of responses for heroin during the reinstatement trial (12.8) paralleled the average responding for heroin during discrimination training (12.6), suggesting that the associations between environmental stimuli and drug availability are long-lasting and powerful motivators of drug-seeking behavior. © 2000 Elsevier Science Inc.

Opioids Discrimination Craving Relapse Self-administration Cue

CLINICAL and human experimental studies indicate that environmental stimuli play an important role in human drug-seeking behavior (3,18,23). In particular, it has been suggested that stimuli previously associated with drug availability elicit craving and may trigger episodes of relapse in abstinent individuals (4–6,16). However, there is still only limited direct evidence showing that environmental cues precipitate relapse, particularly in rodent animal models [reviewed in (17)].

The majority of studies examining heroin "relapse" in animals have employed drug priming or stress to reinstate heroin-seeking behavior (8,19,20). In contrast, only a few studies have examined "relapse" in response to environmental stimuli. A series of studies (10,15) tested the ability of discriminative stimuli to reinstate heroin-seeking behavior in the absence of the primary reinforcer. These experiments have established that heroin-associated stimuli effectively initiate heroin-seeking behavior and support other studies showing that discriminative stimuli may influence later drug consumption (9,11,14,21).

To date, heroin reinstatement using discriminative stimuli has been examined only in an operant runway model of relapse (10,15). However, this model does not allow assessment of the maintenance of heroin-seeking behavior throughout the entire session. Furthermore, these studies examining conditioned heroin-associated stimuli have not assessed the ability of the stimuli to elicit drug-seeking behavior after a period of abstinence longer than 7 days (10,15). As human heroin addicts can relapse even after years of abstinence (4,12), it is likely that discriminative stimuli may continue to elicit heroin-seeking behavior after much longer periods of extinction.

Animal models using a variety of addictive drugs have established that rats previously trained to self-administer drugs will resume responding at a previously active lever when they are exposed to discriminative stimuli (DS) previously predic-

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tive of the drug's availability (1,7,13). The self-administration protocol used in these studies of DS-induced reinstatement of cocaine and alcohol-seeking behavior (1,7,13,24) may allow further analysis of the effects of drug-associated environmental stimuli on heroin-seeking behavior.

To study the role of drug-associated stimuli on heroin-seeking behavior and to examine the possibility of long-lasting effects of environmental stimuli, the present study employed an operant self-administration procedure in which distinct DSs predicted the availability of heroin (DS+) vs. nonreward [saline (DS−)]. Lever pressing behavior then was extinguished during daily sessions in which responding was not reinforced by heroin and the DSs were not presented. Once lever pressing was extinguished, animals were presented on alternate days with the heroin DS+ and DS− but not with heroin or saline. Average lever pressing during these nonreinforced sessions was compared to the average responding for heroin during the discrimination phase.

METHOD

Animals

Thirteen male Wistar rats (250–300 g at the start of the experiment) were housed two per cage in a 12 L:12 D cycle vivarium. The lights went out at 1000 h, and conditioning experiments were conducted during the rats' active (dark) cycle. All procedures conformed to the procedures established by the *National Institutes of Health Guide for the Care and Use of Laboratory Animals*. The Wistar rats were bred at the Beckman Laboratories of The Scripps Research Institute from a stock originally derived from Charles River (Kingston, NY). The rats are bred using a circular pair random system of breeding to maintain genetic heterogeneity, and new breeders are obtained from Charles River as determined by the internal Genetics Advisory Board.

Surgical Procedure

Rats were anesthetized with an oxygen/halothane mixture, and implanted with a silastic catheter into the jugular vein as described by Caine et al. (1993) with minor modifications (2,22). The animals were allowed to recover for a minimum of 7 days, and were flushed before and after the session with 0.15 ml heparin (30 USP units/ml) in physiological saline. Rats also were given daily intravenous antibiotic doses of 0.1 ml of 100 mg/ml sterile ticarcillin disodium and clavulanate potassium for intravenous administration (Timentin; SmithKline Beecham Pharmaceuticals, Philadelphia, PA). The patency of the catheter was periodically tested by intravenous administration of 0.1 ml of 1% methohexital sodium (Jones Medical Industries Inc., St. Louis, MO), which produced loss of muscle tone within a few seconds. During the course of the experiment, two animals were recatheterized in the opposite jugular vein when their original catheter became blocked. After 5 days of recovery, they again were allowed to self-administer. Two animals were removed from the study due to irreparable catheter failure; one animal died.

Apparatus and Training

Animals were tested in sound-attenuated operant chambers equipped with two retractable levers, one in the front and one in the back of the chamber, and a food hopper between them. The chambers were contained within a second outer box, and the pump apparatus used for drug delivery remained outside the outer box. The noise of the pump during drug delivery was, therefore, inaudible from within the chamber. The chamber contained a 1.12-watt white house light 24 cm above the grid box floor, and a small light 4 cm above each lever. During food training, mildly food deprived rats (17–20 g food/day) were trained to lever press the back lever for food reinforcement on a fixed ratio 1, time-out 20-s schedule in which one press resulted in a reward followed by a 20-s time-out period in which lever pressing was not rewarded. When the active lever was pressed, the light above the lever was illuminated during the 20-s time-out. Once the rats were able to acquire at least 50 pellets in 30 min, they were allowed ad libitum access to food and water for the duration of the experiment. Animals then were trained to lever press for heroin. Both the inactive and active levers were extended in all experimental phases.

Discrimination Phase

The training procedures were adapted from Weiss (24,25). On the first 2 days of discrimination training, animals were allowed 2 h access to heroin on a fixed ratio 1, time-out 20-s schedule. Both levers were extended, but only the front lever produced a response. A series of regular intermittent beeps (1 s on, 1 s off; 7 kHz) continued throughout the session (noncontingent stimulus). After animals pressed the front (active) lever, the house light (contingent stimulus) was illuminated during the 20-s time-out. Thus, the DS+ was defined as a combination of regular intermittent beeps and the illumination of the house light following the lever press. A Razel (model A; Razel Scientific Instruments, Stamford, CT) syringe pump delivered 0.1 ml of heroin over 4 s through a polyethylene tube attached to the rats' catheter apparatus in response to lever pressing (0.03 mg heroin/kg/infusion). The tubing was attached via a liquid swivel (model 375; Instech Labs, Plymouth Meeting, VA) and a commercially available cannula connector (Plastics One, Roanoke, VA). An IBM-compatible microcomputer controlled schedule contingencies and data collection. Responses made during the time-out did not result in drug infusion, and did not count toward the response score.

On the second 2 days of training, animals received two separate 1-h self-administration sessions during which the heroin DS+ (noncontingent beep tone and contingent house light) were active and heroin was available. After this, animals had three 1-h sessions per day, 6 days per week. Heroin DS+ were active, and heroin was available in two of these sessions. In the third session, saline was administered in response to lever pressing. Saline availability was signaled by the continuous illumination of the small light above the active (front) lever (noncontingent stimulus) and by a white noise (80–85 dB) during the 20-s time-out (contingent stimulus). Thus, the DS− was defined as the illumination of a small light above the lever and activation of a white noise after delivery of saline. The order of the three sessions was rotated daily, so that the rats could not predict the availability of heroin with the DS+. Animals were returned briefly to their home cages within the experimentation room between sessions. The beginning of each session was signaled by the extension of the levers and the simultaneous presentation of the noncontingent stimulus (beeps in heroin sessions, light in saline session). When the saline session followed a heroin session, rats were returned to their home cages for 30 min so that the effects of heroin from the previous session were minimized.

Conditioning criterion was established to distinguish which animals had learned to discriminate between the DS. Responding during heroin sessions was averaged for 2 days.

Animals reached criterion only if heroin responding on the third day fell within ±20% of this average. The animal must also have responded with five or fewer lever presses during saline sessions for the same 3 consecutive days. This took an average of 19 (±SEM 2.87) sessions. Only lever presses that resulted in a drug infusion were counted; responses made during the 20-s time-out period were not counted. Once the discrimination phase was completed, lever pressing behavior did not result in either heroin or saline infusion for the remainder of the study.

Extinction Phase

After animals had reached the criteria for stimulus discrimination, they experienced daily (6 days per week) 1-h extinction sessions in which both levers were extended but no visual or auditory stimuli were present. The beginning of the session was signaled by the extension of the levers, but lever pressing did not result in infusions. The lever-pressing behavior was considered extinguished when rats pressed on the active lever five or fewer times per session for 3 consecutive days. As during the discrimination training period, responses made during the 20-s time-out period after each press were not included in the animal's total lever-press score per session. Extinction took an average of 30.1 (±SEM 5.02) sessions.

Reinstatement Testing

Two days after their last extinction session, the animals were presented with either the heroin or saline DSs during a 1-h self-administration session. Both contingent and noncontingent stimuli were present. Lever pressing during this session was not reinforced by pump activation or drug infusion. Two days later, the animal was tested by the presence of the opposite DS. Half of the rats were presented with the heroin DS first (DS+), and half with the saline DS first (DS−). As in all phases, responding during the time-out did not count toward each animal's session score. These results were analyzed using a *t*-test with paired groups. A comparison between the responding on the last 3 days of discrimination and responding in the reinstatement test was made using a one-way ANOVA with repeated measures.

RESULTS

Rats that were trained to lever press only in the presence of the DS+ signaling heroin's availability reinstated lever-pressing behavior after extinction in the presence of the heroin DS+ alone. Extinction training took from 2.5 weeks to as long as 11.4 weeks, but animals responded differentially to each DS, regardless of time spent in extinction. The average lever presses per hour for heroin DS+ alone was the same as had been previously established for heroin itself.

Discrimination Phase

Animals exhibited the ability to discriminate between the DS+ signaling heroin availability in an average of 19 sessions (±SEM 2.87). In the last 3 days of discrimination training, the average responding for heroin was 13–14 presses in the first 1-h heroin session and 11–12 presses in the second heroin session. In contrast, animals pressed three to four times during the 1-h session in which saline availability was signaled (Fig. 1A). Animals did not respond differentially on the inactive lever (Fig. 1B).

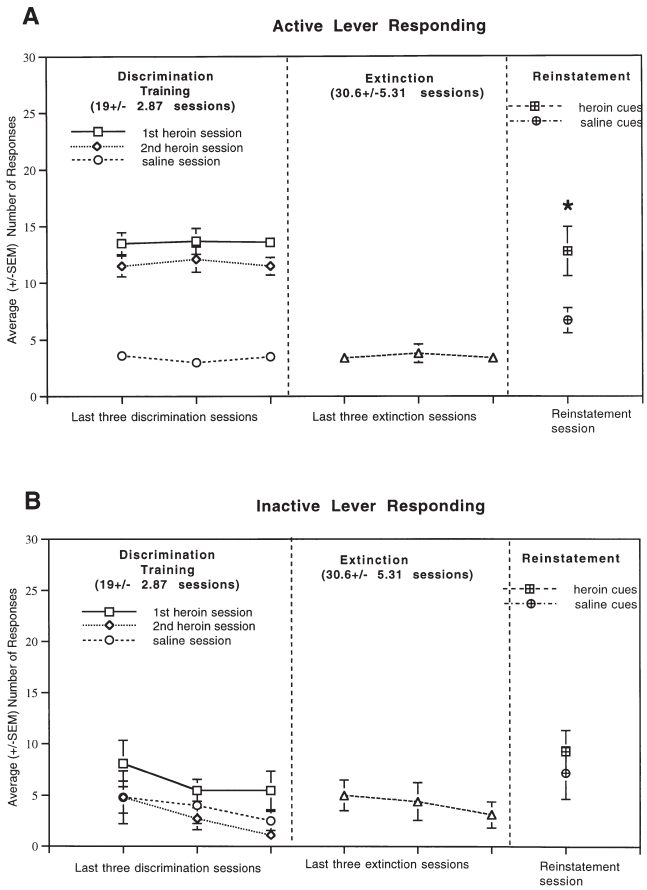

FIG. 1. Heroin-associated stimuli (DS+) specifically reinstate responding after a period of extinction. (A) The line graph represents average responses on the active (front) lever during the last three discrimination sessions, the last three extinction sessions, and the reinstatement trials where either heroin or saline DSs were presented. Half of the animals were presented with the heroin stimuli (DS+) on the first trial day and half with saline stimuli (DS−) on the first trial day. After 2 days, they received the alternate DS. The data from each DS was combined in a single data point. In some cases, the error bars are too small to be seen on the graph. There was a significant difference between responding for the heroin vs. saline DS ($*p < 0.05$). (B) The line graph represents the average responses on the inactive (back) lever during the same time period. There was no significant difference between responding on the active lever for the heroin vs. saline DS during reinstatement.

Extinction Phase

Extinction criterion required animals to press five times or fewer on the active lever during the 1-h extinction session. The extinction training took an average of 30.1 sessions (±SEM 5.02) (Fig. 1A). There was a large range in the amount of time animals took to reach extinction criteria (from 2.5 to 11.4 weeks). The average time spent in extinction was approximately 5.5 weeks (30.1 sessions).

Reinstatement Testing

Even after weeks of abstinence, the heroin DS+ still differentially elicited renewed responding on the active lever

(Fig. 1A). A *t*-test with paired groups revealed that responding in the heroin DS+ session was significantly higher than in the saline DS− session ($p < 0.05$; Fig. 1A). Lever pressing on the inactive lever was not significantly different in response to heroin DS+ vs. saline DS− (Fig. 1B).

A correlation test was performed to assess whether animals that spent a shorter period of time in extinction reinstated responding to heroin-paired stimuli better than animals that spent a longer time in extinction. *r*-Values ($r = 0.017$) showed that there was no correlation between days spent in extinction and the difference between responding for DS+ vs. DS− (Fig. 2).

Upon presentation of the heroin DS+ alone, rats responded at the same level as they had previously responded during the heroin discrimination training phase. The average responding over both heroin sessions in the last 3 days of discrimination training was 12.6 responses per hour. In the reinstatement session, in which animals were presented with the DS+ for heroin but were not reinforced, the average responding was 12.8 responses per hour. A one-way ANOVA with repeated measures showed that this difference was not significant.

Half of the animals ($n = 5$) continued to lever press throughout the 1-h nonrewarded DS+ reinstatement test session. The other half ($n = 5$) responded only during the first 10 min of the DS+ reinstatement test session (Fig. 3B). Comparison to responding patterns during the discrimination sessions in which lever pressing was rewarded with heroin did not reveal a consistent underlying pattern (Fig. 3A). Animals that responded throughout the reinstatement session spent an average of 28 days in extinction, while animals that responded only during the first 10 min of the session spent an average of 32.2 days in extinction.

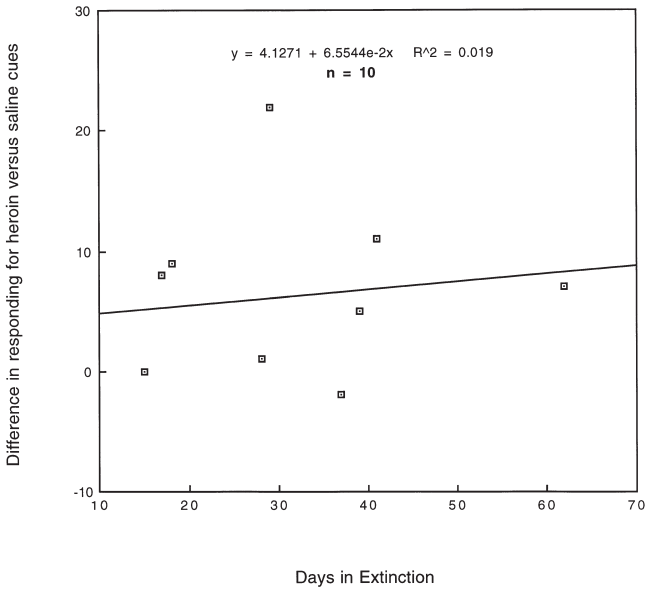

FIG. 2. Lack of correlation between days in extinction and differential responding for heroin DS+. Scatter plot demonstrating that animals that spent the longest amount of time in extinction did not have weaker reinstatement of responding for the heroin stimuli. Two animals spent the same number of days in extinction and had no difference between heroin and saline DS responding and, thus, share a single data point.

Saline responding during the reinstatement trial was elevated. The average responding for saline DS− in the reinstatement session was 6.7 responses while the average responding in the last 3 days of discrimination training was 3.4. A one-way ANOVA with repeated masures showed a significant difference between the average responding for saline DS− on the last 3 days of discrimination training and the reinstatement test day, $F(1, 9) = 8.25$, $p < 0.05$.

DISCUSSION

The results demonstrate that discriminative stimuli previously paired with heroin availability can elicit heroin-seeking behavior in rats in a response-reinstatement model, after periods of abstinence up to 11 weeks. When the animals were presented with the DS+ previously predicting heroin availability, they reinstated lever pressing at 100% of the average heroin-reinforced responses during the discrimination learning phase. These findings suggest that discriminative stimuli associated with heroin availability are both long-lasting and robust activators of heroin-seeking behavior.

This study confirms previous work establishing the ability of DS+ to reinstate heroin-seeking behavior (10,15). However, the present study utilized a combination of noncontingent and contingent (time-out) stimulus paired with heroin availability to reliably reinstate behavior upon reintroduction. As the presentation of the time-out stimulus was temporally contiguous with the drug infusion during discrimination training, this stimulus may have acted as a conditioned reinforcer in reinstatement trials. The combination of these two sources of stimuli predicting heroin appears to be a powerful means of reinstating responding. Whether stimuli contingent or noncontingent to the lever response itself is the important activator of reinstatement remains to be determined.

In other heroin stimuli-induced reinstatement studies using the runway model, rats reached the extinction criterion within 1 week (10,15). In the present study, however, there was a wide range in the amount of time (15–62 sessions) animals took to reach extinction criterion (five or fewer presses per session). The observation that there is high variability in individual animals' resistance to extinction suggests that even without environmental stimuli, a subgroup of animals trained to self-administer heroin persist in heroin-seeking behavior for much longer than others.

Despite the differences in the amount of time elapsed between the last presentation of DS's (2.5 weeks to over 11 weeks), animals that showed little resistance to extinction did not appear to differentially lever press more upon presentation of the heroin DS+ than animals that required extensive extinction training. The behavioral response to the stimuli did not appear to be impaired by the long extinction period in which the stimuli were absent. This suggests that length of time spent in extinction does not affect the salience of heroin-associated stimuli, and may partially reflect the fact that discriminative stimuli were not extinguished. However, it is important to note that the stimuli retained the ability to initiate heroin-seeking behavior even after extended periods of abstinence. This parallels the experience of many human heroin addicts in which heroin-associated stimuli are not extinguished and retain salience despite long periods of heroin abstinence. The fact that saline stimuli induced responding higher than that observed during saline self-administration most likely reflects a general arousal response. However, re-

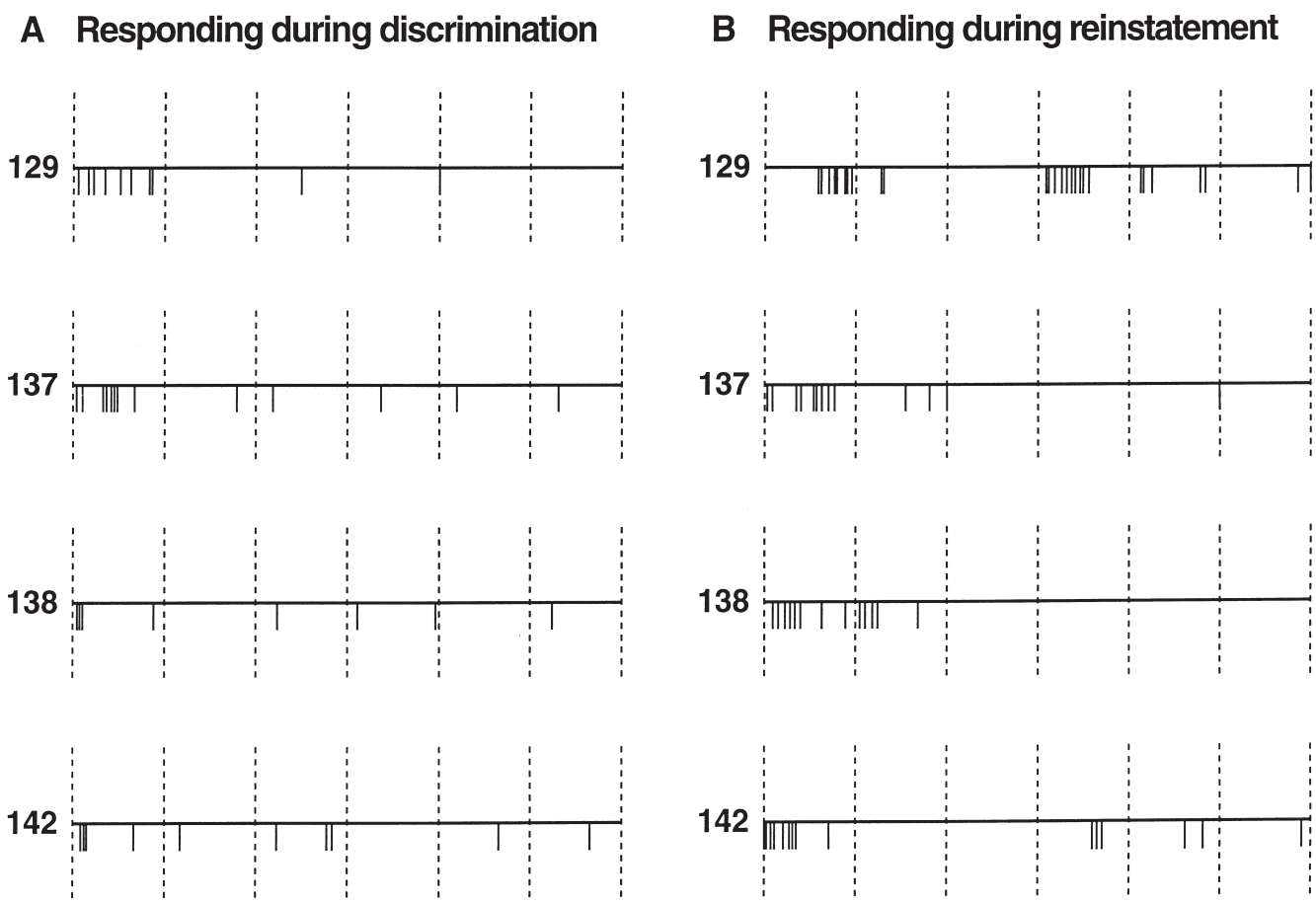

FIG. 3. Comparisons of responding during the discrimination phase and reinstatement test. (A) Ester lines from several animals during the discrimination phase. DS+ was present and lever pressing resulted in heroin reward. The data is taken from a single randomly chosen DS+ session. (B) Ester lines of the same animals during the DS+ reinstatement trial (no heroin reward).

sponding for both saline itself and for saline stimuli alone was overall very low (3.4–6.7 average presses/hour, respectively).

Although previous studies have shown that both footshock stress and priming can precipitate reinstatement of heroin-seeking behavior (8,19,20,22) after an abstinence period of up to 5 days, the present study shows that reinstatement can occur after much longer periods of abstinence. Because, in the present study, animals that reached the extinction criterion quickly were immediately tested for reinstatement, the length of time an animal was abstinent from drug depended on its performance during the extinction training phase. Examination of the persistence of the heroin stimulus effects on longer phases of abstinence will remain for future studies.

Heroin-associated stimuli appear not only to be able to reinstate lever-pressing behavior after long periods of abstinence, but to elicit responding to the same degree as was previously produced by heroin infusions. This is supported by operant runway studies using heroin-associated stimuli, in which animals traversed the runway to the goal box as quickly during the reinstatement trials as during the discrimination trials (15). The pattern of lever pressing during the reinstatement trial fell into two groups. Half of the animals continued to respond throughout the session, and half responded for the first 10 min. However, animals also varied greatly in their pattern of responding during discrimination sessions in which lever pressing was rewarded with heroin. This further reinforces the idea that there is variability between rats in both persistence in heroin-seeking over time as seen in the extinction trials, and in heroin-seeking within the 1-h reinstatement trial in which the DS+ was presented without heroin reward.

The findings in the present study thus suggest that stimuli associated with heroin availability are both long lasting and robust, and are thus likely to play an important role in the reinstatement of drug-seeking behavior in rats. As environmental stimuli previously predictive of heroin availability reliably elicit heroin-seeking behavior in this behavioral model, further studies can provide important information as to the behavioral and neurobiological mechanisms associated with drug relapse.

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REFERENCES

1. Ben-Shahar, O.; Weiss, F.: Environmental cues associated with cocaine availability reinstate cocaine-seeking behavior after prolonged extinction. Soc. Neurosci. Abstr. 24:2173; 1998.
2. Caine, S. B.; Lintz, R.; Koob, G. F.: Intravenous drug self-administration techniques in animals. In: Sahgal, A., ed. Behavioral neuroscience: A practical approach, vol. 2. New York: Oxford University Press; 1993:117–143.
3. Childress, A. R.; McLellan, A. T.; O'Brien, C. P.: Abstinent opiate abusers exhibit conditioned craving, conditioned withdrawal, and reduction in both through extinction. Br. J Addict. 81:644–660; 1986.
4. Childress, A. R.; Ehram, R.; Rohsenow, D. J.; Robbins, S. J.; O'Brien, C. P.: Classically conditioned factors in drug dependence. In: Lowinson, J. H.; Millman, R. B., eds. Substance abuse: A comprehensive textbook, 2nd ed. Baltimore: Williams and Wilkins; 1992:56–69.
5. Childress, A. R.; McLellan, A. T.; Ehrman, R.; O'Brien, C. P.: Extinction of conditioned responses in abstinent cocaine or opioid users. In: Harris, L. S., ed. Problems of drug dependence, 1986 (NIDA Research Monograph, Vol. 76). Rockville, MD: National Institute on Drug Abuse; 1987:189–195.
6. Childress, A. R.; McLellan, A. T.; Ehrman, R.; O'Brien, C. P.: Classically conditioned responses in opioid and cocaine dependence: A role in relapse? In: Ray, B. A., ed. Learning factors in substance abuse (NIDA Research Monograph, Vol. 84). Rockville: National Institute on Drug Abuse; 1988:25–43.
7. Ciccocioppo, R.; Sanna, P. P.; Bloom, F. E.; Weiss, F.: Environmental cues potently reinstate cocaine-seeking behavior and induce cfos after three to four months of abstinence. Soc. Neurosci. Abstr. 25:1999.
8. deWit, H.; Stewart, J.: Drug reinstatement of heroin-reinforced responding in the rat. Psychopharmacology (Berlin) 79:29–31; 1983.
9. Emmett-Oglesby, M. W.; Lane, J. D.: Tolerance to the reinforcing effects of cocaine. Behav. Pharmacol. 3:193–200; 1992.
10. Ettenberg, A.; MacConell, L. A.; Geist, T. D.: Effects of haloperidol in a response-reinstatement model of heroin relapse. Psychopharmacology (Berlin) 124:205–210; 1996.
11. Falk, J. L.; Lau, C. E.: Stimulus control of addictive behavior: Persistence in the presence and absence of a drug. Pharmacol. Biochem. Behav. 50:71–75; 1994.
12. Jaffe, J. H.: Drug addiction and abuse. In: Nies, A. S.; Paylor, P., eds. The pharmacological basis of therapeutics, 8th ed. New York: Pergamon Press; 1990:522–573.
13. Katner, S. N.; Magalong, J. G.; Weiss, F.: Reinstatement of alcohol-seeking behavior by drug-associated discriminative stimuli after prolonged extinction in the rat. Neuropsychopharmacology 20:471–479; 1999.
14. Krank, M. D.; Wall, A. M.: Cue exposure during a period of abstinence reduces the resumption of operant behavior for oral ethanol reinforcement. Behav. Neurosci. 104:725–733; 1990.
15. McFarland, K.; Ettenberg, A.: Reinstatement of drug-seeking behavior produced by heroin-predictive environmental stimuli. Psychopharmacology (Berlin) 131:86–92; 1997.
16. O'Brien, C.; Childress, A.; McLellan, A.; Ehrman, R.; Ternes, J.: Learning factors in substance abuse. In: Ray, B. A., ed. Learning factors in substance abuse (NIDA Research Monograph Vol. 84). Rockville, MD: National Institute on Drug Abuse; 1988:44–61.
17. O'Brien, C. P.; Childress, A. R.; Ehrman, R.; Robbins, S. J.: Conditioning factors in drug abuse: Can they explain compulsion? J. Psychopharmacol. 12:15–22; 1998.
18. O'Brien, C. P.; Ehrman, R.; Ternes, J.: Classical conditioning in human opioid dependence. In: Goldberg, S. R.; Stolerman, I. P.; eds. Behavioral analysis of drug dependence. Orlando, FL: Academic Press; 1986.
19. Shaham, Y.; Rajabi, H.; Stewart, J.: Relapse to heroin-seeking in rats under opioid maintenance: The effects of stress, heroin priming and withdrawal. J. Neurosci. 16:1957–1963; 1996.
20. Shaham, Y.; Stewart, J.: Stress reinstates heroin-seeking in drug-free animals: An effect mimicking heroin, not withdrawal. Psychopharmacology (Berlin) 119:334–341; 1995.
21. Stretch, R.; Gerber, G. J.; Wood, S. M.: Drug-induced reinstatement of amphetamine self-administration behaviour in monkeys. Can. J. Psychol. Rev. Can. Psychol. 27:168–177; 1971.
22. Stewart, J.; Wise, R. A.: Reinstatement of heroin self-administration habits: Morphine prompts and naltrexone discourages renewed responding after extinction. Psychopharmacology (Berlin) 108:79–84; 1992.
23. Ternes, J. W.; O'Brien, C. P.; Grabowski, J.; Wellerstein, H.; Jordan-Hayes, J.: Conditioned drug responses to naturalistic stimuli: Problems of drug dependence. NIDA Research Monograph 27. Washington, DC: YS Government Printing Office; 1980:282–288.
24. Weiss, F.: Cocaine dependence and withdrawal: Neuroadaptive changes in brain reward and stress systems. In: Cocaine and the changing brain (NIH publication #99-4382). Bethesda, MD: NIH; 1999:37–42.
25. Weiss, F.; Ciccocioppo, R.: Enduring conditioned reactivity to cocaine cues: Effects on extinguished operant responding, forebrain dopamine release, and fos immunoreactivity. Behav. Pharmacol. 10 (Suppl. 1): S99; 1999.