

## Perspectives in Pharmacology

# Stress and Cocaine Addiction

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### ABSTRACT

The hypothalamo-pituitary-adrenal (HPA) axis is involved in all aspects of cocaine self-administration. Corticosterone seems to be crucial for the acquisition of drug use since self-administration does not occur unless this stress hormone is increased above a critical reward threshold. Increasing circulating levels of corticosterone also augments sensitivity to low doses of cocaine, possibly from a sensitization-associated phenomenon involving dopamine, suggesting that exposure to stress can increase individual vulnerability to cocaine. Drugs affecting the synthesis and/or secretion of corticosterone decrease ongoing, low-dose cocaine self-administration. When higher doses falling on the descending limb of the cocaine dose-response curve are self-administered, plasma corticosterone can still reach this reward threshold even when synthesis is inhibited and drug intake is not affected. Corticotropin-releasing hormone (CRH) seems to play a more prominent role in the maintenance of

cocaine self-administration and may even be involved in the incentive motivation for the drug. Corticosterone and CRH are also critical for the stress- and cue-induced reinstatement of extinguished cocaine-seeking behavior. Therefore, cocaine self-administration may represent an attempt to seek out specific sensations, with the internal state produced being very similar to that perceived by individuals who engage in risky, thrill-seeking behavior. During abstinence, exposure to stressors or cocaine-associated cues can stimulate the HPA axis to remind the individual about the effects of cocaine, thus producing craving and promoting relapse. Stress reduction, either alone or in combination with pharmacotherapies targeting the HPA axis may prove beneficial in reducing cravings and promoting abstinence in individuals seeking treatment for cocaine addiction.

The role of stress and the subsequent activation of the hypothalamo-pituitary-adrenal (HPA) axis in drug addiction has been under investigation in a number of laboratories for several years now. Subsequently, a number of excellent review articles have recently been published in an attempt to summarize the relevant research findings and to provide a rational explanation for these data (Bardo et al., 1996; Goeders, 1997, 2002; Kreek and Koob, 1998; Piazza and Le Moal, 1998; Koob, 1999; Shaham et al., 2000; Sarnyai et al., 2001). Since it is beyond the scope of this article to provide a comprehensive review of all of the literature related to stress and drug addiction, the reader is advised to consult the review articles listed above for a more detailed analysis. The purpose of this article is to review the work we have conducted investigating the role for the HPA axis in cocaine reward, to reconcile our data with the results obtained in other labora-

tories, and to present our own theoretical perspective on this subject.

When one considers the role of stress in cocaine reward and how activation of the HPA axis augments the motivation and/or vulnerability for cocaine use, the same questions continue to be asked. How can a stimulus (i.e., stress) that is generally regarded as something to avoid or escape actually increase the perception of reward associated with drug self-administration? Furthermore, how can a drug (i.e., cocaine) that in and of itself activates the HPA axis be one of the most reinforcing drugs ever studied? This article will examine these questions primarily in the context of cocaine self-administration in rats.

### The HPA Axis and Cocaine

The HPA axis is initially activated by the secretion of corticotropin-releasing hormone (CRH) from the hypothalamus (Turnbull and Rivier, 1997; Sarnyai et al., 2001). CRH-containing neurons projecting from the parvocellular division of the paraventricular nucleus to

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**ABBREVIATIONS:** HPA, hypothalamo-pituitary-adrenal; CRH, corticotropin-releasing hormone; ACTH, adrenocorticotropin hormone; CP-154,526, butyl-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-ethylamine.

the external zone of the median eminence release the peptide into the adenohipophyseal portal circulation in response to stress. The binding of CRH to receptors located in the anterior pituitary results in the synthesis of proopiomelanocortin, a large precursor protein that is cleaved to produce several smaller biologically active peptides, including  $\beta$ -endorphin and adrenocorticotropin hormone (ACTH). ACTH diffuses through the general circulation until it reaches the adrenal glands, where it stimulates the biosynthesis and secretion of adrenocorticosteroids (i.e., cortisol in humans or corticosterone in rats). The type I mineralocorticoid receptor has a high affinity for corticosterone and is usually fully occupied at basal concentrations of the hormone. This receptor also displays a high affinity for the mineralocorticoid aldosterone. The type II glucocorticoid receptor has a lower affinity for corticosterone and is more likely to be occupied when plasma corticosterone is elevated (e.g., during "stress"). This receptor also has a high affinity for the synthetic glucocorticoid dexamethasone.

Scientists have been aware of the existence of a complex relationship between HPA axis activation and the endocrine and neurobehavioral effects of cocaine for several years now (Piazza and Le Moal, 1998; Koob, 1999; Goeders, 2002). Acute, noncontingent cocaine administration increases plasma levels of ACTH,  $\beta$ -endorphin, and corticosterone (in rats) and cortisol (in nonhuman primates). These cocaine-induced increases in adrenocorticosteroids seem to be mediated by the cocaine-induced release of CRH from parvocellular neurons in the paraventricular nucleus (Sarnyai et al., 2001; Goeders, 2002). Acute cocaine administration decreases CRH-like immunoreactivity in the hypothalamus, hippocampus, and frontal cortex while increasing it in the amygdala, indicating that cocaine can also affect CRH activity in areas located outside the hypothalamus. In clinical studies (Mello and Mendelson, 1997), the acute intravenous administration of cocaine increases the secretion of cortisol and ACTH in chronic cocaine users, as does smoked cocaine. The intranasal administration of cocaine also increases cortisol secretion in male volunteers without a history of drug abuse. Plasma cortisol,  $\beta$ -endorphin, and ACTH are elevated in cocaine addicts on the day of admission into treatment centers, and cocaine-dependent individuals often display abnormal patterns of HPA axis activity. Clearly, cocaine itself stimulates many of the same neurochemical and hormonal systems also activated by exposure to stress. Accordingly, one might ask how a compound that directly stimulates the body's responses to stress could also be so addictive. As will become evident below, stress and cocaine interact to affect reward differently during the various phases associated with the etiology of cocaine self-administration and withdrawal.

### The Acquisition of Cocaine Self-Administration

During acquisition, an animal comes into contact with cocaine and its rewarding effects for the first time (Goeders, 2002). This is also when the animal learns to make the response that leads to cocaine delivery, thereby producing reinforcement. Environmental events that decrease the lowest dose of cocaine that is recognized by the animal as a reinforcer are considered to be events that increase vulnerability or the propensity for an animal to acquire self-administration. Acquisition can also be facilitated by events that decrease the time required to reach a specified behavioral criterion indicative of self-administration.

The ability of stressors to alter the acquisition of psychomotor stimulant self-administration has received considerable attention (Piazza and Le Moal, 1998; Goeders, 2002). The acquisition of amphetamine and cocaine self-administration is enhanced in rats exposed to a wide variety of either physical (e.g., social isolation or tail pinch) or social (e.g., exposure to the threat of an attack from an aggressive male rat) stress. We have investigated the effects of exposure to response-contingent ("controllable stress") and noncontingent ("uncontrollable stress") electric footshock on the acquisition

of intravenous cocaine self-administration in rats (Goeders and Guerin, 1994). In these experiments, one rat from a group of three randomly received an electric footshock when it pressed a response lever that also resulted in the presentation of food (response-contingent shock). Although this resulted in a conflict between obtaining food reinforcement and avoiding footshock, these animals controlled if and when shock was delivered. Shock presentation for the second rat in each triad was yoked to the first rat so that the second rat received footshock regardless of whether it had pressed its food response lever at all (noncontingent shock). Therefore, these rats had no control over the delivery of the stressor. The third rat in each triad responded under the same schedule of food reinforcement as the other two rats but was never shocked. Self-administration was trained with an extremely low dose of cocaine during the first week of testing, and this concentration was subsequently doubled each week. When a full range of doses is investigated in this way, an inverted "U"-shaped dose-response curve is typically generated. In general, lower doses contained within the ascending portion of this curve are believed to be more related to cocaine reward than those falling on the descending limb, which is also affected by the unconditioned nonspecific effects of these higher doses of cocaine (Woods et al., 1987).

Exposure to uncontrollable footshock shifted the ascending limb of the cocaine dose-response curve upward and to the left, indicating that these rats were more sensitive to low doses of cocaine than rats exposed to response-contingent or no shock. Interestingly, increased sensitivity to cocaine was positively correlated with stress-induced increases in plasma corticosterone, and self-administration did not occur unless plasma corticosterone was increased above a critical level or threshold (Goeders and Guerin, 1996a; Goeders, 2002). Electric footshock did not affect responding maintained by higher doses of cocaine that fell on the descending limb of the dose-response curve, possibly because the cocaine infusions alone were sufficient to increase plasma corticosterone above this critical reward threshold in the absence of footshock. This phenomenon seems to be relatively specific for the acquisition of cocaine self-administration since, in our hands, neither exposure to footshock (Goeders and Guerin, 1996a) nor exogenous injections of corticosterone (Goeders and Guerin, 1999) affect ongoing self-administration. Thus, it seems that once this "reward threshold" is crossed, further stress-induced increases in plasma corticosterone are without additional effects on drug intake.

Since plasma corticosterone was positively associated with the ability of uncontrollable footshock to shift the ascending limb of the acquisition dose-response curve upwards and to the left, we next investigated the effects of exogenous injections of corticosterone on the acquisition of cocaine self-administration (Mantsch et al., 1998). Rats were treated daily, 15 min before each self-administration session with corticosterone (2.0 mg/kg i.p. suspended in saline) or saline. These injections began 2 weeks before the start of self-administration testing to mimic the stress experiment described above as closely as possible. Similar to what we observed with electric footshock, daily pretreatment with corticosterone also produced a leftward shift in the ascending limb of the dose-response curve for the acquisition of self-administration, indicating that corticosterone-treated rats were more sensitive to low doses of cocaine than were rats pretreated with saline. In a related experiment, rats were bilaterally adrenalectomized before acquisition testing (Goeders and Guerin, 1996b). This surgery effectively removed the final step in HPA axis activation, which is the synthesis and secretion of corticosterone. These adrenalectomized rats did not self-administer cocaine at any dose tested even though they quickly learned to respond on another lever for food pellets, indicating that the rats could still learn and perform the necessary lever-pressing response. These data suggest that plasma corticosterone may be critical for the acquisition of cocaine self-administration to occur in rats.

As reviewed above, corticosterone binds to both mineralocorticoid and glucocorticoid receptors. Therefore, rats were pretreated daily with the mineralocorticoid receptor agonist, aldosterone (0.1 mg/kg i.p.; 15 min), or the glucocorticoid receptor agonist dexamethasone

(0.1 mg/kg i.p.; 60 min) as described above for corticosterone to distinguish between the potential roles for the two types of adrenocorticosteroid receptors in the effects of corticosterone on the acquisition of cocaine self-administration (Mantsch et al., 1998). Aldosterone treatment had little or no effect on the acquisition of self-administration, suggesting that mineralocorticoid receptors were not involved. Surprisingly, dexamethasone-treated rats did not acquire cocaine self-administration at any dose tested. However, at this relatively high dose, dexamethasone pretreatment completely inhibited the corticosterone response to cocaine and reduced basal corticosterone below detectable levels (Mantsch et al., 1998), most likely due to the activation of negative feedback mechanisms. Therefore, since the end result with respect to corticosterone secretion was similar to what we had observed following adrenalectomy, the failure of these animals to acquire cocaine self-administration essentially replicated the results from our surgical adrenalectomy experiments (Goeders and Guerin, 1996b).

How does exposure to uncontrollable stress and elevated plasma corticosterone increase sensitivity to low doses of cocaine? This phenomenon probably occurs by a process analogous to sensitization (Piazza and Le Moal, 1998) whereby repeated intermittent injections of cocaine increase the behavioral and neurochemical responses to subsequent exposure to the drug. In fact, our acquisition experiments were specifically designed to test cocaine doses in an ascending order since exposure to higher doses of psychomotor stimulants can sensitize rats to lower doses, resulting in the acquisition of self-administration at doses of these drugs that would not otherwise maintain responding (Goeders, 2002). Interestingly, exposure to stressors or injections of corticosterone can also result in sensitization to the behavioral and neurochemical (e.g., nucleus accumbens dopamine) responses to cocaine (Rouge-Pont et al., 1995; Prasad et al., 1998), and these effects are attenuated in adrenalectomized rats (Prasad et al., 1998; Przegalinski et al., 2000) or when corticosterone synthesis is inhibited (Rouge-Pont et al., 1995). The ability of uncontrollable electric footshock or corticosterone injections to facilitate the acquisition of cocaine self-administration may therefore result from a similar sensitization phenomenon, perhaps involving dopamine (Goeders, 1997; Piazza and Le Moal, 1998). Although exposure to the stressor itself may be aversive, the net result is reflected as an increased sensitivity to low doses of cocaine. Therefore, if certain individuals are more sensitive to stress (Piazza and Le Moal, 1998) and/or find themselves in an environment where they do not feel that they have adequate control over this stress (Levine, 2000), then these individuals may be more likely to use cocaine and other drugs of abuse as well.

Although sensitization may be attenuated in adrenalectomized rats, this does not fully explain why these rats did not learn to self-administer cocaine when relatively high doses were tested since sensitization is less likely to be involved in the self-administration of these higher doses. Obviously, changes in a number of neurochemical and hormonal systems (e.g., CRH, ACTH, norepinephrine, and vasopressin) would be observed in adrenalectomized rats. Interestingly, adrenalectomy also reduces dopamine receptor binding (Biron et al., 1992) and dopamine transporter binding selectively in the shell of the nucleus accumbens (Sarnyai et al., 1998). Since dopamine is a major mediator of cocaine reward (Piazza and Le Moal, 1998; Koob, 1999), adrenalectomy might compromise cocaine-induced activity in critical brain reward systems by these decreases in dopaminergic neurotransmission. This reduced brain reward activity would, in turn, inhibit the acquisition of cocaine self-administration in adrenalectomized rats.

### The Maintenance of Cocaine Self-Administration

During the maintenance of self-administration, the animal has already learned that the drug is a reinforcer and what responses are required for its subsequent presentation (Goeders, 2002). Maintenance

studies can provide useful information regarding the direct neurobehavioral interactions between environmental events and drug reinforcement. In contrast to the effects observed during acquisition, neither exogenous injections of corticosterone (Goeders and Guerin, 1999) nor exposure to electric footshock (Goeders and Guerin, 1996a) significantly alter the maintenance of cocaine self-administration. This inability to affect ongoing drug use is probably related to the fact that plasma corticosterone is significantly elevated in a dose-related manner during cocaine self-administration (Goeders et al., 1998), and further increases in corticosterone are without effect since a threshold critical for reward has already been crossed (Goeders, 2002). However, low-dose cocaine self-administration can be attenuated by drugs that inhibit the synthesis and/or release of corticosterone (Goeders, 2002). Pretreatment with the benzodiazepines chlordiazepoxide (Goeders et al., 1989) and alprazolam (Goeders et al., 1993) decreases ongoing cocaine self-administration in rats. This is not a nonspecific effect on the ability of the rats to respond since tolerance rapidly developed to the effects of alprazolam on food-maintained responding. Furthermore, the benzodiazepines were probably reducing rather than augmenting cocaine reward since the effects of chlordiazepoxide were attenuated when the cocaine dose was increased. Similar effects are observed when rats are pretreated with the corticosterone synthesis inhibitors metyrapone (Goeders and Guerin, 1996b) or ketoconazole (Goeders et al., 1998). However, the magnitude of this effect depends on the unit dose of cocaine. With lower doses of cocaine, the inhibition of corticosterone synthesis and/or secretion reduces plasma concentrations of the hormone below the critical reward threshold, and cocaine self-administration is significantly attenuated (Goeders, 2002). If the dose of cocaine is sufficiently increased, plasma corticosterone can still reach this threshold even though synthesis is suppressed and drug use is not affected (Goeders et al., 1998). In fact, ketoconazole does not affect cocaine self-administration in rhesus monkeys even when cocaine-induced increases in plasma cortisol and ACTH are significantly attenuated (Broadbear et al., 1999). These data suggest that although corticosterone is involved in cocaine reward, it plays a relatively minor role in the maintenance of cocaine self-administration, and then only when low-unit doses are self-administered.

Cocaine-induced increases in plasma corticosterone ultimately result from the effects of the drug on CRH secretion from the hypothalamus (Sarnyai et al., 2001; Goeders, 2002). Pretreatment with CP-154,526, a centrally active small molecule CRH1 receptor antagonist, significantly attenuated, and in some cases completely eliminated, cocaine self-administration without affecting food-maintained responding during the same session (Goeders and Guerin, 2000). Drug intake was decreased across all doses of cocaine tested, with the dose-response curve for cocaine self-administration effectively shifted downward and flattened. Responding on the cocaine lever following CP-154,526 pretreatment was significantly suppressed even during the first 15 min of the session, which is when rats typically sample the cocaine lever during extinction (Goeders et al., 1998; Peltier et al., 2001), suggesting that CRH may also be involved in the conditioned effects of cocaine (DeVries and Pert, 1998; Sarnyai et al., 2001; Goeders and Clampitt, 2002). These data underscore a critical involvement of CRH in ongoing cocaine self-administration and further suggest a role for the HPA axis in cocaine reward. This involvement becomes even more paramount during cocaine craving and the relapse to cocaine use.

### The Reinstatement of Extinguished Cocaine Seeking

Reinstatement is a preclinical approach that is widely regarded as an animal model of the propensity to relapse to drug use (Shaham et al., 2000), involving mechanisms related to the development and expression of craving. With this model, animals are taught to self-administer a drug until stable drug intake is maintained and are then subjected to prolonged periods of extinction training or abstinence.

nence. Once the criteria for extinction are met or following a specified period of abstinence, the ability of specific stimuli to reinstate responding on the manipulandum previously associated with the delivery of drug infusions is taken as a measure of drug seeking. This reinstatement of drug-seeking behavior can be elicited by priming injections of the drug itself or by exposure to brief periods of intermittent electric footshock. Although the role for the HPA axis in stress-induced reinstatement was recently extensively reviewed (Shaham et al., 2000), the HPA axis does not seem to be involved in cocaine-induced reinstatement (Mantsch and Goeders, 1999; Goeders, 2002). However, clinical studies have demonstrated that simple exposure to environmental stimuli or cues previously associated with cocaine use can produce intense drug craving (O'Brien et al., 1992), suggesting that exposure to a physical stressor or a "taste" of cocaine itself are not necessary prerequisites for the development of craving in humans (Goeders and Clampitt, 2002). Preclinical investigations have also demonstrated that cue-induced reinstatement may indeed be an important and valid animal model of drug craving (Meil and See, 1996). Therefore, this section will focus on the involvement of the HPA axis in the cue-induced reinstatement of extinguished cocaine seeking.

Rats were trained to self-administer cocaine, with cocaine delivery paired with the presentation of a tone and the illumination of a house light (Goeders and Clampitt, 2002). Once a stable baseline of cocaine self-administration was observed, lever pressing was extinguished to less than 20% of baseline rates. During reinstatement testing, responding resulted in the presentation of a conditioned cue or reinforcer (i.e., the house light and tone previously paired with self-administered cocaine). The response-contingent presentation of the conditioned reinforcer reliably reinstated extinguished cocaine-seeking behavior, whereas the noncontingent presentation of the same stimulus did not. Increases in plasma corticosterone were evident during cocaine self-administration and during extinction and reinstatement testing. However, although plasma corticosterone returned to basal levels by the end of the session during extinction, it remained elevated through the end of the session during reinstatement, suggesting that cue-induced reinstatement was associated with HPA axis activation. Pretreatment with the corticosterone synthesis inhibitor ketoconazole reversed the conditioned reinforcer-induced reinstatement of extinguished cocaine-seeking behavior and also attenuated the conditioned increases in plasma corticosterone observed during reinstatement. Pretreatment with the CRH1 receptor antagonist CP-154,526 resulted in a similar decrease in cocaine seeking (Goeders and Clampitt, 2002). Recent preliminary data suggest that the benzodiazepines alprazolam and oxazepam also attenuate cue-induced reinstatement. Taken together, these data suggest an important role for the HPA axis in the ability of environmental cues to stimulate cocaine-seeking behavior in rats.

Since the corticosterone synthesis inhibitor ketoconazole was effective in blocking the ability of conditioned cues to reinstate extinguished cocaine seeking in rats, we conducted a small, open-label pilot study to determine the effects of chronic high-dose ketoconazole administration on cocaine craving in humans (unpublished observations). Five adult male and female cocaine users were enrolled into a 6-week study. The subjects reported to the clinic twice per week, and blood and urine were collected to determine plasma cortisol and the presence of cocaine. Subjective measures of anxiety, depression, and cocaine craving were also assessed, as were any adverse effects. The dose of ketoconazole was gradually increased from 600 to 1000 mg/day during the first 2 weeks and remained at 1000 mg/day for the remainder of the study. Chronic treatment with ketoconazole resulted in significant decreases in subjective reports of anxiety, depression, and cocaine craving in all five subjects. The subjects, however, reported that if they did use cocaine while on ketoconazole therapy, they could still get high, which is in agreement with other clinical (Ward et al., 1998) and animal data (Broadbear et al., 1999; Mantsch and Goeders, 1999; Filip et al., 2000) that suggested that ketoconazole does not block the subjective effects of cocaine. Never-

theless, two of these subjects were actually cocaine free at the end of the study even though no psychotherapy for substance dependence was provided. The only adverse effects reported were an upset stomach and nausea, which were easily mitigated by reducing the dose of ketoconazole. Although this experiment will have to be replicated in a larger, placebo-controlled, double-blind study, these data suggest that we are on the right track with our preclinical studies and that this line of research merits further study. The development of drugs that reduce HPA axis activity, especially in response to cocaine-associated cues, may represent an exciting approach for the discovery of novel pharmacotherapies for the treatment of cocaine addiction in humans (Goeders, 2002b).

## Conclusions

The data reviewed above may seem somewhat counterintuitive. Cocaine can induce anxiety and panic in humans and anxiogenic-like responses in animals through its effects on CRH release (Goeders, 1997, 2002). Therefore, one might expect that augmenting HPA axis activity would produce an additive increase in the aversive effects of cocaine and reduce the motivation for the drug. During acquisition, however, exposure to aversive, stressful stimuli may actually sensitize individuals, making them more sensitive to cocaine reward. Once self-administration has been acquired, the positive aspects of cocaine reward probably mitigate the anxiogenic effects of cocaine.

However, another characteristic of cocaine self-administration is that drug delivery, and the resulting cocaine-induced stimulation of the HPA axis, is under the direct control of the individual. This is an important consideration since the controllability and predictability of a stressor significantly decrease its aversive effects (Levine, 2000). The individual controls when cocaine is administered and, therefore, when this activation of the HPA axis also occurs. This controlled activation of the HPA axis may result in the production of an internal state of arousal or stimulation that is actually sought by the individual (Goeders, 2002). This internal state may be analogous to novelty or sensation seeking that has been reported in humans (e.g., thrill seekers) and suggested to be involved in drug reward (Bardo et al., 1996; Dellu et al., 1996; Scourfield et al., 1996). Cocaine self-administration may represent an attempt to seek out specific sensations, with the internal state produced being very similar to that perceived by individuals who engage in risky thrill-seeking behavior (Goeders, 2002). During abstinence, exposure to stressors or cocaine-associated cues can stimulate the HPA axis to remind the individual about the effects of cocaine, thus producing craving and promoting relapse. Therefore, continued investigations into how stress and the subsequent activation of the HPA axis affect cocaine self-administration will result in the identification of more effective and efficient treatment for cocaine abuse in humans. Stress reduction, either alone or in combination with pharmacotherapies targeting the HPA axis, may prove beneficial in reducing cravings and promoting abstinence in individuals seeking treatment for cocaine addiction.

## References

- Bardo MT, Donohew RL, and Harrington NG (1996) Psychobiology of novelty seeking and drug seeking behavior. *Behav Brain Res* 77:23–43.
- Biron D, Dauphin C, and Di Paolo T (1992) Effects of adrenalectomy and glucocorticoids on rat brain dopamine receptors. *Neuroendocrinology* 55:468–476.
- Broadbear JH, Winger G, and Woods JH (1999) Cocaine-reinforced responding in

- rhesus monkeys: pharmacological attenuation of the hypothalamic-pituitary-adrenal axis response. *J Pharmacol Exp Ther* **280**:1347–1355.
- Dellu F, Piazza PV, Mayo W, Le Moal M, and Simon H (1996) Novelty-seeking in rats—biobehavioral characteristics and possible relationship with the sensation-seeking trait in man. *Neuropsychobiology* **34**:136–145.
- DeVries AC and Pert A (1998) Conditioned increases in anxiogenic-like behavior following exposure to contextual stimuli associated with cocaine are mediated by corticotropin-releasing factor. *Psychopharmacol* **137**:333–340.
- Filip M, Nowak E, Siwanowicz J, and Przegalinski E (2000) Effects of corticosterone and its synthesis blockade on the cocaine-induced discriminative stimulus effects in rats. *Pol J Pharmacol* **52**:411–421.
- Goeders NE (1997) A neuroendocrine role in cocaine reinforcement. *Psychoneuroendocrinology* **22**:237–259.
- Goeders NE (2002) The HPA axis and cocaine reinforcement. *Psychoneuroendocrinology* **27**:13–33.
- Goeders NE and Guerin GF (1994) Non-contingent electric footshock facilitates the acquisition of intravenous cocaine self-administration in rats. *Psychopharmacol* **114**:63–70.
- Goeders NE and Guerin GF (1996a) Role for corticosterone in intravenous cocaine self-administration in rats. *Neuroendocrinology* **64**:337–348.
- Goeders NE and Guerin GF (1996b) Effects of surgical and pharmacological adrenalectomy on the initiation and maintenance of intravenous cocaine self-administration in rats. *Brain Res* **722**:145–152.
- Goeders NE and Guerin GF (1999) Pretreatment with corticosterone or dexamethasone fails to affect ongoing cocaine self-administration in rats. *Neuroscience Abstr* **25**:1872.
- Goeders NE and Guerin GF (2000) Effects of the CRH receptor antagonist CP-154,526 on intravenous cocaine self-administration in rats. *Neuropsychopharmacol* **23**:577–586.
- Goeders NE and Clampitt DM (2002) Potential role for the HPA axis in the conditioned reinforcer-induced reinstatement of extinguished cocaine seeking in rats. *Psychopharmacol*, in press.
- Goeders NE, McNulty MA, and Guerin GF (1993) Effects of alprazolam on intravenous cocaine self-administration in rats. *Pharmacol Biochem Behav* **44**:471–474.
- Goeders NE, McNulty MA, Mirkis S, and McAllister KH (1989) Chlordiazepoxide alters intravenous cocaine self-administration in rats. *Pharmacol Biochem Behav* **33**:859–866.
- Goeders NE, Peltier RL, and Guerin GF (1998) Ketoconazole reduces low-dose cocaine self-administration in rats. *Drug Alcohol Depend* **53**:67–77.
- Koob GF (1999) Stress, corticotropin-releasing factor and drug addiction. *Ann NY Acad Sci* **897**:27–45.
- Kreek MJ and Koob GF (1998) Drug dependence: stress and dysregulation of brain reward pathways. *Drug Alcohol Depend* **51**:23–47.
- Levine S (2000) Influence of psychological variables on the activity of the hypothalamic-pituitary-adrenal axis. *Eur J Pharmacol* **405**:149–160.
- Mantsch JR and Goeders NE (1999) Ketoconazole does not block cocaine discrimination or the cocaine-induced reinstatement of cocaine-seeking behavior. *Pharmacol Biochem Behav* **64**:65–73.
- Mantsch JR, Saphier D, and Goeders NE (1998) Corticosterone facilitates the acquisition of cocaine self-administration in rats: opposite effects of the glucocorticoid receptor agonist, dexamethasone. *J Pharmacol Exp Ther* **287**:72–80.
- Meil WM and See RE (1996) Conditioned cued recovery of responding following prolonged withdrawal from self-administered cocaine in rats: an animal model of relapse. *Behav Pharmacol* **7**:754–763.
- Mello NK and Mendelson JH (1997) Cocaine's effects on neuroendocrine systems: clinical and preclinical studies. *Pharmacol Biochem Behav* **57**:571–599.
- O'Brien C, Childress AR, Ehrman R, Robbins S, and McLellan AT (1992) Conditioning mechanisms in drug dependence. *Clin Neuropharmacol* **15** (Suppl 1 Pt A): 66A–67A.
- Peltier RL, Guerin GF, Dorairaj N, and Goeders NE (2001) The effects of saline substitution on responding and plasma corticosterone in rats trained to self-administer different doses of cocaine. *J Pharmacol Exp Ther* **299**:114–120.
- Piazza PV and Le Moal M (1998) The role of stress in drug self-administration. *Trends Pharmacol Sci* **19**:67–74.
- Prasad BM, Ulibarri C, and Sorg BA (1998) Stress-induced cross-sensitization to cocaine: effect of adrenalectomy and corticosterone after short- and long-term withdrawal. *Psychopharmacol* **136**:24–33.
- Przegalinski E, Filip M, Siwanowicz J, and Nowak E (2000) Effect of adrenalectomy and corticosterone on cocaine-induced sensitization in rats. *J Physiol Pharmacol* **51**:193–204.
- Rouge-Pont F, Marinelli M, Le Moal M, Simon H, and Piazza PV (1995) Stress-induced sensitization and glucocorticoids. II. Sensitization of the increase in extracellular dopamine induced by cocaine depends on stress-induced corticosterone secretion. *J Neurosci* **15**:7189–7195.
- Sarnyai Z, McKittrick CR, McEwen BS, and Kreek MJ (1998) Selective regulation of dopamine transporter binding in the shell of the nucleus accumbens by adrenalectomy and corticosterone-replacement. *Synapse* **30**:334–337.
- Sarnyai Z, Shaham Y, and Heinrichs SC (2001) The role of corticotropin-releasing factor in drug addiction. *Pharmacol Rev* **53**:209–243.
- Scourfield J, Stevens DE, and Merikangas KR (1996) Substance abuse, comorbidity and sensation seeking: gender differences. *Compr Psychiatry* **37**:384–392.
- Shaham Y, Erb S, and Stewart J (2000) Stress-induced relapse to heroin and cocaine seeking in rats: a review. *Brain Res Rev* **33**:13–33.
- Turnbull AV and Rivier C (1997) Corticotropin-releasing factor (CRF) and endocrine responses to stress: CRF receptors, binding protein and related peptides. *Proc Soc Exp Biol Med* **215**:1–10.
- Ward AS, Collins ED, Haney M, Foltin RW, and Fischman MW (1998) Ketoconazole attenuates the cortisol response but not the subjective effects of smoked cocaine in humans. *Behav Pharmacol* **9**:577–586.
- Woods JH, Winger GD, and France CP (1987) Reinforcing and discriminative stimulus effects of cocaine: analysis of pharmacological mechanisms, in *Cocaine: Clinical and Biobehavioral Aspects* (Fisher S, Raskin A, and Uhlenhuth EH eds) pp 21–65, Oxford University Press, New York.

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