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## The role of corticosterone in food deprivation-induced reinstatement of cocaine seeking in the rat

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**Abstract** *Rational and objectives:* Acute 1-day food deprivation stress reinstates heroin seeking in rats, but the generality of this effect to other drugs, and its underlying mechanisms, are largely unknown. Here we studied whether food deprivation would reinstate cocaine seeking and whether the stress hormone, corticosterone, is involved in this effect. *Methods:* Rats were trained to press a lever for cocaine for 10–12 days (0.5–1.0 mg/kg per infusion, IV, 4 h/day) and were then divided into four groups that underwent different manipulations of plasma corticosterone levels: (1) bilateral adrenalectomy (ADX) surgery, (2) ADX surgery+50-mg corticosterone pellets (ADX+P), (3) ADX surgery+50-mg corticosterone pellets+4-h access (0800–1200 hours) to corticosterone (50 µg/ml) dissolved in a drinking solution (ADX+P/W), or (4) sham surgery. Next, rats were given 7–12 days of extinction training (during which lever presses were not reinforced with cocaine), and after reaching an extinction criterion they were tested for reinstatement of cocaine seeking following exposure to 21 h of food deprivation. *Results:* Food deprivation was found to reinstate cocaine seeking in sham-operated rats, but not in rats in which circulating corticosterone was removed (ADX group). In addition, the effect of food deprivation on reinstatement of cocaine seeking was significantly attenuated in rats maintained on basal diurnal levels of corticosterone (ADX+P group). However, food deprivation reinstated cocaine seeking in rats with limited daily access to additional corticosterone in the drinking water

(ADX+P/W group). In this group, corticosterone levels were twice as high as the ADX+P group but were significantly lower than those of sham rats. *Conclusions:* The present data, together with previous work on footshock-induced reinstatement of drug seeking, suggest that corticosterone plays a permissive role in stress-induced reinstatement of cocaine seeking, yet its effects are not associated with the stressor-induced increases in plasma corticosterone levels.

**Keywords** Adrenalectomy · Cocaine · Corticosterone · Extinction · Food deprivation · Reinstatement · Relapse · Stress

### Introduction

It has been reported that stressful life events are associated with craving and relapse to drugs in humans (Kreek and Koob 1998; Sinha 2001). Using a reinstatement model of drug relapse (Stewart and de Wit 1987), several studies have shown that an intermittent footshock stressor reinstates drug seeking in rats, an effect mediated by central noradrenaline and extra-hypothalamic corticotropin-releasing factor (CRF) systems (Shaham et al. 2000; Le and Shaham 2002). Recently, we found that another environmental stressor, acute 1-day food deprivation, reliably reinstates heroin seeking (Shalev et al. 2000) via a leptin-dependent mechanism (Shalev et al. 2001, 2002). These data are in agreement with previous reports showing that 1 day of food deprivation increases sensitivity to lateral hypothalamus brain stimulation reward (BSR) (Carr and Simon 1984), and that 1 day of food restriction (about 30–40% of free-feeding daily ration) increases drug self-administration (Carroll and Meisch 1984) and provokes reinstatement of cocaine seeking (Carroll 1985). This latter effect, however, was only present if rats had experienced food deprivation during cocaine self-administration training. Other studies have shown that chronic food restriction (several weeks of 30–40% of free-feeding daily ration) increases sensitivity

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to drug-induced lowering of threshold for BSR (Carr 1996; Cabeza de Vaca and Carr 1998) and enhances the rewarding effects of opioid and stimulant drugs, as measured by the drug self-administration (Carroll and Meisch 1984) and the conditioned place preference (Gaiardi et al. 1987; Cabib et al. 2000) procedures.

Here we studied whether the effect of 1-day food deprivation on reinstatement, previously found with heroin-trained rats, generalizes to rats with a history of cocaine self-administration. We also determined whether the stress hormone, corticosterone, is involved in this effect. Food deprivation is known to activate the hypothalamic-pituitary-adrenal (HPA) axis, leading to enhanced secretion of corticosterone (Marinelli et al. 1996; Dallman et al. 1999). Previous studies have demonstrated an important role of corticosterone and glucocorticoid receptors in the initiation and maintenance of cocaine self-administration (Goeders and Guerin 1996; Piazza and Le Moal 1996, 1997; Goeders 1997), locomotor response to cocaine (Sarnyai 1998), and psychostimulants sensitization (Rivet et al. 1989; Marinelli et al. 1994, 1997; De Vries et al. 1996), but see (Badiani et al. 1995; Schmidt et al. 1999). In addition, adrenalectomy (ADX) or pharmacological blockade of corticosterone secretion attenuates the enhancement of the locomotor activating effects of opioid and stimulant drugs by food restriction (Deroche et al. 1995; Marinelli et al. 1996). Similar manipulations also attenuate the enhancement of cocaine, alcohol and heroin (females only) self-administration by chronic food restriction (Hansen et al. 1995; Campbell and Carroll 2001; Carroll et al. 2001).

In this report, we determined the effect of removing circulating corticosterone by ADX on food deprivation-induced reinstatement of cocaine seeking. ADX leads to alterations in CRF and ACTH secretion and disrupts energy balance, effects that are reversed by providing exogenous corticosterone replacement (Dallman et al. 1995; Schulkin et al. 1998). Thus, we also studied the effect of food deprivation on reinstatement in two groups of ADX rats. The first group was given corticosterone replacement via pellets to maintain basal diurnal levels of corticosterone (ADX+P). The second group was given corticosterone pellets and additional limited nocturnal access (4 h) to corticosterone dissolved in the drinking solution (ADX+P/W) in order to induce corticosterone levels that are higher than those of the ADX/P group during tests for reinstatement (see Marinelli et al. 1994; Badiani et al. 1995).

## Materials and methods

### Subjects and apparatus

Fifty-two male Long-Evans rats (Charles River, Raleigh, N.C., USA; 350–400 g) were used. Rats were transferred to the self-administration chambers 5–7 days following surgery for implantation of the intravenous (IV) catheters, where they were chronically housed under a reversed 12-h:12-h light-dark cycle (lights on 1000 hours). Water and food were freely available, except when

food deprivation conditions were applied (see below). Each chamber had two levers located 9 cm above the floor, but only one lever (an active, retractable lever) activated the infusion pump (Razel Sci., Stamford, Conn., USA). Presses on the other lever (an inactive, stationary, non-retractable lever) were recorded, but did not activate the pump. The body weight of the rats was measured daily. The experimental procedures followed the Guide for the Care and Use of Laboratory Animals (1996) and were approved by the local Animal Care and Use Committee.

### Surgery

Rats were implanted under anesthesia (a mixture of xylazine+ketamine, 10+100 mg/kg, IP) with IV Silastic catheters (Dow Corning, Midland, Mich., USA) into the right jugular vein as previously described (Shalev et al. 2000). After surgery, catheters were flushed every 24–48 h with sterile saline (0.05 ml). Bilateral ADX was rapidly (3–5 min) performed via the dorsal approach with the rats under isoflurane (Abbot Laboratories, North Chicago, Ill., USA) anesthesia, between 2200 and 2400 hours. A single 50-mg corticosterone or placebo pellet (21-day release; Innovative Research of America, Sarasota, Fla., USA) was implanted subcutaneously at the time of surgery. Sham-operated rats were exposed to the same procedure as the ADX rats, with the exception that the adrenals were not removed and pellets were not implanted. After surgery, ADX rats were given physiological saline in their drinking bottles.

### Drugs

Cocaine HCl (NIDA, USA) was dissolved in sterile saline. Corticosterone 21-sulfate (Sigma, St Louis, Mo., USA) was dissolved in saline (50 µg base/ml).

### Procedures

The experiment included three phases: self-administration training, extinction training and tests for reinstatement. Nine of the 52 subjects were excluded due to unstable and low cocaine intake (six rats; a mean of less than eight infusions per 2 h and high daily variations in lever-pressing behavior), unsuccessful adrenalectomy (two rats), or failure to reach the extinction criterion by the end of the study (one rat). One rat from the ADX+P/W group (see below) was excluded due to a very high drug intake (a mean higher than 40 infusions per 2 h over the last 3 days of training). The data described below refer only to the rats that were included in the analyses. Training was conducted for 10–12 days, two 2-h sessions/day that were separated by 4 h. The first session of each day started at the onset of the dark cycle. Each session began with the insertion of the active lever into the chamber and the illumination of a cue light above this lever for 30 s. A red houselight was turned on for the entire session. Each response on the active lever resulted in the delivery of 1.0 mg/kg (first 6–7 days) or 0.5 mg/kg (last 4–5 days) of cocaine and the initiation of a 20-s timeout period. During this period, lever presses were not reinforced, and the cue light was turned on. At the end of each session, the houselight was turned off and the active lever was retracted. The dose of cocaine was reduced to 50% of the initial training dose during the last 4–5 days of training in order to verify that rats acquired robust cocaine-taking behavior as indicated by an increase in responding to compensate for the decrease in the drug dose (see Yokel 1987).

Following training, rats were left undisturbed for 2 days. Rats were divided into four corticosterone manipulation groups: (1) adrenalectomy (ADX), (2) adrenalectomy with corticosterone pellet (ADX+P), (3) adrenalectomy with corticosterone pellet and 4-h access (0800–1200 hours) to corticosterone (50 µg/ml) dissolved in their drinking saline solution (ADX+P/W), or (4) sham surgery. The experimental manipulation of the ADX+P/W condition leads to plasma corticosterone levels that are significantly higher than those

of the ADX+P condition at the end of the period of limited access to corticosterone in the drinking solution (Marinelli et al. 1994; Badiani et al. 1995).

After surgery and 2 days of recovery, the extinction phase started. During the extinction phase, the conditions were identical to those of the training phase, with the exception that the cocaine syringes were removed. For the first 5–6 days, rats were given two 2-h extinction sessions/day. Subsequently, the number of sessions was reduced to one 2-h session/day, and rats were given two to six daily extinction sessions until they reached the extinction criterion of 20 responses or less on the previously active lever. At this point, rats were tested for food deprivation-induced reinstatement under extinction conditions. Food deprivation was accomplished by removing the food hoppers from the chambers for 21 h prior to the 2-h test session. The food hoppers were brought back to the chambers at the end of the test session.

#### Plasma corticosterone determination

At the end of the experiments, rats were rapidly decapitated during the first hour of the dark cycle (the time of the onset of the tests for reinstatement). Trunk blood was collected into heparinized vials, and plasma was removed and stored at  $-70^{\circ}\text{C}$ . Plasma samples were then analyzed for corticosterone levels by a radioimmunoassay (ICN Biomedicals, Costa Mesa, Calif., USA).

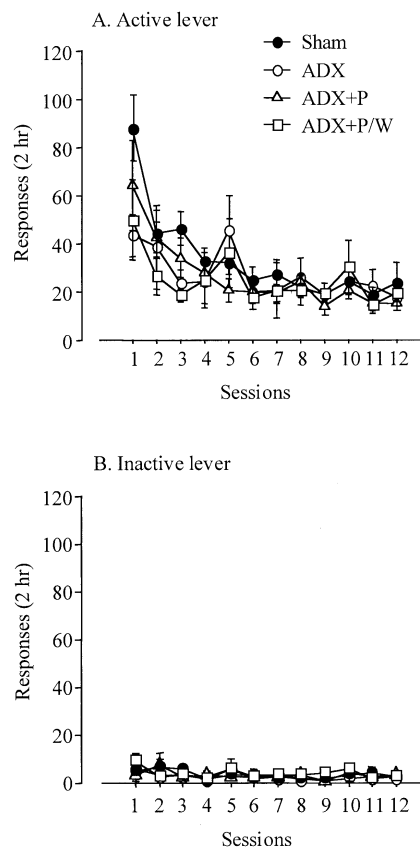
#### Statistical analyses

Data from the tests for reinstatement were analyzed separately for total non-reinforced responses on the previously active lever and responses on the inactive lever. The last day of extinction served as the baseline, satiated condition, against which the effect of food deprivation on lever-pressing behavior was compared. Data were analyzed with repeated measures ANOVA, using a between-subjects factor of Group (sham, ADX, ADX+P, ADX+P/W) and a within-subjects factor of Food deprivation (food deprived, food satiated). Significant effects were followed by post-hoc contrasts (Fisher's PLSD). Plasma corticosterone levels were analyzed with one-way ANOVA, using a between-subjects factor of Group (sham, ADX, ADX+P, ADX+P/W), followed by post-hoc comparisons. Significant differences are reported for  $P < 0.05$ .

## Results

### Training and extinction phases

Rats demonstrated reliable cocaine self-administration as indicated by the increase in responding when the unit dose was decreased from 1.0 to 0.5 mg/kg per infusion. The mean  $\pm$  SEM numbers of infusions per 2-h session on the last 3 days with a unit dose of 1.0 mg/kg in the sham, ADX, ADX+P, and ADX+P/W groups were  $16.6 \pm 2.3$ ,  $14.3 \pm 2.5$ ,  $15.6 \pm 1.7$  and  $16.9 \pm 3.2$ , respectively. The mean numbers of infusions per session on the last 3 days with a unit dose of 0.5 mg/kg in the sham, ADX, ADX+P, and ADX+P/W groups were  $25.8 \pm 3.4$ ,  $20.6 \pm 2.8$ ,  $25.4 \pm 2.4$  and  $32.1 \pm 2.2$ , respectively. The lever-pressing behavior of the rats during extinction is shown in Fig. 1. Responding on the previously active lever decreased significantly over sessions [ $F(11,418) = 12.1$ ,  $P < 0.001$ ], but there were no significant Group or Group by Session interaction effects. However, as can be seen in Fig. 1a, during the first session of extinction, the response rate on the active lever in the sham group was higher than in the ADX group.

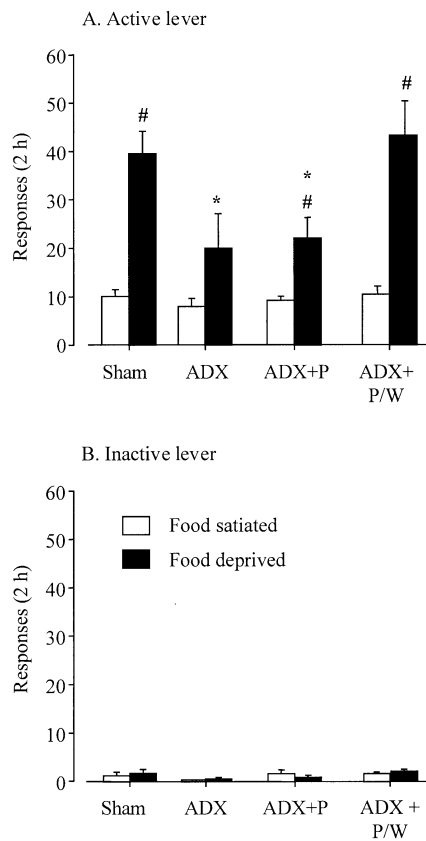


**Fig. 1** Lever-pressing behavior during extinction. **A** Mean  $\pm$  SEM number of responses on the previously active lever during the first 12 sessions of extinction of cocaine seeking in sham ( $n = 13$ ), ADX, ( $n = 10$ ), ADX+P, ( $n = 12$ ), and ADX+P/W ( $n = 7$ ) groups. *P* Corticosterone replacement pellets (50 mg, 21-day release) were implanted at the time of the ADX surgery. *P/W* Corticosterone-21 sulfate was dissolved (50  $\mu\text{g}/\text{ml}$ ) in saline used as the drinking solution for ADX rats following the surgery, and was presented daily to the rats for 4 h (0800–1200 hours). **B** Mean number of responses on the inactive lever during the first 12 sessions of extinction

Nonetheless, a separate analysis performed on the number of responses during the first session of extinction revealed that the Group effect was not significant. Finally, on the 3 days prior to the test for food deprivation-induced reinstatement the body weight gain was not significantly different among the experimental groups (mean  $\pm$  SEM weight gain/3 days of  $5.8 \pm 2.7$ ,  $7.1 \pm 1.9$ ,  $3.5 \pm 1.7$  and  $7.7 \pm 0.9$  g in the sham, ADX, ADX+P and ADX+P/W, respectively).

### Test for reinstatement

Food deprivation increased responding on the previously active lever, an effect attenuated by the ADX and ADX+P conditions but not by the ADX+P/W condition (Fig. 2a). The statistical analysis revealed a significant effect of Group [ $F(3,38) = 5.2$ ,  $P < 0.01$ ], Food deprivation [ $F(1,38) = 59.5$ ,  $P < 0.001$ ] and Group by Food deprivation [ $F(3,38) = 3.6$ ,  $P < 0.05$ ]. In all the groups, lever pressing on



**Fig. 2** Test for reinstatement. **A** Mean $\pm$ SEM number of responses on the previously active lever during the test for reinstatement of cocaine seeking following 21 h of food deprivation in sham ( $n=13$ ), ADX, ( $n=10$ ), ADX+P ( $n=12$ ) and ADX+P/W ( $n=7$ ) groups. *P* Corticosterone replacement pellets (50 mg, 21-day release) were implanted at the time of the ADX surgery. *P/W* Corticosterone-21 sulfate was dissolved (50  $\mu$ g/ml) in saline used as the drinking solution for ADX rats following the surgery, and was presented daily to the rats for 4 h (0800–1200 hours). **B** Mean number of responses on the inactive lever during testing. \*Different from the sham group,  $P<0.05$ . #Different from the food satiated condition within each group,  $P<0.05$

the inactive lever was low (Fig. 2b) and was not altered by the experimental manipulations. Although no statistically significant differences in drug taking during training were detected, an examination of the group means revealed a higher intake for the lower dose of cocaine in the ADX+P/W group (see above). To explore the possibility of an interaction between cocaine intake and food deprivation-induced reinstatement, we also conducted an analysis with the mean number of infusions per session on the last 3 days with a unit dose of 0.5 mg/kg as a covariate. The results of this analysis were similar to those found using ANOVA [Group  $F(3,37)=4.4$ ,  $P<0.01$ , Food deprivation  $F(1,37)=9.9$ ,  $P<0.01$  and Group by Food deprivation  $F(3,37)=3.6$ ,  $P<0.05$ ], suggesting that cocaine intake during the last 3 days of training cannot explain the data obtained during tests for reinstatement. In addition, because responding in the ADX group was lower than that of the Sham group on session 1 of extinction, an additional analysis was performed using

active lever responses during this session as a covariate. This ANCOVA revealed significant effects of Group [ $F(3,37)=4.6$ ,  $P<0.01$ ], Food deprivation [ $F(1,37)=11.9$ ,  $P<0.01$ ] and Group by Food deprivation [ $F(3,37)=3.2$ ,  $P<0.05$ ], suggesting that responding during session 1 of extinction cannot account for the data obtained during tests for reinstatement.

No significant group differences were observed for body weight loss following 1 day of food deprivation (mean $\pm$ SEM body weight loss in the sham, ADX, ADX+P, and ADX+P/W groups was 23.3 $\pm$ 1.2, 23.1 $\pm$ 1.9, 20.6 $\pm$ 2.6, and 24.0 $\pm$ 2.5 g, respectively). Finally, ADX significantly decreased plasma corticosterone levels to values that were below the detection limit of the assay (10 ng/ml). The addition of corticosterone via pellets to ADX rats significantly increased ( $P<0.05$ ) plasma levels to basal diurnal values typically observed in the middle of the light phase (mean $\pm$ SEM: 25.4 $\pm$ 7.0 ng/ml) (see Badiani et al. 1995). These basal values were significantly lower ( $P<0.01$ ) than those of the ADX+P/W rats (51.4 $\pm$ 3.8 ng/ml). Corticosterone levels in all the corticosterone-manipulated rats were significantly lower than those of the sham rats (180.3 $\pm$ 20.2 ng/ml; all  $P$  values $<0.01$ ), in which the hormone levels reflect the diurnal peak at the onset of the dark cycle.

## Discussion

We found that acute, 1-day food deprivation reinstates cocaine seeking, an observation that extends our findings with heroin-trained rats (Shalev et al. 2000). We also found that corticosterone is involved in food deprivation-induced reinstatement of cocaine seeking. The effect of food deprivation was blocked by ADX and providing exogenous corticosterone to ADX rats to maintain basal diurnal levels of the hormone (ADX+P group) did not restore this effect. However, food deprivation reinstated cocaine seeking in rats with limited 4-h daily access to additional corticosterone replacement in the drinking solution (ADX+P/W group). In this group, corticosterone levels were twice as high as the ADX+P group but were significantly lower than those of sham rats. These data suggest that corticosterone plays a permissive/modulatory role in stress-induced reinstatement of cocaine seeking, yet its effects are not associated with the stressor-induced increases in plasma corticosterone levels. Our finding extends previous data on the role of corticosterone in the effect of chronic food restriction on drug-induced locomotor activity (Piazza and Le Moal 1996) and drug self-administration (Hansen et al. 1995; Campbell and Carroll 2001; Carroll et al. 2001). In contrast, several reports have shown that corticosterone is not involved in the effect of chronic food restriction on BSR (Abrahamsen et al. 1995; Abrahamsen and Carr 1996). These different findings may suggest that corticosterone is uniquely involved in the effect of food restriction on drug-controlled behavior.

The finding that acute food deprivation reinstates cocaine seeking extends an earlier report on the effect of 1

day of food restriction (30–40% of free-feeding) on reinstatement of cocaine seeking (Carroll 1985). In this earlier study, acute food restriction reinstated cocaine seeking only in rats with a history of exposure to this condition during drug self-administration. In the present study, we found, however, that 1 day of food deprivation reinstates cocaine seeking in rats that were not deprived during training. The more severe food deprivation in our experiment may account for these different results. Another finding in our study is that group differences were not observed for lever-pressing behavior during the extinction phase. These data are in agreement with previous reports on the lack of effect of the ADX or ADX+P conditions on extinction responding in rats previously trained to self-administer cocaine (Erb et al. 1998), heroin (Shaham et al. 1997), alcohol (Le et al. 2000) or non-drug reinforcers (Mason 1983; but see Micco et al. 1979; Thomas and Papini 2001).

Several studies have explored the role of corticosterone in reinstatement of cocaine seeking, but its role in this behavior is not clear. Deroche et al. (1997) found that corticosterone administration reinstates cocaine seeking following extinction. However, ADX or administration of ketoconazole, an anti-fungal agent that also blocks corticosterone synthesis, had no effect on reinstatement induced by priming injections of cocaine (Erb et al. 1998; Mantsch and Goeders 1999b). Mantsch and Goeders (1999a) found that ketoconazole attenuates footshock stress-induced reinstatement of cocaine seeking. However, ketoconazole completely blocked footshock-induced reinstatement but only partially attenuated footshock-induced rise in corticosterone. This discrepancy suggests that some non-specific effects of ketoconazole, other than its effect on corticosterone, contribute to its effect on footshock-induced reinstatement. Furthermore, Erb et al. (1998) found that while ADX attenuates footshock stress-induced reinstatement of cocaine seeking, this effect of ADX was reversed by corticosterone replacement via pellets. These data suggest that while a certain level of corticosterone is necessary for footshock to induce cocaine seeking, the increase in corticosterone release induced by this stressor does not play a role in its effect on reinstatement.

In parallel to the report of Erb et al. (1998) with a footshock stressor, the present data suggest a permissive/modulatory role for corticosterone in reinstatement of cocaine seeking induced by food deprivation. Food deprivation is known to increase plasma corticosterone levels in rats (Dallman et al. 1999). Our findings, however, imply that a certain “threshold” level of plasma corticosterone is required for food deprivation to induce reinstatement of cocaine seeking, but this level is much lower than the plasma corticosterone levels during food deprivation (Dallman et al. 1999) or during the onset of the dark cycle under satiated conditions (present data). Interestingly, the plasma levels of corticosterone induced by the CORT+P/W condition in the present study were similar to the levels of the hormone following the pellet replacement treatment in the study of Erb et al. (1998).

A possible explanation for the effect of ADX on food deprivation-induced reinstatement of cocaine seeking is that this manipulation suppresses feeding behavior and/or a state of hunger in the absence of food. As mentioned above, however, on the 3 days prior to food deprivation the body weight gain was not significantly different among the experimental groups. In addition, we recently found that ADX has no effect of food deprivation-induced reinstatement of heroin seeking (U. Shalev, unpublished observations). Thus, it is unlikely that hunger per se can account for the effect of ADX on food deprivation-induced reinstatement of cocaine seeking. In addition, based on the somewhat lower response rate of the ADX rats on session 1 of extinction, it is possible that the effect of ADX on food deprivation-induced reinstatement of cocaine seeking is due to a non-specific effect of this manipulation on instrumental responding. However, it is unlikely that performance deficits can explain the present data. First, analysis of the reinstatement data with the response rate on session 1 of extinction as a covariate (ANCOVA) suggests that response rate during this session does not account for the data obtained during tests for food deprivation-induced reinstatement (see Results). Second, as mentioned above, ADX had no effect on food deprivation-induced reinstatement in heroin-trained rats. Third, in previous studies it was found that ADX has no effect on resistance to extinction and on footshock-induced reinstatement of alcohol or heroin seeking (Shaham et al. 1997; Le et al. 2000).

Finally, we speculate that the modulatory effect of corticosterone on food deprivation-induced reinstatement is mediated by the type-II glucocorticoid receptor. There are two types of receptor systems for corticosterone in the brain: type-I, mineralocorticoid receptors (MR) with high affinity for corticosterone, and type-II glucocorticoid receptors (GR) with lower affinity but higher specificity for corticosterone (Hollenberg et al. 1985; Arriza et al. 1987). The diurnal basal levels of corticosterone that were induced by the pellet treatment could saturate the MR but scarcely occupy the GR (De Kloet and Reul 1987). Thus, we suggest that the higher levels of the hormone induced by the additional access to corticosterone in the drinking solution in our study, or by the corticosterone pellet replacement treatment in the study of Erb et al. (1998), resulted in the recruitment of sufficient GR to allow for the expression of stress-induced reinstatement of cocaine seeking.

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