Corticosterone Facilitates the Acquisition of Cocaine Self-Administration in Rats: Opposite Effects of the Type II Glucocorticoid Receptor Agonist Dexamethasone

JOHN R. MANTSCH, DAVID SAPHIER and NICK E. GOEDERS

Departments of Pharmacology and Therapeutics (J.R.M., D.S., N.E.G.) and Psychiatry (N.E.G.), Louisiana State University Medical Center, Shreveport, Louisiana

Accepted for publication May 18, 1998

ABSTRACT

The effect of corticosterone on the acquisition of cocaine-seeking behavior was investigated in rats using ascending dose-response curves for intravenous cocaine self-administration. Rats pretreated daily with corticosterone (2.0 mg/kg i.p.) acquired cocaine self-administration at a lower dose compared with vehicle-treated controls. In contrast, daily corticosterone pretreatment did not alter food-maintained responding. Cocaine self-administration was not affected by the type I (mineralocorticoid) receptor agonist, aldosterone (100 μg/kg). However, rats treated with the type II (glucocorticoid) receptor agonist, dexamethasone (10 or 100 μg/kg) did not acquire self-administration at any dose tested. The 100 μg/kg dose of dexamethasone attenuated food-reinforced behavior and decreased body weight, but these effects were not observed with the 10 μg/kg dose. Dexamethasone dose-dependently attenuated the plasma corticosterone response to self-administered infusions or intraperitoneal injections of cocaine, indicating that the ability of dexamethasone to block cocaine-induced corticosterone secretion may have contributed to its effects on self-administration. Administration of aldosterone (100 μg/kg) together with 10 μg/kg dexamethasone restored self-administration to the level of vehicle-treated rats, suggesting that type I receptor occupation by corticosterone may be required for the acquisition of this behavior. These results indicate that stress-induced corticosterone secretion may provide a substrate through which stressors interact with cocaine reinforcement. Additionally, the finding that dexamethasone blocks the acquisition of cocaine self-administration may be relevant to the development of novel approaches to the treatment of cocaine addiction.

The characterization of factors that contribute to the onset of compulsive drug-seeking behavior is crucial to the formulation of effective treatment strategies for drug abuse. It is estimated that out of the total population of individuals who initially try cocaine, only 10% to 15% will eventually become addicted (Gawin, 1991). Others are able to use cocaine casually over extended periods of time without ever progressing to compulsive use (Siegel, 1984). Although there are no reliable predictors of individual vulnerability to cocaine addiction in humans (Gawin, 1991), it is likely that environmental variables are critical determinants. Exposure to stressful environmental stimuli has been reported to enhance individual sensitivity to the behavioral (Antelman et al., 1980; MacLennan and Maier, 1983) and neurochemical (Sorg and Kalivas, 1991) effects of psychostimulants in rats. These observations have been extended to include the effects of stressors on the reinforcing properties of psychostimulants. It has been demonstrated that isolation housing (Schenk et al., 1987), repeated tailpinch (Piazza et al., 1990), social stress (Miczek and Mutschler, 1996), daily exposure to uncontrollable electric footshock (Goeders and Guerin, 1994), and the “stress” of witnessing another rat being subjected to shock (Ramsey and Van Ree, 1993) all facilitate the acquisition of intravenous cocaine or amphetamine self-administration in rats. In consideration of these findings, it can be hypothesized that the interaction between stressors and cocaine occurs as a result of the activation of one or more common pharmacological effector systems.

The HPA axis is commonly activated by cocaine and stressors. Acute cocaine administration stimulates the release of β-endorphin, ACTH and corticosterone in rats (Moldow and Fischman, 1987). Similar to the stressor-induced secretion of ACTH and corticosterone (Rivier and Plotsky, 1986), this response appears to be dependent on CRF (Rivier and Vale, 1987). Cocaine also stimulates the release of cortisol in hu-
Corticosterone, Dexamethasone and Cocaine Self-Administration

Materials and Methods

Subjects. Ninety adult, male Wistar rats (Harlan Sprague Dawley, Indianapolis, IN) 80 to 100 days old at the start of the experiments were used. Fifty rats were used to investigate the effects of daily drug pretreatments on ascending dose-response curves for intravenous cocaine self-administration. The remaining 40 rats were used to determine the effects of these pretreatments on the plasma corticosterone response to intraperitoneal injections of cocaine. All rats were housed individually in cages equipped with a laminar flow unit and air filter in a temperature- and humidity-controlled, AAA-type II GR in the effects of corticosterone on self-administration in rats. The potential roles of type I MR and MR agonist DEX.

Experimental apparatus. Modified plastic and stainless steel operant conditioning chambers contained in sound-attenuating cubicles (Med-Associates, Lafayette, IN) were used for the self-administration experiments. The operant chambers were equipped with two retractable response levers with stimulus lights located above each lever. One lever was mounted on the front wall of the chamber next to a food pellet dispenser. The other lever was mounted in the center of the back wall. The cubicles were also equipped with an exhaust fan that supplied ventilation and white noise to mask extraneous sound. Programming and data collection were performed using Med-PC software and an IBM-compatible personal computer and interface system (Med-Associates).

Measurement of locomotor responses to novelty and cocaine. Rats were initially screened for their locomotor responses to a novel environment and to an acute intraperitoneal injection of cocaine. It has been reported that the behavioral responses to novelty of individual rats can predict their propensity to self-administer amphetamine (Piazza et al., 1989). To control for this potential source of variability, rats were assigned to the drug treatment groups so that the mean locomotor responses to novelty and cocaine did not significantly differ between groups. Locomotor testing was conducted in 48 cm long × 25 cm wide Plexiglas chambers contained within a photocell apparatus (Coulbourn, Allentown, PA) consisting of two photocell beams evenly spaced across the length of each chamber. The number of individual breaks of the front and back beams, consecutive beam breaks (crossovers), and total locomotor activity was measured immediately for 60 min. On day 2, the locomotor response to an injection of saline (0.9% NaCl, 1 ml/kg i.p.) was recorded after a 60-min acclimation period. On day 3, the locomotor response to an acute injection of cocaine HCl (15 mg/kg i.p., National Institute on Drug Abuse) was recorded after acclimation.

Food-reinforced responding. Rats were initially trained to respond under a fixed-ratio 1 (FR1) schedule of food reinforcement during daily sessions. At the start of these sessions, the food (front) lever was extended and the corresponding stimulus light was illuminated. Each response on the food lever resulted in the presentation of a single food pellet (45 mg) into the dispenser. This was immediately followed by a 25-sec timeout period during which the lever was retracted and the stimulus light extinguished. Sessions
were terminated after 60 min or when 100 food pellets were delivered. Once stable patterns of food-reinforced responding were observed (i.e., 100 food pellets obtained in 10 min or less for ~1 week), food sessions were only conducted once weekly to control for potential nonspecific effects of the drug treatments on operant behavior.

**Acquisition of intravenous cocaine self-administration.** The acquisition of intravenous cocaine self-administration was determined using an ascending dose-response curve as previously reported (Goeders and Guerin, 1994). Rats were allowed to self-administer cocaine or vehicle (heparinized 0.9% NaCl bacteriostatic saline) under an FR1 schedule of reinforcement during daily 1-hr sessions. During these sessions, only the drug (back) lever was extended and the corresponding stimulus light illuminated. Each depression of the lever resulted in an intravenous infusion (200 µl over 5.6 sec) of cocaine or vehicle solution followed by a 20-sec timeout period during which the lever was retracted and the stimulus light extinguished. During the initial 2 weeks of the study, a base line for responding on the drug lever was established with only vehicle available for self-administration. This was followed by the initiation of the daily drug treatment regimen (see below). Drugs were administered daily for 2 weeks before the determination of the dose-response curve. During this 2-week period, no behavioral experiments were performed. These treatments persisted daily throughout the course of the experiment. Rats were then tested for the acquisition of intravenous cocaine self-administration using an ascending cocaine dose-response curve. During dose-response testing, food sessions were conducted on Mondays and self-administration sessions were conducted on Tuesday through Friday. Control rates of responding were established with only vehicle available for self-administration during the first week. Rats were then tested with a very low dose of cocaine (0.03125 mg/kg/inf) that is not normally self-administered by rats in our laboratory. This dose was doubled weekly so that each rat was tested with 0.0, 0.03125, 0.0625, 0.125, 0.25, 0.5, and 1.0 mg/kg/inf cocaine. Subsequent to dose-response determination in each rat, cocaine self-administration was extinguished by replacing the cocaine solution with vehicle for 4 consecutive sessions.

**Drug treatments.** Rats were divided into 6 treatment groups. All treatments were administered daily, starting 2 weeks before dose-response testing and continuing through the remainder of the experiment. Rats received daily i.p. injections of VEH (bacteriostatic saline 0.9% NaCl, n = 10), CORT (2.0 mg/kg, suspended in saline, n = 7; Sigma, St. Louis), ALDO (100 µg/kg dissolved in saline, n = 7; Sigma), DEX (10 or 100 µg/kg dissolved in saline, n = 6 for each; Sigma) or a combination of DEX and ALDO (10 µg/kg DEX and 100 µg/kg ALDO, n = 6). During dose-response testing, the presession treatment time for each of the drugs was 15 min except for DEX, which was administered 60 min before the sessions.

**Plasma corticosterone responses to self-administered infusions of cocaine.** The plasma corticosterone response to single self-administered infusions of cocaine was determined in some rats as follows. Rats were placed in the self-administration chambers as described above. After the self-administration of single infusions of vehicle, 0.0625, 0.25 or 1.0 mg/kg/inf cocaine, the session was terminated and blood for plasma corticosterone determination was obtained 15 min postinfusion from the catheter (when possible) or from the tail vein under light methohexitol sodium (5.0 mg/kg i.v.) anesthesia (Goeders and Guerin, 1996b). Blood (~500 µl) was collected into heparinized tubes and placed on ice. Blood was centrifuged to allow separation of plasma, which was collected and frozen at −20°C until needed. Plasma corticosterone was measured using the Immunochem™ Double Antibody Corticosterone assay kit (ICN Biomedical, Irvine, CA).

**Plasma corticosterone responses to intraperitoneal injections of cocaine.** The effects of drug treatments on the plasma corticosterone response to i.p. injections of cocaine was measured in an additional 40 rats. As above, these rats received daily i.p. injections of VEH, CORT, ALDO or one of the two doses of DEX (n = 8/group). For these experiments, blood for plasma corticosterone determination was obtained from the tail vein of conscious rats after 2 weeks of habituation to the blood sampling procedure as described previously (Simar et al., 1997). Rats were wrapped in a hand towel, and 1 to 2 mm was cut from the tip of the tail. Corticosterone was measured as described above. All blood sampling was performed between 9:00 a.m. and noon. On the first day of drug treatments (acute) the corticosterone response to an i.p. injection of 20 mg/kg cocaine was determined 20 min postinjection. This was followed by 2 weeks of drug treatments, during which no sampling was performed. A dose-response curve for the plasma corticosterone response to i.p. injections of cocaine after chronic drug treatments was then determined. Rats were tested for their corticosterone responses to 0.0, 5.0, 10.0 and 20.0 mg/kg cocaine (i.p., 20 min postinjection). The sequence of cocaine dosing was randomized and blood samples were obtained no more than twice weekly for 3 weeks. The plasma corticosterone response to 20 mg/kg cocaine was also tested after a 3-day treatment washout to determine the persistence of the effects of the drug treatments on the corticosterone response to cocaine. All drugs were administered 45 min before cocaine injections except for DEX, which was administered 90 min before cocaine. These pretreatment times were chosen so that they would correspond with points in the middle of the 60-min self-administration sessions from the previous experiments. At the end of the experiment, these rats were killed by decapitation and thymus and adrenals were dissected so that their weights could be determined.

**Statistical analysis.** Data collected during the self-administration experiments included the mean number of infusions self-administered per session for each dose of cocaine and the mean rates of food-reinforced responding during the weekly food sessions. Self-administration sessions were conducted Tuesday through Friday, and the means were determined from data from the final 3 sessions (i.e., Wednesday through Friday) for each dose. The acquisition of cocaine self-administration was defined as the lowest dose at which the mean number infusions/session was significantly greater than the base-line measurements (P < .05). The significance of the differences between drug and vehicle treatment conditions and between doses of cocaine within treatment groups was determined using repeated measures analysis of variance (ANOVA). Post-hoc analyses were performed using the Fisher’s Protected Least Significant Difference test (Fisher’s PLSD). The significance of differences in the mean corticosterone responses (ng/ml) to cocaine were determined as described above. One-way ANOVA was used to determine any significance of differences in body, thymus and adrenal weights between groups.

**Results**

The 6 treatment groups did not significantly differ in their mean body weights or locomotor responses to novelty or acute injections of cocaine (15 mg/kg i.p.) at the start of the experiment (data not shown).

**Effects on food-reinforced responding.** Table 1 shows the base-line rates of food-reinforced responding (responses/min ± S.E.M.) and the effects of the various treatments on food reinforcement at timepoints corresponding to the doses of cocaine that were available for self-administration each week. A significant effect of the 100 µg/kg dose of DEX on food-reinforced responding was observed over time (Time effect, F(7,173) = 5.861, P < .0001; Time × Treatment interaction, F(7,2) = 4.103, P < .0001). The rate of responding was significantly decreased from base line at the timepoints corresponding to weeks during which 0.25 and 1.0 mg/kg/inf cocaine were available for self-administration (P < .05 for each). At the 1.0 mg/kg/inf timepoint, the response rate in 100 µg/kg DEX-treated rats was also significantly less than in VEH controls (P < .05). This effect on food-reinforcement...
was not apparent in rats treated with the 10 μg/kg dose of DEX. No other significant differences in food-reinforced responding within or between treatment groups were observed.

Effects on the acquisition of intravenous cocaine self-administration. The effect of daily pretreatment with CORT (2.0 mg/kg i.p.) on the ascending dose-response curve for iv cocaine self-administration is illustrated in figure 1. The acquisition of cocaine self-administration by both VEH- and CORT-treated rats was indicated by a significant effect of dose [Dose effect, F(6,109) = 6.41, P < .0001]. CORT-treated rats acquired cocaine self-administration at a lower dose (0.0625 mg/kg/infusion; P < .05 vs. base line) than VEH-treated controls (0.125 mg/kg/infusion; P < .0001). A significant treatment effect of CORT was also observed [Treatment effect, F(1,109) = 5.699, P < .05]. The mean number of infusions/session at the 0.0625 mg/kg/infusion dose of cocaine in CORT-treated rats was significantly greater than in VEH-treated rats (P < .05). The effects of daily pretreatments with ALDO (100 μg/kg i.p.) or DEX (10 or 100 μg/kg i.p.) are shown in figure 2A. In ALDO-treated rats, a significant effect of dose was observed [Dose effect, F(6,114) = 3.495, P < .001]. Similar to the VEH controls, rats from the ALDO group acquired cocaine self-administration at the 0.125 mg/kg/infusion dose (P < .05). No significant differences between ALDO- and VEH-treated rats were observed. Although there was no significant effect of treatment in rats treated daily with the 10 or 100 μg/kg doses of DEX compared with VEH, a significant interaction between dose and treatment was observed [Treatment × Dose, F(2,6) = 2.350, P < .05]. In contrast to VEH-treated rats, significant acquisition of cocaine self-administration did not occur at any dose of cocaine tested in rats treated with either dose of DEX. A small but statistically non-significant trend toward acquisition was observed in the 10 μg/kg DEX group at the 0.5 mg/kg/infusion dose of cocaine. Figure 2B shows the effects of coadministration of 100 μg/kg ALDO on the 10 μg/kg DEX-induced suppression of cocaine self-administration. No significant differences in self-administration were observed at any dose between rats treated with the DEX/ALDO combination and those treated with 10 μg/kg dose of DEX alone. However, a significant effect of dose was observed [Dose effect, F(1,83) = 3.498, P < .01]. In contrast to rats treated with 10 μg/kg DEX alone, rats treated with the DEX/ALDO combination did acquire self-administration at the 0.125 mg/kg/infusion dose as defined by a significantly greater number of infusions/session at this dose compared with base line (P < .05). Significant differences from base line were also observed at the 0.25 and 0.5 mg/kg/infusion doses of cocaine in this group.

Extinction of cocaine-reinforced responding. In VEH-treated rats, replacement of the cocaine solution with saline for 4 consecutive days after the determination of the dose-response curves produced a pattern of extinction characterized by a high level of responding on day 1 (51.63 ± 6.57 responses per session) followed by a progressive decline in responding from days 2 to 4. On day 4, the mean number of infusions per session (15.13 ± 3.16) approached that observed under base-line conditions. Similar extinction patterns were observed in the CORT and ALDO treatment groups (data not shown). During extinction, there was a significant effect of day [F(3,139) = 34.18, P < .0001] and an interaction between extinction day and drug treatment [Day × Treatment, F(3,4) = 3.20, P < .01]. On day 1, the mean numbers of responses in the 10 and 100 μg DEX groups (24.75 ± 11.35 and 18.4 ± 6.2 respectively) were significantly less than the number of responses in VEH-treated rats (P < .05 for each). No significant differences in responding were observed between groups on extinction days 2 through 4.

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**TABLE 1**

Rates of food-reinforced responding (responses/min ± S.E.M.) in drug treatment groups during food sessions corresponding to the weeks during which the various doses of cocaine were available for self-administration.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Base line</th>
<th>0.0</th>
<th>0.03125</th>
<th>0.0625</th>
<th>0.125</th>
<th>0.25</th>
<th>0.5</th>
<th>1.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEH</td>
<td>16.71 ± 1.38</td>
<td>16.18 ± 1.65</td>
<td>17.10 ± 1.82</td>
<td>16.02 ± 1.75</td>
<td>17.18 ± 1.69</td>
<td>17.29 ± 1.26</td>
<td>16.80 ± 1.55</td>
<td>15.50 ± 1.04</td>
</tr>
<tr>
<td>CORT</td>
<td>17.76 ± 1.15</td>
<td>17.55 ± 1.59</td>
<td>17.53 ± 1.22</td>
<td>18.27 ± 1.31</td>
<td>18.62 ± 1.28</td>
<td>19.35 ± 1.09</td>
<td>18.18 ± 1.17</td>
<td>18.90 ± 1.66</td>
</tr>
<tr>
<td>ALDO</td>
<td>16.08 ± 0.63</td>
<td>15.41 ± 0.95</td>
<td>15.38 ± 1.09</td>
<td>16.60 ± 0.86</td>
<td>16.05 ± 0.98</td>
<td>16.01 ± 0.89</td>
<td>17.41 ± 1.98</td>
<td>15.73 ± 1.98</td>
</tr>
<tr>
<td>DEX (10 μg/kg)</td>
<td>19.02 ± 1.23</td>
<td>18.94 ± 1.38</td>
<td>15.35 ± 2.39</td>
<td>17.13 ± 1.40</td>
<td>15.53 ± 1.84</td>
<td>17.96 ± 2.39</td>
<td>16.02 ± 1.73</td>
<td>14.01 ± 1.60</td>
</tr>
<tr>
<td>DEX (100 μg/kg)</td>
<td>18.91 ± 1.02</td>
<td>19.42 ± 2.37</td>
<td>16.52 ± 1.68</td>
<td>14.67 ± 3.27</td>
<td>13.49 ± 3.25</td>
<td>10.64 ± 3.59</td>
<td>11.52 ± 3.04</td>
<td>8.36 ± 3.15.b</td>
</tr>
<tr>
<td>DEX + ALDO</td>
<td>15.50 ± 1.37</td>
<td>15.03 ± 1.05</td>
<td>14.81 ± 0.93</td>
<td>15.56 ± 1.01</td>
<td>13.86 ± 1.93</td>
<td>12.87 ± 2.28</td>
<td>14.20 ± 2.50</td>
<td>13.09 ± 1.16</td>
</tr>
</tbody>
</table>

* P < .05 vs. VEH control.
  b P < .05 vs. base line.

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**Fig. 1.** Ascending dose-response curves for intravenous cocaine self-administration in rats pretreated daily with CORT (2.0 mg/kg; n = 7) or VEH (n = 10). Data points represent the mean number of infusions per session (± S.E.M.) for each dose of cocaine. The significance of the differences between treatments or doses was determined using repeated measures analysis of variance followed by post-hoc testing using the Fisher’s Least Significant Difference test. The acquisition of cocaine self-administration was defined by the lowest dose of cocaine in each treatment group at which the mean number of infusions/session was significantly greater than base line responding. * P < .05 vs. base line.

**** P < .05 CORT vs. VEH.
Corticosterone responses to self-administered infusions of cocaine. The effects of daily pretreatments with VEH, DEX (10 or 100 µg/kg) or ALDO (100 µg/kg) on the plasma corticosterone response to single self-administered iv infusions of cocaine are presented in figure 3. Despite a trend toward increases in plasma corticosterone with increasing doses of cocaine in VEH-treated rats, no significant effect of dose was observed. However, there was a highly significant effect of treatment \[F(3,67) = 61.790, \text{P} < .0001\]. DEX dose-dependently suppressed the plasma corticosterone responses to infusions of saline and at the 0.0625, 0.25, and 1.0 mg/kg/infusion doses of cocaine. Significant decreases compared with VEH-treated controls were observed in both the 10 µg/kg (\text{P} < .05 for all) and 100 µg/kg (\text{P} < .01 for all) treatment groups. In the 100 µg/kg DEX group, plasma corticosterone was almost unmeasurable (i.e., <5 ng/ml) after the infusion of each dose of cocaine. Coadministration of ALDO (100 µg/kg) with 10 µg/kg DEX failed to reverse the inhibitory effects of DEX on the plasma corticosterone response to cocaine.

Corticosterone responses to intraperitoneal injections of cocaine. The effects of daily pretreatments with VEH, CORT, ALDO, and DEX (10 and 100 µg/kg) on the plasma corticosterone response to i.p. injections of cocaine are illustrated in figures 4 and 5. Figure 4 shows the effects of chronic treatment with these drugs on the plasma corticosterone response to a randomized sequence of i.p. injections with various doses of cocaine (0, 5, 10, and 20 mg/kg). Significant effects of cocaine dose (Dose effect, \(F(3,146) = 2.916, \text{P} < .05\)) and drug treatment (Treatment effect, \(F(4,146) = 80.280, \text{P} < .0001\)) were observed. In VEH-treated rats, cocaine produced a dose-dependent increase in plasma corticosterone with significant increases compared with the 0 mg/kg dose after the administration of 10 (\text{P} < .01) and 20 (\text{P} < .001) mg/kg.
The corticosterone responses to i.p. injections of 20 mg/kg cocaine after acute and chronic treatment with VEH, CORT, ALDO, and DEX (both doses) and after a 3-day treatment washout period are depicted in figure 5. Significant differences between treatment groups [F(4,97) = 60.658, P < .0001] and between 20 mg/kg cocaine dosing conditions [F(2,97) = 5.171, P < .05] were observed, as was a significant interaction between treatment and dosing conditions [F(4,2) = 3.536, P < .01]. No significant differences in the plasma corticosterone response to 20 mg/kg cocaine (i.p.) were observed after acute or chronic treatment with VEH, CORT, or ALDO, or after a 3-day washout of these daily treatments. In rats treated with 100 μg/kg DEX, the plasma corticosterone response to 20 mg/kg cocaine after a single treatment with DEX was significantly greater than the response after chronic (at least 2 weeks) DEX administration (P < .01). The plasma corticosterone response to 20 mg/kg cocaine was not restored after the termination of treatment for 3 consecutive days. Under all dosing conditions, the corticosterone response to cocaine in 100 μg/kg DEX-treated rats was significantly less than in VEH-treated rats (P < .001). No differences between acute and chronic treatment with the 10 μg/kg dose of DEX were observed in the plasma corticosterone responses to 20 mg/kg cocaine. In both cases, the corticosterone responses were significantly less than those observed in VEH-treated controls (P < .001). However, the plasma corticosterone response to cocaine in this group was almost completely restored to concentrations observed in VEH-treated rats after a 3-day washout period during which DEX treatment was discontinued. The response after DEX “washout” was significantly greater than that observed after either acute or chronic treatment with 10 μg/kg DEX (P < .0001 for both). However, the corticosterone response to cocaine was still significantly less than that displayed in VEH-treated rats after the same washout period (P < .05).

**Effects on body, thymus and adrenal weights.** The effects of the various treatments on mean body, thymus and adrenal weights and on the ratios of adrenal and thymus to body weight at the end of the experiment are represented in table 2. Significant effects of treatments were observed on body weight [F(4,39) = 17.066, P < .0001], thymus weights [F(4,39) = 114.486, P < .0001], adrenal weight [F(4,39) = 18.848, P < .0001], the ratio of thymus/body weights [F(4,35) = 109.951, P < .0001] and the ratio of adrenal/body weight [F(4,39) = 13.516, P < .0001]. Significant decreases in thymus weight (P < .05) and thymus/body weight (P < .01) were observed in CORT-treated rats compared with VEH-treated controls. An inverse proportion exists between the activation of type II receptors in the thymus and thymus weight, making this variable a useful measure of peripheral type II receptor occupancy (Akana et al., 1985). CORT treatment did not significantly affect total body or adrenal weights. Significant dose-related effects of DEX on all of the above measures were observed. Daily administration of 100, but not 10, μg/kg DEX resulted in a significant decrease in body weight at the end of the experiment compared with VEH-treated controls (P < .0001). Significant reductions in thymus weight and thymus/body weight were also observed in rats treated with 10 and 100 μg/kg DEX (P < .0001 for all comparisons). In the 100 μg/kg group, the thymus was indiscernable (thymus weights of 0 were used for statistical analysis). Significant decreases in adrenal weights and adrenal/body weight ratios.
compared with VEH-treated rats (P < .0001 for both) were observed in rats treated with 100, but not 10, μg/kg DEX. This difference probably reflects atrophy of the adrenals as a result of negative feedback of DEX on ACTH secretion.

**Discussion**

The results of these experiments demonstrate that daily pretreatment with CORT (2.0 mg/kg i.p.) facilitates the acquisition of cocaine-seeking behavior in rats, as observed by a leftward and upward shift in the ascending dose-response curve for intravenous cocaine self-administration. CORT-treated rats acquired self-administration at a lower dose of cocaine than did VEH-pretreated rats (0.0625 g/kg vs. 0.125 mg/kg infusion). In contrast, no significant differences in food-maintained responding were observed between these treatment groups. The present results are consistent with findings that corticosterone is necessary for the establishment and maintenance of cocaine self-administration in rats (Goeders and Guerin, 1996a; 1996b; Deroche et al., 1997) and with reports that CORT-pretreated rats are more sensitive to the reinforcing (Piazza et al., 1991) and locomotor activating (Marinelli et al., 1997; Cador et al., 1993) effects of psycho-stimulants.

Previous studies from this laboratory have demonstrated that daily preexposure to uncontrollable EFS facilitates the acquisition of cocaine self-administration in rats (Goeders and Guerin, 1994). In these experiments, a significant positive correlation was observed between the effects of EFS on plasma corticosterone and on self-administration (Goeders and Guerin, 1996a), suggesting that the facilitation of self-administration by EFS may have been mediated by corticosterone. In the present experiment, the CORT dosing regimen was designed to mimic the schedule of EFS exposure used in these previous studies. CORT treatment increased plasma corticosterone concentrations by almost 200% (e.g., >300 ng/ml). Although these concentrations are higher than those observed after EFS in the previous experiments (e.g., 200 ng/ml; Goeders and Guerin, 1996a), they are still within the EFS stress-induced range under certain conditions (unpublished observations). The finding that corticosterone and EFS produce similar effects on cocaine self-administration provides further evidence that corticosterone may be a substrate through which environmental variables interact with the reinforcing effects of cocaine.

Corticosterone produces many of its effects by binding to two types of cytosolic receptors (Joëls and De Kloet, 1994). The type I (mineralocorticoid) receptor has a higher affinity for corticosterone and is usually occupied at basal concentrations of the hormone. In contrast, the type II (glucocorticoid) receptor has a lower affinity for corticosterone and is more likely to be occupied when corticosterone concentrations are elevated (e.g., during “stress” or after cocaine administration). To determine the roles of type I and type II receptors in the effects of corticosterone on cocaine self-administration, rats were treated daily with the type I receptor agonist, ALDO, or the type II receptor agonist, DEX, and ascending dose-response curves for cocaine self-administration were determined.

Daily administration of either ALDO or DEX failed to produce CORT-like effects on the acquisition of cocaine self-administration. Interestingly, however, DEX-treated rats did not acquire self-administration at any dose. This effect was associated with significant attenuations of food-maintained responding and weight loss in rats treated with 100 μg/kg but not 10 μg/kg DEX. In rats treated with 10 μg/kg DEX, no significant differences from baseline were observed in self-administration despite a trend toward acquisition at the higher doses of cocaine. Compared with the other treatment groups, DEX-treated rats also displayed a significantly attenuated extinction response pattern when the cocaine was replaced with saline.

The finding that DEX-treated rats did not acquire cocaine self-administration was unexpected. However, these results are consistent with reports that DEX pretreatment blocks the locomotor stimulating effects of cocaine and amphetamine in mice (Capasso et al., 1996). We hypothesized that the effects of DEX may have been a result of feedback inhibition of the HPA response to cocaine, since the dose-response curves for cocaine self-administration in the DEX-treated groups resembled those observed in ADX rats (Goeders and Guerin, 1996a; Deroche et al., 1997). In addition to mediating many of the physiological effects of glucocorticoids, type II receptors are also important for negative feedback on the HPA axis in response to elevated corticosterone (Dallman et al., 1994). Thus, administration of DEX has been reported to attenuate the plasma corticosterone responses to stressors (Donald, 1966) and cocaine (Simar et al., 1997). In the present study, treatment with DEX produced dose-dependent decreases in the plasma corticosterone response to either i.p. or single self-administered iv infusions of cocaine. In fact, in both DEX-treated groups, plasma corticosterone was also significantly decreased after saline administration, suggesting that basal concentrations of the hormone were reduced. Cocaine-induced increases in corticosterone were restored after DEX treatment was discontinued for 3 days in the 10 μg/kg but not the 100 μg/kg DEX group. Thus, daily pretreatment with 10 μg/kg DEX blocked cocaine self-administra-

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**TABLE 2**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Body Weight</th>
<th>Thymus Weight</th>
<th>Adrenal weight</th>
<th>Thymus/body weight</th>
<th>Adrenal/body weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEH</td>
<td>347.63 ± 3.93</td>
<td>236.00 ± 4.99</td>
<td>67.38 ± 5.02</td>
<td>0.68 ± 0.02</td>
<td>0.19 ± 0.01</td>
</tr>
<tr>
<td>CORT</td>
<td>352.63 ± 3.05</td>
<td>204.13 ± 12.40</td>
<td>74.75 ± 4.89</td>
<td>0.58 ± 0.03</td>
<td>0.21 ± 0.02</td>
</tr>
<tr>
<td>ALDO</td>
<td>357.63 ± 3.39</td>
<td>223.63 ± 11.18</td>
<td>78.50 ± 4.24</td>
<td>0.63 ± 0.03</td>
<td>0.22 ± 0.01</td>
</tr>
<tr>
<td>DEX (10 μg/kg)</td>
<td>338.50 ± 4.23</td>
<td>143.88 ± 10.35</td>
<td>60.00 ± 2.38</td>
<td>0.43 ± 0.04</td>
<td>0.18 ± 0.01</td>
</tr>
<tr>
<td>DEX (100 μg/kg)</td>
<td>308.38 ± 7.62</td>
<td>0.00</td>
<td>35.25 ± 2.31</td>
<td>N/A</td>
<td>0.11 ± 0.01</td>
</tr>
</tbody>
</table>

* P < .0001 vs. VEH control.  
+ P < .01 vs. VEH control.  
+ Thymus was indiscernible in these rats.
tion without producing long-term suppression of the HPA axis. In both the 10 and 100 μg/kg DEX groups, significant decreases in the plasma corticosterone response to cocaine were observed after a single DEX pretreatment. For the 100 μg/kg dose of DEX, the corticosterone response to cocaine was further diminished after chronic DEX treatment compared with its acute administration, suggesting a cumulative effect of the DEX treatment.

Based on the decreases in thymus weight observed in the DEX-treated rats, it is probable that DEX was occupying type II receptors peripherally. Peripheral type II receptors, most likely in the anterior pituitary, are believed to be important for the feedback inhibitory effects of DEX on the HPA axis (De Kloet et al., 1974). However, in the present study, the extent to which type II receptors within the brain were occupied is unknown. DEX penetrates the brain relatively poorly (Rees, 1974) and may even be actively transported out the central nervous system (De Kloet, 1997). Western blot analysis of brain tissue from the DEX-treated rats indicated that no significant down-regulation of type II receptors occurred in a number brain regions (unpublished observation). Thus, it is possible that the present findings reflect the unusual pharmacodynamic profile of DEX itself, rather than the effects of central type II receptor occupation.

Under basal corticosterone concentrations, type I receptors are predominantly occupied, while type II receptors remain largely unbound (Joels and De Kloet, 1994). In the present study, plasma corticosterone was 60 ng/ml or less in rats treated with 10 μg/kg DEX and was virtually undetectable in rats treated with 100 μg/kg DEX under all conditions. In either case, it is likely that plasma concentrations of corticosterone were low enough that type I receptors were not fully occupied. Thus, DEX treatment may have resulted in a physiologically abnormal state in which type II receptors were bound but type I receptor occupation was submaximal. Although it had no effects on cocaine self-administration by itself, coadministration of the type I receptor agonist ALDO (100 μg/kg) with DEX (10 μg/kg) restored self-administration to levels observed in VEH-treated rats. This DEX/ALDO combination, at the doses used, did not produce CORT-like effects on self-administration (e.g., facilitation of acquisition vs. VEH-treated rats). The restoration of self-administration by ALDO was not accompanied by a reversal of the DEX-induced suppression of the corticosterone response to cocaine. Thus, type I receptor occupation by basal corticosterone concentrations may be necessary for the acquisition of cocaine self-administration. These findings are consistent with reports that the occupation of type I receptors is required for the locomotor stimulating effects of cocaine (Marinelli et al., 1997).

It has been demonstrated that exposure to stress or treatment with CORT, but not DEX, facilitates ethanol self-administration in rats (Fählke et al., 1995). In these experiments, the effects of CORT were not blocked by antagonists at type I (RU 28318) or type II (RU 38486) receptors, indicating that CORT may have been acting independently of these receptors. A non-MR/GR effect of CORT could explain the ability of DEX to prevent the acquisition of cocaine self-administration despite its occupation of type II receptors. In such a scenario, the type II receptor-mediated feedback inhibition of the HPA axis by DEX could block any non-GR effects of corticosterone related to reinforcement by preventing the release of the hormone in response to cocaine.

An important role for the mesocorticolimbic dopaminergic (DA) system in drug reinforcement has been clearly established (Koob, 1992). It has been demonstrated that the facilitation of the acquisition of cocaine self-administration by social stress is associated with an enhancement of DA transmission within this system (Tidey and Miczek, 1997). It has also been reported that corticosterone in the range of stress-induced concentrations can stimulate the release of DA in the nucleus accumbens (Piazza et al., 1996). Thus, corticosterone, and its effects on mesocorticolimbic DA transmission, may be an interface through which “stress” and cocaine reinforcement interact.

In summary, the results from these experiments demonstrate that daily pretreatment with corticosterone facilitates the acquisition of intravenous cocaine self-administration in rats. These findings suggest that corticosterone may provide a substrate through which environmental factors interact with the reinforcing effects of cocaine and other drugs of abuse. Differences in plasma corticosterone before or at the time of cocaine exposure may be critical determinants of whether or not individuals will progress to compulsive drug use and may provide a target for clinical intervention once self-administration has been established. Finally, the findings that daily treatment with dexamethasone blocks the acquisition of cocaine self-administration may be relevant to the development of novel pharmacotherapeutic approaches to the treatment of cocaine addiction.

Acknowledgments

The authors gratefully acknowledge G. F. Guerin, G. E. Farrar, and E. Padgett for their expert technical assistance and Drs. A. J. Dunn and J. D. Steketee for their invaluable advice.

References


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