



Research report

Conditioned release of corticosterone by contextual stimuli associated with cocaine is mediated by corticotropin-releasing factor

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Abstract

Elevated blood concentrations of corticosterone (CORT), an adrenal steroid associated with stress responses, is one of the endocrine correlates of cocaine treatment. Experiment 1 confirmed and extended previous findings that chronic cocaine treatment does not alter corticosteroid responses to cocaine. In Experiment 2, conditioned endocrine effects of cocaine were examined in three groups of rats after 7 consecutive days of treatment. Cocaine-induced conditioning was achieved using a simple contextual design. In group 1 (paired), rats were injected with cocaine (30 mg/kg), then immediately placed into a locomotor activity chamber for 30 min. One hour after the rats were returned to their home cages, they received an injection of saline. In group 2 (unpaired), rats were injected with saline, then immediately placed into a locomotor activity chamber for 30 min. One hour after the rats were returned to their home cages, they received an injection of cocaine (30 mg/kg). Rats in group 3 (control) received only saline injections, but otherwise were treated as animals in the other treatment groups. On the test day (Day 8), all rats were placed immediately into the locomotor apparatus for 30 min prior to collection of a blood sample. Blood CORT concentrations and locomotor activity in the paired group were significantly higher than in the unpaired and control groups. However, pretreatment of the rats in Experiment 3 with the corticotropin-releasing factor (CRF) antagonist, α -helical CRF₉₋₄₁ (1 μ g, i.c.v.), on the test day, prior to exposure to cocaine-associated contextual cues, attenuated the subsequent conditioned increase in blood CORT concentrations. These data represent the first demonstration of classical conditioning of a steroid hormone response to stimuli associated with a psychoactive drug in rats and suggest that the effect is mediated by endogenous CRF. Because the hypothalamic–pituitary–adrenal (HPA) axis has been implicated in modulating the actions of cocaine, it is plausible that such conditioned increases in CORT release by cocaine-associated cues may further predispose an organism to the reinforcing effects of the drug or enhance the susceptibility to drug-taking behavior. Alternatively, such conditioned effects may be related to the anxiogenic properties of cocaine. Further understanding of the conditioned effects of hormones in the development and expression of addictive behaviors may provide new insights into treatment of drug addiction. © 1998 Elsevier Science B.V.

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1. Introduction

Through classical conditioning, environmental, situational, and interoceptive cues associated with cocaine and other drugs of abuse develop the ability to elicit some of the behavioral and physiological effects produced by the drug alone [30,31,46]. The classical conditioning of drug effects to external and interoceptive cues in animals may underlie the development of incentive motivation, which is probably the principle neurobehavioral substrate responsible for craving [32,45]. Clinical studies also have revealed

that drug-associated cues are capable of inducing increases in autonomic function (e.g., heart rate, blood pressure, skin temperature, respiration, and galvanic skin response), as well as strong sensations of drug craving in drug addicts [8,9].

Cocaine produces a variety of physiological and behavioral effects including increases in spontaneous locomotor activity, alterations in autonomic function and changes in endocrine activity. Principal among the endocrine effects of cocaine is its ability to increase the activity of the hypothalamic–pituitary–adrenal (HPA) axis. Cocaine, for example, induces dramatic elevations in corticosterone (CORT) and adrenocorticotropin (ACTH) following either systemic [7,21,24,29,36,49,50] or i.c.v. [42] injections. Co-

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caine-induced increases in CORT appear to be dependent upon intact endogenous corticotropin-releasing factor (CRF) function in the brain [40,43], presumably at the hypothalamic level [6], and may be mediated in part through serotonergic and dopaminergic activation [3,23].

Although the conditioned behavioral effects of cocaine have been extensively studied [32,46], relatively little is known regarding the ability of drug-associated cues to elicit alterations in endocrine function which may be relevant to understanding addictive processes [32,45]. A recent clinical study has found that cocaine-associated cues presented to drug addicts increased plasma levels of cortisol and ACTH [2]. Elucidating the role of hormones in the development and expression of addictive processes may provide new insights for the treatment of drug addiction. The purpose of the present study was to determine whether contextual cues associated with the pharmacological effects of cocaine could develop the ability to elicit increases in HPA activity concomitant with conditioned increases in locomotor output in rats, and to determine the role of endogenous CRF in these effects.

2. Materials and methods

2.1. Subjects

Male Sprague–Dawley rats (Taconic Farms, Germantown, NY) weighing between 250–350 g were group housed and maintained on a 12 h light–dark cycle (lights on at 0700 h, EST). Food and water were available ad libitum in the home cage. Animals were adapted to the vivarium conditions for at least 1 week before experimentation began. Animals were handled daily from the day of arrival until they were assigned to a treatment group approximately 1 week later. Behavioral testing and blood samples were collected between 1300 h and 1600 h.

2.2. Drug

Cocaine hydrochloride (Sigma, St. Louis) was dissolved in sterile isotonic saline at a concentration of 30 mg/ml. Animals were injected i.p. with 1 ml/kg of the cocaine solution or sterile isotonic saline.

2.3. Apparatus

Locomotor activity was assessed in Digiscan photocell activity monitors (Omnitech Electronics, Columbus, OH) which were constructed from clear Plexiglas (30.5 cm high \times 42 cm wide \times 42 cm long). The activity monitors were enclosed in sound-attenuating compartments equipped with a 15 W fluorescent light and a ventilating fan. A one-way mirror (21 \times 21 cm²), mounted in the door, allowed for the visual observation of the animals during testing. A series of equally spaced infrared photocell detectors, mounted 4 cm from the floor surface, were located

along two adjacent walls of the chamber. Interruptions of the infrared light sources by the animal were recorded and stored by an IBM AT computer. The chambers were scented with peppermint extract to enhance the saliency of the environmental cues.

2.4. Hormone assay

Trunk blood was collected between 1300 h and 1600 h in EDTA-treated tubes and stored on ice prior to centrifugation. The samples were centrifuged at 3000 rpm for 15 min, and the serum collected from each sample was aliquoted and stored at -70°C . CORT concentrations were determined using a standard radioimmunoassay kit (ICN Biomedicals, Costa Mesa, CA). The samples were run in duplicate, while the standards were run in triplicate.

2.5. Experiment 1. The effects of acute and repetitive cocaine administration on corticosterone

Prior to evaluating possible conditioned effects of cocaine on CORT release, it was first necessary to establish the magnitude of the unconditioned effects in the present laboratory setting and to determine if there was any alteration in the CORT response following repetitive administrations according to a schedule similar to the one to be used in the conditioning study. The rats in the study received all injections of drug or vehicle i.p. within their home cages. The repetitively treated group (COC/COC) was injected for 7 days with 30 mg/kg of cocaine HCl. The saline control group (SAL/SAL) and the acute cocaine group (SAL/COC) received saline injections (1 ml/kg, i.p.) for 7 days. On day 8, rats in the COC/COC and SAL/COC groups were injected with 30 mg/kg cocaine while the animals in the SAL/SAL group were injected with saline. Thirty minutes after the injections on day 8, the rats were transported, one at a time, to a room adjacent to the vivarium for rapid decapitation and trunk blood collection.

2.6. Experiment 2. The effects of cocaine-associated contextual cues on blood corticosterone concentrations

Cocaine-induced conditioning was achieved using a simple contextual design. Three groups of rats were employed. On days 1–7, rats in the first group (paired) were injected with 30 mg/kg of cocaine HCl i.p. and placed in the peppermint-scented locomotor activity chambers for 30 min. One hour following return to the home cages, the rats were injected with saline. Animals in the second group (unpaired) were treated in a similar fashion but received injections of saline (1 ml/kg) prior to placement in the locomotor activity chambers and cocaine (30 mg/kg) in the home cage. The third group (control) received saline injections in both environments. The room containing the locomotor activity chambers was located adjacent to the

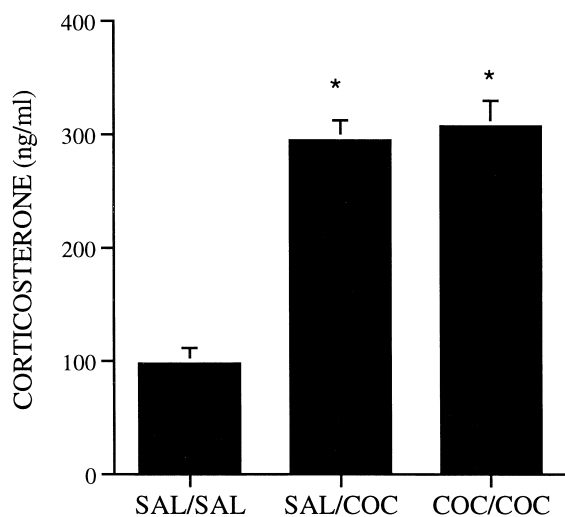


Fig. 1. Serum CORT concentrations (mean \pm S.E.M.) 30 min after administration of cocaine (30 mg/kg; i.p.) in repetitively (COC/COC) and acutely-treated (SAL/COC) rats or following chronic saline administration (SAL/SAL). An asterisk indicates a significant increase ($P < 0.05$) in CORT levels relative to the SAL/SAL group.

vivarium. The animals were transported between the two rooms in polycarbonate cages ($20 \times 25 \times 45 \text{ cm}^3$) containing wood chips. On day 8, all rats were removed from their home cages and placed, without injection, into the peppermint-scented locomotor activity chambers for 30 min. At the end of this interval, they were transported to an adjacent room for decapitation and trunk blood collection. We have previously shown significant conditioned effects of cocaine using a similar design even after one training session [17,18]. Such conditioned effects are reflected by significantly higher locomotor output in the paired group on the test day relative to the unpaired and control groups.

2.7. Experiment 3. Role of CRF in the conditioned increases in corticosterone following exposure to cocaine-associated contextual cues

A 23 gauge stainless steel guide cannula (16 mm) was stereotaxically implanted 1.5 mm dorsal to the lateral cerebral ventricle (AP: 7.9 mm; LAT: 1.7 mm; DV: 6.9 mm relative to interaural zero with the incisor bar at -3.5 mm) in anesthetized rats (chloral hydrate, 400 mg/kg i.p.). A minimum of 10 days following surgery was allowed for recovery. The animals were handled daily following surgery. The rats were randomly assigned to the paired, unpaired or control groups and trained for 5 days in the conditioning paradigm described in Experiment 2. On the 6th day (test day), the rats in the three treatment groups received an i.c.v. injection of either 1 μg α -helical CRF_{9–41} (Penninsula Laboratories) or the vehicle (sterile water, pH 6.7) through a 30 gauge injector which extended 1.5 mm past the end of the guide cannula. A total of 30 min after the i.c.v. injection, the rats were placed into the peppermint-scented locomotor chambers. After 30 min in

the peppermint-scented locomotor chambers, the animals were removed and blood samples were collected as described above.

At the conclusion of the experiment, cannula patency and placement was verified via post mortem injection of dilute Cresyl violet. The brains were removed and cuts were made at four anterior–posterior levels parallel to the coronal plane. Staining was observed throughout the lateral ventricles for all experimental animals except one, which was removed from the data analysis.

2.8. Statistical analysis

The data are presented as mean \pm S.E.M. The data were analyzed by analysis of variance (ANOVA). When the

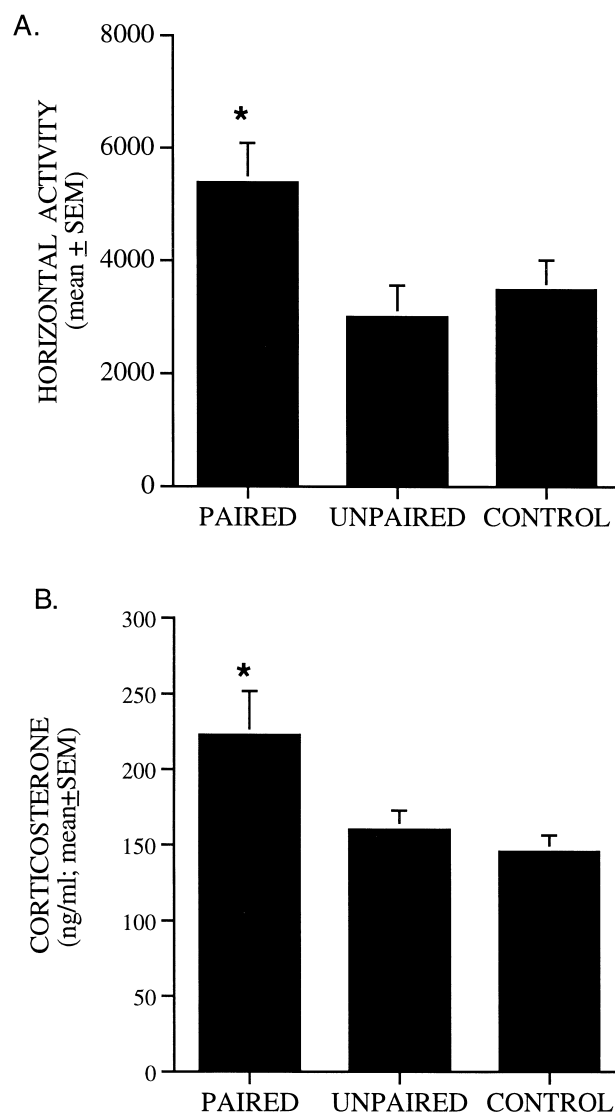


Fig. 2. (A) Mean horizontal activity (\pm S.E.M.) recorded in peppermint-scented photocell locomotor chambers during the 30-min test session and (B) mean serum CORT concentrations (\pm S.E.M.) measured at the end of the locomotor session on the test day. An asterisk indicates a significant increase ($P < 0.05$) in locomotor activity or blood CORT concentrations in the paired group relative to the unpaired and control groups.

ANOVA indicated a significant difference among treatment groups ($P \leq 0.05$) Fisher's PLSD test was used to compare the paired group to the unpaired and control groups.

3. Results

3.1. Experiment 1. The effects of acute and repetitive cocaine administration on corticosterone

Blood CORT concentrations 30 min following injection of saline were approximately 100 ng/ml. Cocaine injections in the SAL/COC and COC/COC groups elevated

CORT to approximately 300 ng/ml in each group (Fig. 1). A one-way ANOVA indicated a significant treatment effect ($F_{(2,21)} = 34.80$, $P < 0.01$). Post-hoc comparisons using Fisher's PLSD revealed that CORT levels of both the repeatedly injected cocaine group (COC/COC; $n = 9$) and the acute cocaine group (SAL/COC; $n = 8$) were significantly greater than the CORT levels of the saline control group (SAL/SAL; $n = 7$). No significant difference appeared between the CORT response of the COC/COC group and the SAL/COC group, suggesting that repeated administration of cocaine at a dose of 30 mg/kg does not result in either sensitization or tolerance of the corticosteroid response to cocaine.

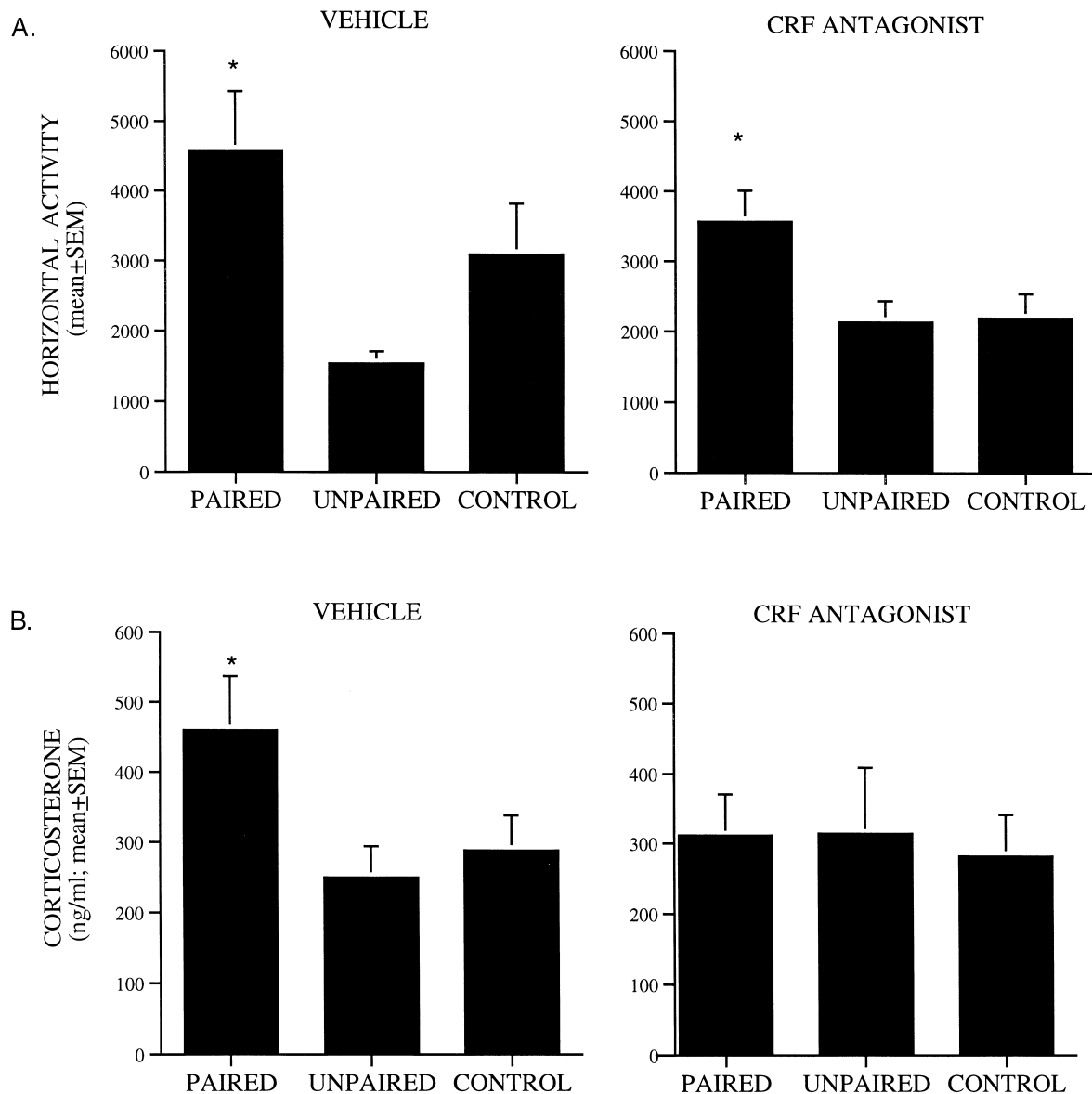


Fig. 3. (A) Mean horizontal activity (\pm S.E.M.) recorded in peppermint-scented photocell locomotor chambers during the 30-min test session and (B) mean serum CORT concentrations (\pm S.E.M.) measured at the end of the locomotor session on the test day. A total 30 min prior to placement in the locomotor apparatus, animals were treated i.c.v. with either a CRF antagonist ($1 \mu\text{g}$ α -helical CRF₉₋₄₁) or the vehicle. An asterisk indicates a significant increase ($P < 0.05$) in locomotor activity or blood CORT levels in the paired group relative to the unpaired and control groups.

3.2. Experiment 2. The effects of cocaine-associated contextual cues on blood corticosterone concentrations

A one-way ANOVA revealed a significant treatment effect on locomotor activity ($F_{(2,26)} = 4.46$, $P < 0.05$). Post-hoc comparisons using Fisher's PLSD test indicated significant differences between the paired group ($n = 10$) and the unpaired ($n = 9$) and control ($n = 10$) groups. The paired group on the test day (Day 8) had levels of locomotor activity that were significantly greater than both the unpaired and control groups, which did not differ significantly from each other (Fig. 2A). The critical comparison for illustrating the presence of conditioning is between the paired and unpaired groups which received equivalent exposure to cocaine but in different contexts. Such behavioral differences on the test day can only be accounted for by assuming that the environmental and contextual cues had acquired the ability to elicit increases in locomotor output in the paired group. The differences in locomotor output between the paired and unpaired groups on the test day have been shown to be established by associative learning mechanisms in previous studies from this laboratory [31,41].

A one-way ANOVA revealed a significant treatment effect on CORT levels ($F_{(2,26)} = 4.50$, $P < 0.05$). Fisher's PLSD test for post-hoc comparisons revealed that the CORT levels in the paired group were greater than both the unpaired and control groups, which did not differ significantly from each other (Fig. 2B). It is unlikely that elevated CORT levels in the paired group reflect increases in locomotor activity in the paired rats because there was not a significant correlation between locomotor activity counts and CORT concentration in the three treatment groups on the test day ($r^2:0.03$, correlation:0.18). It is, therefore, unlikely that the increased locomotor activity in the paired group is directly responsible for the concomitant increase in CORT levels.

3.3. Experiment 3. Role of CRF in the conditioned increases in corticosterone following exposure to cocaine-associated contextual cues

The data from one animal were excluded from the analyses because post mortem examination indicated that the cannula was not properly implanted. Exposure to cocaine-associated contextual stimuli for 30 min on the 5 training days was sufficient to produce conditioned increases in locomotor activity on the test day (Day 6) in paired rats that had been pre-treated with either 1 μg α -helical CRF₉₋₄₁ or the vehicle. ANOVA revealed a significant treatment effect on locomotor activity in animals pre-treated on the test day with α -helical CRF₉₋₄₁ ($F_{(2,26)} = 4.75$, $P < 0.05$; Fig. 3A). Post-hoc comparisons using Fisher's PLSD indicate that locomotor activity was significantly greater in the α -helical CRF₉₋₄₁-treated paired ($n = 10$) than unpaired ($n = 9$) and control ($n = 10$)

groups. In the vehicle-treated groups, ANOVA followed by post-hoc comparisons using Fisher's PLSD indicate that locomotor activity was significantly greater in the paired ($n = 9$) than unpaired ($n = 10$) and control ($n = 9$) groups ($F_{(2,25)} = 5.97$, $P < 0.05$; Fig. 3A).

Among the animals that had been pre-treated with α -helical CRF₉₋₄₁, ANOVA did not reveal a significant treatment effect among the paired, unpaired and control groups in blood CORT levels following exposure to cocaine-associated contextual cues ($F_{(2,26)} = 0.06$, $P > 0.05$; Fig. 3B). There was, however, a significant treatment effect among the animals that had been pre-treated with the vehicle ($F_{(2,25)} = 3.63$, $P < 0.05$; Fig. 3B). As in Experiment 2, Fisher's PLSD test for post-hoc comparisons revealed a significant increase in CORT levels of the paired group compared to the unpaired and control groups.

4. Discussion

In agreement with previous reports [7,21,23,29,36,40,43,49,50], i.p. injections of cocaine in this study produced dramatic elevations in CORT when measured 30 min after administration of cocaine. Repetitive administrations of cocaine for 7 days failed to alter the effect of a subsequent cocaine challenge on CORT release, indicating that neither sensitization nor tolerance accompany chronic cocaine exposure at a dose of 30 mg/kg. Other investigators have reported similar findings [4,25,36,49]. Because no tolerance is observed in the elicited effects of cocaine on CORT, it can be assumed that the unconditioned effects were constant across the conditioning schedule. The most significant finding to emerge from these studies is that cocaine-associated contextual cues acquired the ability to elicit conditioned increases in CORT which were substantial but somewhat smaller in magnitude than those seen following treatment with 30 mg/kg of cocaine (the unconditioned response). Concomitant with conditioned increases in CORT, contextual stimuli associated with cocaine also elicited significant increases in locomotor activity. Such conditioned motoric effects of psychomotor stimulants in other studies appear to involve glutamatergic mechanisms [14,52] and the release of mesolimbic dopamine by drug-associated cues [17]. It is unlikely, however, that similar processes underlie the conditioned release of CORT reported in this study because no relationship appeared between the conditioned increases in locomotor activity and elevations in CORT.

Cocaine produces its pharmacological effects primarily by inhibiting the re-uptake of dopamine, norepinephrine, and serotonin, which results in an elevation of these brain amines in the synaptic cleft. Presumably, the ability of cocaine to enhance CORT release is somehow related to such initial actions of the drug. There is evidence that serotonergic, as well as dopaminergic, mechanisms underlie the ability of cocaine to elevate CORT. For example,

cocaine-induced CORT release has been blocked by haloperidol and selective D₁ and D₂ dopamine antagonists [3], serotonergic depletion with 5,7-dihydroxytryptamine and *P*-chlorophenylalanine and blockade of serotonergic function with the 5-HT₂–5HT_{1C} antagonist ritanserin [23,26]. Since cocaine also enhances noradrenergic and adrenergic activity, it is possible that some of its actions on HPA axis function may be mediated through these catecholaminergic systems as well. Electrophysiological and anatomical data support the existence of facilitatory input arising from medullary catecholaminergic groups to neurosecretory cells in the paraventricular nucleus (PVN) of the hypothalamus [12,38]. The i.c.v. and intra-PVN injections of norepinephrine and epinephrine elicit increases in plasma ACTH and CRF [37,48] while lesions of the ventral noradrenergic bundle inhibit stress-induced ACTH and CORT release [47].

Although the initial actions of cocaine on CORT release appear to involve catecholaminergic and serotonergic pathways, the ultimate effects are likely to be mediated by endogenous CRF. Cocaine stimulates hypothalamic CRF secretion in vitro [6]. In addition, cocaine-induced increases in plasma ACTH and CORT are inhibited by intraventricular pre-treatment with either CRF anti-serum [40] or the CRF antagonist, α -helical CRF_{9–41} [43]. The conditioned CORT effects described in this study also appear to be mediated by the release of CRF (Fig. 3B). The precise circuitry through which sensory conditioned stimuli gain access to the hypothalamic neurosecretory cells remains to be determined but may involve catecholaminergic or serotonergic pathways. We have previously reported, for example, that contextual cues are able to increase the release of dopamine in the meso-accumbens system [17]. Interestingly, pre-treatment with α -helical CRF_{9–41} failed to alter conditioned increases in locomotor activity, suggesting that these effects are independent of CRF activation.

What are the implications of conditioned CORT release for understanding the addictive process? Piazza et al. [34] have suggested that stress-related activity of the HPA axis may play a role in the pathogenesis of psychostimulant addiction. Stress [19,20,33], as well as CORT injections [33], have been reported to enhance the acquisition of cocaine and amphetamine self-administration in rats. Furthermore, CORT injections [5,13,22] enhance the stimulatory effects of cocaine and amphetamine, while adrenalectomy and metyrapone have the opposite effect [4,28,35]. It is possible that the conditioned release of CORT by cocaine-associated stimuli may further predispose an organism to the reinforcing effects of the drug, or enhance susceptibility to drug-taking behavior. Alternatively, the release of CORT could play a role in producing an internal state which may initiate or precipitate craving and relapse. The induction of negative mood states (e.g., anger, depression, or anxiety) elicit increases in drug craving and relapse in cocaine and heroin addicts [8,10,51]. It is also

conceivable that an environmental stressor which activates the HPA axis (resulting in the increase in CORT) produces part of the interoceptive stimulus complex associated with cocaine. Since cocaine-associated cues are capable of eliciting craving in addicts [9], it is plausible that interoceptive stimuli associated with the effects of CORT could play a role in triggering a motivational state following an external stressor. Finally, it is also possible that the conditioned release of CORT is not associated with the positive reinforcing actions of cocaine. In addition to euphoria and a feeling of well-being, cocaine also produces a variety of negative symptoms including nervousness, anxiety, fear, depression, and irritability [39,44]. The anxiogenic effects of cocaine have also been demonstrated in a variety of animal models [11,15,16,53]. The conditioned release of CORT by cocaine-associated stimuli may simply reflect the conditioned anxiogenic effects of the drug. Indeed, preliminary studies from this laboratory indicate that contextual stimuli associated with cocaine are capable of producing long-lasting anxiogenic effects in rats as measured in the elevated plus-maze (DeVries et al., unpublished observations). Cocaine addicts presented with cocaine-associated cues report increases in anxiety as well as craving [2]. Such conditioned effects were also accompanied by increases in HPA activity [2]. These conditioned anxiogenic effects of cocaine may also be relevant for understanding the development and persistence of panic attacks in cocaine addicts [1,27]. It is possible that panic attacks could be triggered long after discontinuation of the drug by cocaine-associated cues which have the ability to activate the HPA axis. Further work is clearly needed to understand fully the neural substrates underlying the conditioned activation of the HPA axis by cocaine-associated stimuli and the relevance of such activation to the addictive process.

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