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# Cocaine- but not food-seeking behavior is reinstated by stress after extinction

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**Abstract** Reinstatement of drug-seeking behavior after extinction constitutes a potential animal model of relapse to drug abuse. In a typical reinstatement experiment, previously drug-trained rats undergo extinction during which responding is no longer followed by drug delivery. After significant extinction is observed, rats are then exposed to an event expected to reinstate drug-seeking behavior. Using this procedure, it has been recently reported that footshock stress leads to reinstatement of drug-seeking in heroin-trained, presently drug-free rats. The purpose of the present study was to assess the generality of this effect of stress. Here we report that 15 min of intermittent footshock (0.86 mA; 0.5 s on, with a mean off period of 40 s) reinstated selectively cocaine-seeking behavior after 14 extinction sessions (rats were previously trained on a FR1 TO 20 s to obtain cocaine at a dose of 0.25 mg/infusion). In contrast, under similar experimental conditions, the same stressor did not reinstate food-seeking in food-trained rats after seven extinction sessions (rats were previously trained on a FR1 TO 20 s to obtain six food pellets). Rather, when the basal level of responding was sufficiently high, footshock stress induced a significant suppression of the instrumental performance. These data are discussed in light of several behavioral mechanisms which may explain the specificity of stress in reinstating drug-seeking behavior and not food-seeking behavior.

**Key words** Drug self-administration · Cocaine · Extinction · Reinstatement · Drug-seeking · Drug relapse · Stress · Footshock · Internal state · Context

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## Introduction

The treatment of drug addiction is complicated by the chronic relapsing nature of this behavioral disorder. Indeed a high rate of relapse is commonly observed following successful short-term or even long-term abstinence (Jaffe 1990; McLellan et al. 1992; Vaillant 1992). In this context, understanding the factors contributing to the precipitation of relapse constitutes an important step for the development of treatment strategies. Because of the difficulty of studying these factors in human addicts, efforts have been recently made to develop animal models capturing some important features of relapse in human addicts (Markou et al. 1993; Koob 1995). A well-studied model of relapse in animals involves a reinstatement procedure (Gerber and Stretch 1975; Stewart and De Wit 1987). Briefly, rats are first trained to self-administer a given drug. After having reached a stable drug intake, subjects undergo extinction during which responding is no longer reinforced by the delivery of the drug. When significant extinction is observed, rats are then exposed to different events in an attempt to reinstate drug-responding.

By using the reinstatement procedure, it has been shown that noncontingent re-exposure to the training drug itself consistently reinstated drug-seeking behavior. Drug-induced reinstatement has been observed in stimulant (Gerber and Stretch 1975; De Wit and Stewart 1981; Slikker et al. 1984) and opiate self-administration (Davis and Smith 1976; De Wit and Stewart 1983). Reinstatement can also be induced by drugs other than the training drug. For example, cocaine-seeking behavior is reinstated by morphine (De Wit and Stewart 1981), by the dopaminergic direct agonist, bromocriptine (Wise et al. 1990), or by caffeine (Worley et al. 1994). The observation that drug re-exposure reinstates drug-seeking behavior in animals is congruent with those few laboratory studies performed in human drug addicts showing an enhanced craving and motivation to engage in drug-taking behavior following

re-exposure to the abused drug (Ludwig et al. 1974; Jaffe et al. 1989; for a recent review, de Wit 1996).

Recently, it has been reported that a brief aversive stressor (a series of intermittent footshock) was able to reinstate heroin-seeking behavior after extinction (Shaham and Stewart 1995). This reinstatement did not result from a general behavioral activation induced by the stressor, since responding was selectively renewed on the lever associated previously with heroin delivery. This finding suggests a causal role for stressful events in relapse to drug self-administration, and corroborates clinical observations which have associated stressful events or negative mood states with relapse or an enhanced craving for the abused drug (Shiffman and Wills 1985; Childress et al. 1987; Brandon 1994). Moreover, this finding was consistent with previous laboratory studies in rodents which showed an aversive event was able to increase both stimulant (Piazza et al. 1991; Ramsey and Van Ree 1993; Goeders and Guerin 1994) and opiate (Shaham and Stewart 1994) self-administration. Taken together, these data point to a major role of stress in the maintenance and relapse of drug-seeking behavior.

The purpose of the present study was to assess the generality of stressor-induced reinstatement of drug-seeking behavior. First, the ability of an electrical footshock stressor to reinstate seeking of a drug other than an opiate (i.e., a stimulant) was evaluated. This issue was important to determine whether reinstatement of drug-seeking by footshock is specific to opiates or whether it can be generalized to other drugs of abuse. For that, the effect of footshock was tested in cocaine-trained rats after extinction. Second, the ability of footshock to reinstate seeking of a reinforcer other than a drug (i.e., food) was assessed. This experiment allowed a determination of whether footshock interacts specifically with drug reinforcement processes or acts in a more general way by prompting the reinstatement of all positively reinforced behaviors. For that, after extinction, food-trained rats were exposed to footshock stress and their performance was compared to that of cocaine-trained rats. Finally, to determine whether the subject motivational state at the time of testing could influence footshock-induced reinstatement, food-trained rats were tested in two different motivational conditions, food-restricted or sated.

## Materials and methods

### Subjects

Twenty-two male Wistar rats (Charles River, Hollister, Calif., USA), weighing 320–430 g at the start of the behavioral training, were used. The rats were housed in groups of two or three and maintained in a light- (12-h light-dark cycle; lights on at 10 a.m.) and temperature-controlled vivarium. All behavioral testing occurred during the dark phase of the light-dark cycle. Food and water were freely available, except when otherwise specified by the experimental design. All procedures were conducted in conformity with the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

### Surgical procedure

Anesthetized rats (halothane-oxygen mixture, 1.0–1.5% halothane) were prepared with catheters for cocaine self-administration in the jugular vein as described previously (Caine et al. 1993), with minor modifications (Emmett-Oglesby and Lane 1992). Briefly, the catheters consisted of a 13 cm length of silastic tubing fitted to a guide cannula bent at a right angle and encased in dental cement anchored with 1-in square durable mesh. The tubing was passed subcutaneously from the animal's back to the right external jugular vein. All animals were allowed to recover for a minimum of 5 days before given access to cocaine. Catheters were flushed daily with approximately 0.15 ml sterile physiological saline containing heparin (30 USP units/ml).

### Apparatus

Cocaine self-administration and food training were conducted in the same standard operant chambers, housed in sound-attenuating cubicles. Each chamber was equipped with two retractable levers and a food hopper. The two levers were mounted 3 cm above the grid floor on either side of the food hopper. The food hopper was mounted 2 or 3 cm above the floor at the center of the right wall adjacent to the Plexiglas front door. Food pellets (45 mg) were delivered by means of an automatic food dispenser fixed to the outside wall of the chamber. Drug infusions were delivered by a Razel (model A) syringe pump activated for 4 s to deliver cocaine in a volume of 0.1 ml through a Tygon tube attached to the catheter on the animal's back via a liquid swivel (model 375; Instech Labs, Plymouth Meeting, Va., USA) and a commercially available cannula connector (Plastics One, Roanoke, Va., USA ). Schedule contingencies and data collection were controlled by an IBM-compatible microcomputer.

### Electric footshock

Except for the current intensity, the parameters of the footshock were selected based on what was used in a prior study (Shaham and Stewart 1995). Footshock (alternating current; 0.86 mA; 0.5-s trains) were delivered through a scrambler (Coulbourn Instruments) to the grid floor of the operant chamber. They were administered during a period of 15 min in an intermittent manner according to a variable interval schedule (mean interval: 40 s; range: 10–70 s).

### Drug

Cocaine HCl was obtained from the National Institute on Drug Abuse and was dissolved in sterile physiological saline (0.9%). The training dose was 0.25 mg cocaine HCl per infusion.

### Behavioral procedures

#### *Effect of footshock on cocaine-seeking behavior*

Six rats were used in this experiment. These subjects, in addition to the intravenous catheter, also had an intracerebroventricular cannula through which they had received a vehicle infusion (distilled water, pH = 6.7) as the control group for a previous study.

Animals were trained on a fixed-ratio 1 (FR1) schedule of cocaine self-administration. At the beginning of each daily 2-h session, the rats received two non-contingent infusions of the training dose of cocaine (0.25 mg/infusion), after which the levers were extended. The extension of the levers signaled the start of the session. During a session, only responding on one of the two levers (active lever) resulted in the delivery of one infusion of cocaine and initiated a 20-s time-out (TO 20 s) period (during which time lever presses were counted but had no scheduled consequences). The TO period was signaled by a light cue which was located above the active lever. Responses on the other lever (inactive lever) were counted but had no programmed consequences. The position of the active and inactive levers was counterbalanced between rats.

Following 15 sessions of cocaine self-administration during which the cocaine intake had stabilized (variation between the last three self-administration sessions less than 15%), rats were placed in extinction. During each daily 2-h extinction session, pumps were turned off so that presses on the active lever resulted only in the presentation of the light cue previously associated with cocaine infusions. Moreover, throughout extinction, rats were not connected to the infusion system. This procedure was intended to equalize the conditions of extinction with those to be used during testing sessions.

Following 14 sessions of extinction, rats were given a control (day 15) and a footshock testing session (day 16). During the control testing session, the typical 2-h extinction session was preceded by a 15-min period in the operant box with no footshock delivered, while during the footshock testing session, the session was preceded by 15 min of intermittent footshock. During both testing sessions, cocaine was not available and rats were not connected to the infusion system to avoid potential damaging effects resulting from the jumping behaviors induced by footshock stress.

### *Effects of footshock on food-seeking behavior*

This experiment involved 16 naive rats. The day before the start of training, all food was removed from the home cage. On all subsequent days, 14 g of chow pellets was made available for each rat after each training session. Rats maintained on this food-restriction regimen were trained on a fixed-ratio 1 (FR1) schedule of food reinforcement. The session onset was signaled by extension of the levers. During a 40-min session, only responding on one of the two levers (active lever) resulted in food delivery and initiated a time-out (TO) period (during which time lever presses were counted but had no scheduled consequences). The TO period was signaled by a light cue which was located above the lever. Responses on the other lever (inactive lever) were counted but had no programmed consequences. The position of the active and inactive levers was counterbalanced between rats. The number of pellets earned and the duration of TO varied as training progressed (first step: two pellets, TO 1 s; second step: four pellets, TO 5 s; third step: six pellets, TO 10 s; final step: six pellets, TO 20 s). The increase in the quantity of the reinforcer was intended to create a situation in which rats had to consume the reinforcer during the TO period. As such, this schedule mimicked approximately the situation of a rat self-administering cocaine in which the level of TO responses is low.

Following 16 sessions of food training, all rats were put in extinction but in two different motivational conditions. Throughout the extinction phase and during testing sessions, one group (food-s, $n = 8$) was returned to the initial ad libitum access to chow pellets in their home cages, and a second group (food-r, $n = 8$) remained in the food-restriction regimen. During each daily 40-min extinction session, presses on the active lever resulted in the presentation of the light cue associated previously with food pellets and activation of the food dispenser but no pellets were delivered in the food hopper (they were collected in a plastic tube attached to the outside wall of the operant chambers). During extinction, rats of the food-r group no longer had the opportunity to earn food pellets in addition to their daily diet. They were then supplemented with an amount of chow pellets equivalent to the amount they earned during the last session of food training (i.e., an average of 14 g).

Following seven sessions of extinction, rats were tested in a manner identical to the cocaine-trained rats (control testing session on day 8 and footshock testing session on day 9). During those two final testing sessions, food was not available.

### Data analysis

In each experiment, the total number of responses (TO responses included) served as the dependent variable. The inclusion of TO responses in the performance is justified because during both extinction and testing sessions, all of the responses emitted were non-reinforced. In addition, separate analyses performed on either the first responses which initiated the TO period or those produced during it yielded a similar statistical outcome during testing sessions. In cocaine-trained rats, the influence of extinction conditions on responding on the active lever was assessed by using a one-way analysis of variance (ANOVA) with repeated measures (16 daily sessions in total: the two last sessions of cocaine self-administration followed by 14 extinction sessions). In food-trained rats, data were subjected to a two-way ANOVA, with one between subjects factor (experimental groups: food-r, food-s) and with repeated measures on the second factor (nine daily sessions in total: the two last food training sessions followed by seven extinction sessions). Post-hoc comparisons between the last session of cocaine self-administration or food training and all of the subsequent extinction sessions were performed by using the Student's *t*-test. Because the variance increased with the size of the means, a square root transformation was applied to the data of the final two testing sessions to conform to the assumptions of analysis of variance for homogeneity of error of variance (Winer 1971). These data were analyzed with a two-way ANOVA, with one between subjects factor (experimental groups: cocaine-trained, food-r, food-s), and with repeated measures on the second factor (control versus footshock testing session). Post-hoc comparisons for interactions were carried out by tests for simple main effects. Similar analyses were independently performed on the performance recorded on the inactive lever.

## Results

### Extinction of cocaine-seeking behavior

Figure 1 depicts the total number of responses (including TO responses) on the active and inactive levers during the two last sessions of cocaine self-administration and during extinction sessions. For presses on the active lever, a one-way analysis of variance (ANOVA) revealed an effect of session ($F_{15,75} = 7.74$, $P < 0.0001$). Post-hoc comparisons revealed that active lever presses during the first session of extinction were significantly higher than during the last cocaine self-administration session (*t*-test, $P < 0.01$). Active lever presses, however, decreased progressively during the remaining sessions, and on extinction sessions 6, 7, 8, 9, 11, 13 and 14 became lower than lever presses recorded during the last cocaine self-administration session (*t*-test, $P$s $< 0.05$). Presses on the inactive lever were low during cocaine self-administration and increased slightly though not significantly during extinction sessions ($F_{15,75} = 1.76$, NS).

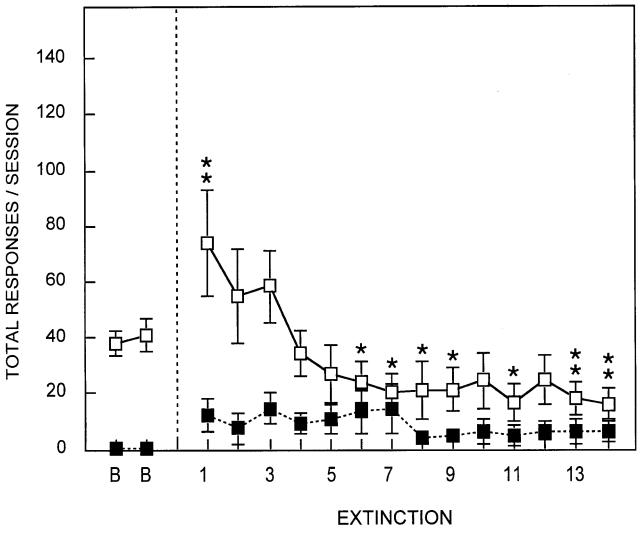


**Fig. 1** Extinction of cocaine-seeking behavior in cocaine-trained rats ($n = 6$). Each point represents the mean (± SEM) total responses on the active and inactive lever in a 2-h session of either cocaine self-administration (*B*, for baseline responding) or extinction (14 sessions in total). During extinction, lever presses were without consequences. $^{**}P < 0.01$; $^{*}P < 0.05$, different from the last session of cocaine self-administration. □ Active, ■ inactive

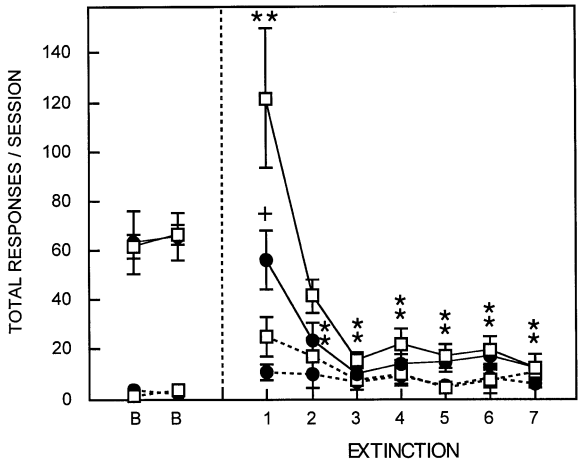


**Fig. 2** Extinction of food-seeking behavior in food-restricted ($n = 8$) and food-sated rats ($n = 8$). Each point represents the mean (± SEM) total responses on the active (*solid line*) and inactive (*broken line*) lever per 40-min session [food training (*B*, for baseline responding) or extinction (seven sessions in total) sessions]. During extinction, lever presses were without consequences. $^{**}P < 0.01$, different from the performance on the active lever observed during the last session of food training (for both food-r and food-s rats when stars are placed on top of the two symbols representing their respective performance). $+P < 0.05$, different from the performance observed in food-restricted rats during the first extinction session. □ Food-r, ● food-s

## Extinction of food-seeking behavior

Figure 2 depicts the total number of responses (including TO responses) on the active and inactive levers during the two last sessions of food training and during extinction sessions. For presses on the active lever, a two-way ANOVA revealed a significant effect of session ($F_{8,112} = 24.4$, $P < 0.0001$) and a Group × Session interaction ($F_{8,112} = 3.39$, $P < 0.005$). There was no significant effect of the group factor ($F_{1,14} = 4.34$, NS). To evaluate the source of the interaction, repeated one-way ANOVAs were performed for each session independently. Both groups showed a similar performance during the last two food training sessions ($F$s < 1). Group performance, however, differed during the first extinction session during which the food-r group exhibited a higher level of presses than the food-s group ($F_{1,14} = 5.27$, $P < 0.05$). This difference was due to the fact that only the performance of the food-r group increased during the first extinction session compared to that observed during the last food training session ($t$-test, $P < 0.01$). In both groups, however, lever presses decreased progressively across repeated extinction sessions. In the food-r group, the performance recorded during extinction sessions 3, 4, 5, 6 and 7 was lower than that recorded during the last food training session ($t$-test, $P$s < 0.05). In group food-s, the performance on extinction sessions 2, 3, 4, 5, 6 and 7 was lower than that recorded during the last food training session ($t$-test, $P$s < 0.05). Presses on the inactive lever were low during food-training and increased consistently throughout extinction ($F_{8,112} = 6.26$, $P < 0.0001$). This latter pattern was not significantly influenced by the motivational condition of the rat (Group × Session interaction, $F_{8,112} = 1.81$, NS).

## Effect of stress on cocaine- and food-seeking behavior

Figure 3A depicts the total number of presses on the active lever during both the control and footshock testing sessions. A two-way ANOVA revealed a significant effect of testing session ($F_{1,19} = 6.14$, $P < 0.05$) and a Group × Testing Session interaction ($F_{2,19} = 20.97$, $P < 0.0001$). No significant main effect of group was observed ($F_{2,19} = 2.64$, NS). The source of the interaction was analyzed by performing simple main effect tests. Footshock induced a strong reinstatement of responding on the active lever only in cocaine-trained rats ($F_{1,19} = 39.14$, $P < 0.01$). No significant effect of footshock was detected in the food-r group ($F_{1,19} = 0.15$, NS), and a suppressive effect of footshock was observed in the food-s group ($F_{1,19} = 5.33$, $P < 0.05$). Figure 3B represents responding on the inactive lever during both the control and footshock testing session. A two-way ANOVA revealed no significant effect of group ($F_{2,19} = 0.22$, NS), no significant effect of testing session ($F_{1,19} = 0.92$, NS) and no Group × Testing Session interaction ($F_{2,19} = 0.29$, NS).

The differential effect of footshock in food-r and food-s rats could have resulted from a performance effect – the responding of food-r rats during the control testing session may have been too low for a

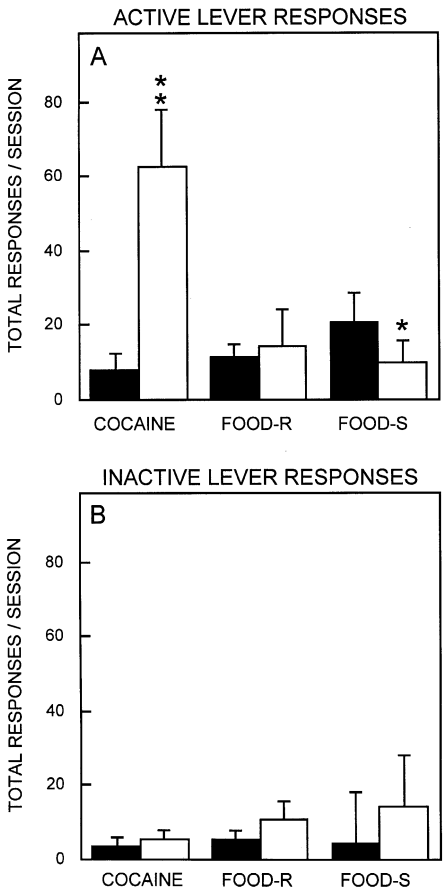


**Fig. 3A, B** Effect of intermittent footshock on cocaine- and food-seeking behavior after extinction. **A** Each bar represents the mean (± SEM) total presses on the active lever in a 2-h extinction session following a 15 min shock-free period (control testing session) or 15 min of intermittent footshock (0.86 mA; 0.5 s on, with a mean off period of 40 s) in either cocaine-trained ($n = 6$) or food-trained [food-restricted (food-r, $n = 8$) or food-sated (food-s, $n = 8$) at the time of testing] rats. During these testing sessions, presses were without consequences. $^{**}P < 0.01$; $^{*}P < 0.05$, different from the control testing session. **B** Same, but for presses on the inactive lever. ■ Control, □ footshock

suppressive effect. To address this question, an additional group of food-r rats ($n = 8$), rats with a general higher performance, was tested and footshock induced a significant suppression of the performance oriented on the active lever (from 26.25 ± 5.62 to 9.75 ± 3.40; *t*-test, $P < 0.05$). No significant effect on responding on the inactive lever was detected (*t*-test, NS) (data not shown).

## Discussion

The present study showed that the exposure to an uncontrollable brief stressor leads to reinstatement of cocaine-seeking behavior following extinction. This effect did not result from a nonspecific activational effect of the stressor because reinstatement was selectively directed on the lever previously associated with cocaine delivery. This finding extends prior data obtained in heroin-trained rats (Shaham and Stewart 1995) and replicates a study reported recently (Erb et al. 1996), suggesting that the stressor effect transcends the specific pharmacological actions of drugs of abuse. It remains, however, to determine empirically whether the same kind of stressor can also reinstate seeking for other drugs, such as nicotine and alcohol. Most importantly, under similar experimental conditions, the same stressor did not reinstate food-seeking behavior in previously food-trained rats. These findings are important for the interpretation of stressor-induced reinstatement of drug-seeking behavior.

The specificity of the stressor on cocaine-seeking appears not to result from differences in the instrumental situation used for cocaine and food reinforcement. First, in the present experiment, both cocaine- and food-trained rats were trained on a FR1 TO 20 s. Second, both groups of rats "consumed" their respective reinforcer during the TO period, in this way ensuring that the rats' exposure to the TO cue was similar. Third, both the baseline and the extinction curve observed in food-trained rats and in cocaine-trained rats confirmed that both groups of rats had learned to associate the active lever with their respective reinforcer. Extinction of responding shows also that, in both groups, those cues previously associated with cocaine delivery (e.g., TO cue) and which have been shown to acquire conditioned reinforcing properties (de Wit and Stewart 1981; Weissenborn et al. 1995) progressively lose them during extinction (see also Davis and Smith 1976). Finally, the extinction curve for cocaine-trained rats was similar to food-restricted rats, and dissimilar to the extinction curve for food-sated rats, suggesting that cocaine-trained rats, during extinction, could be in a motivational condition akin to a restriction state from the drug.

The inability of the stressor to reinstate food-seeking allows one to eliminate several putative explanations of stressor-induced reinstatement of drug-seeking behavior. In the present study and in a prior study (Shaham and Stewart 1995), levers extended immediately after the end of the intermittent footshock. Under these conditions, it is possible that rats could have accidentally learned that lever presses were contingently associated with the cessation of footshock delivery. According to this hypothesis, the reinstatement phenomenon would not reflect drug-seeking behavior per se but rather footshock avoidance. This hypothesis, however, is not valid because one should have observed a similar effect in food-trained rats. Particularly fatal to this hypothesis is the fact that, regardless of the current motivational state of the animal, an unconditioned suppression of responding was observed in food-trained rats following exposure to the stressor. This suppression was particularly evident when the basal responding was sufficiently high, ruling out the problem of a floor effect.

Recently, it has been suggested that a stressor, like a priming injection of the drug, could have a general facilitatory influence on appetitive behaviors by enhancing the response eliciting properties of the incentive cues present in the situation (Shaham and Stewart 1995). More specifically, according to this hypothesis, a stressed rat resumes responding on the drug-associated lever because the lever cues have recovered their previously extinguished incentive properties. Such a view predicts that the stressor should have a similar effect on other positively reinforced behaviors. In the present study footshock did not reinstate but rather suppressed responding on a lever previously associated with food, a point which is incompatible with such a hypothesis.

Finally, it is possible that, in drug-trained rats, the stressor generates an internal condition partly similar to the drug state. By re-establishing the *internal context* present during drug self-administration, the stressor could signal to the rat that the drug is again available upon its response (i.e., the end of extinction condition). This analysis is compatible with recent data showing that previously extinguished Pavlovian and instrumental conditioned responses are renewed by changing the external or internal context which prevailed during extinction (here, the term "context" is used to designate the background external and internal stimuli present during conditioning or extinction; for reviews, see Overton 1985; Bouton and Swartzentruber 1991; Bouton 1993, 1994). In support of this contention, it has been recently reported that intermittent footshock similar to those used in the present study induced "cocaine responses" in a drug discrimination paradigm (Mantsch et al. 1996). An additional argument comes from drug-induced reinstatement of drug-seeking behavior. It appears that the effectiveness of a test drug to reinstate drug-seeking is related to its discriminative similarity with the training drug. The greater the similarity, the more pronounced is the reinstatement effect (Slikker et al. 1984; Stewart and De Wit 1987). These data point to an important role in the reinstatement process for the internal cues produced by the reinstating event.

The view that a stressor mimics parts of the internal state induced by the drug has several advantages compared to a simple motivational account. First, it explains the specificity of the stressor to act on drug-seeking behavior by postulating common internal cues, and thus predicts that a stressor should not reinstate responding for a reinforcer of which the internal cues do not overlap with those of the stressor. The nature as well as the extent to which stress-induced internal cues are similar to drug cues remain unclear, however. For example, in a recent study, heroin- and stress-induced reinstatement of heroin-seeking behavior were differentially antagonized by dopaminergic drugs (Shaham and Stewart 1996). This result could argue against the view that stress- and drug-induced relapse depend on common internal cues. This argument should be tempered, however, because they could have arisen downstream from (or in parallel to) the neural site of DA action. In another recent study, it was reported that *spontaneous* withdrawal from chronic opiate intoxication reinstated heroin-seeking behavior after extinction (Shaham et al. 1996). Since the cues of drug withdrawal probably differ from the primary drug effects, these data could suggest the cues involved in reinstating drug-seeking behavior are generated by compensatory physiological processes which are known to be activated following drug action onto its receptors (Maldonado et al. 1996) and which could also be activated by a stressor. This issue warrants further studies.

The second advantage of the above hypothesis is that it is free from a theoretical difficulty that a simple motivational account cannot address. That is, a simple motivational mechanism does not explain how following stress, a rat, even strongly motivated, could actively engage in a behavior which, during extinction, it has learned was without consequence. Postulation of a mechanism which is based on an internal contextual change can address this question because a context appears to work as an "occasion setter" (or instrumental discriminative stimulus, see Rescorla 1992; Colwill 1993) – it sets the occasion when a particular response will be efficacious by predicting the availability of a reinforcer (Bouton 1993, 1994). It is important to note that the critical action of an occasion setter resides in its ability to *modulate* the behavioral expression of a previously established conditioned instrumental and Pavlovian association, and not in its ability to *elicit* directly conditioned responding (for an account of the distinction between modulation and elicitation, see Holland 1992; Rescorla 1992; Swartzentruber 1995).

In summary, the present findings bring some light on the behavioral mechanism by which an aversive stressor reinstates drug-seeking behavior: i) the stressor effect does not depend on the specific pharmacological actions of the drug; ii) the stressor effect is not related to a simple avoidance contingency; iii) the stressor effect does not appear to result from a general incentive motivational consequence. At present, the most promising explanation is to view the action of a stressor (and of the drug itself) as inducing an internal context which predicts drug availability.

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