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The HPA axis and cocaine reinforcement

Nick E. Goeders^{a, b*}

^a *Department of Pharmacology and Therapeutics, Louisiana State University Health Sciences Center, PO Box 33932, 1501 Kings Highway, Shreveport, LA 71130-3932, USA*

^b *Department of Psychiatry, Louisiana State University Health Sciences Center, Shreveport, LA 71130-3932, USA*

Abstract

Scientists have been aware of the existence of a complex relationship between stress and the subsequent activation of the hypothalamic–pituitary–adrenal (HPA) axis and the endocrine and neurobehavioral effects of cocaine for many years now. Our research program has focused on the involvement of HPA axis activation in cocaine reinforcement using the intravenous self-administration model. Behaviorally, there are at least three general phases in the etiology of drug self-administration to consider: acquisition, maintenance and reinstatement. We have investigated the role for the HPA axis during each of these three phases. Corticosterone is necessary during acquisition; self-administration does not occur unless this stress-related hormone is increased above a threshold critical for reward. Sensitivity to low doses of cocaine falling on the ascending limb of the acquisition dose-response curve can be augmented by increasing circulating levels of corticosterone, but similar treatments do not affect responding maintained by higher doses. In a similar vein, ongoing, low-dose cocaine self-administration is decreased by drugs affecting the synthesis and/or secretion of corticosterone. When higher doses falling on the descending limb of the cocaine dose-response curve are self-administered, plasma corticosterone can still reach this hypothetical reward threshold even when synthesis is inhibited, and drug intake is not affected. On the other hand, the self-administration of doses falling on both the ascending and descending limbs of the cocaine dose-response curve can each be attenuated by drugs that block central corticotropin-releasing hormone (CRH) receptors. Finally, corticosterone and CRH are also critical for the stress- and cue-induced reinstatement of extinguished cocaine-seeking behavior, demonstrating an involvement of the HPA axis in the relapse to cocaine use as well. Continued investigations into how stress and the subsequent activation of the HPA axis affect cocaine self-administration will likely result in

* Tel.: +1-318-675-7863; fax: +1-318-675-7857.

E-mail address: ngoede@lsuhsc.edu (N.E. Goeders).

the identification of more effective and efficient treatment for cocaine addiction. © 2001 Elsevier Science Ltd. All rights reserved.

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1. Introduction

The hypothalamic–pituitary–adrenal (HPA) axis consists of a complex, well-regulated interaction between the brain, anterior pituitary gland, and adrenal cortex. The initial step in the activation of the HPA axis is the neuronal-regulated secretion of the peptide corticotropin-releasing hormone (CRH). Although CRH is distributed in a number of brain regions, it is those CRH-containing neurons localized in the parvocellular division of the paraventricular nucleus (PVN) of the hypothalamus projecting to the external zone of the median eminence that initiate the HPA axis activity. These neurons release the peptide into the adenohipophyseal portal circulation in a circadian manner or in response to neuronal stimulation. The interaction of CRH with receptors located on anterior pituitary corticotrophs results in the synthesis of proopiomelanocortin (POMC), a large precursor protein which is proteolytically cleaved to produce several smaller biologically active peptides, including β -endorphin and adrenocorticotropin hormone (ACTH). POMC-derived ACTH diffuses through the general circulation until it reaches the adrenal glands. There it stimulates the biosynthesis of adrenocorticosteroids, most notably the glucocorticoids, cortisol (in humans) and corticosterone (in rats), which results in their secretion from the adrenal cortex. Two types of adrenocorticosteroid receptors have been identified, both of which bind corticosterone (Joëls and de Kloet, 1994). The Type I mineralocorticoid receptor has a higher 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. In contrast, 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.

2. Cocaine and the HPA axis

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 (Goeders, 1997). Acute, non-contingent cocaine administration increases plasma levels of ACTH, β -endorphin and corticosterone in rats (Moldow and Fischman, 1987; Forman and Estilow, 1988; Levy et al., 1991; Saphier et al., 1993) and in non-human primates (Sarnyai et al., 1996). These cocaine-induced increases in ACTH and corticosterone are blocked in rats by pretreatment with the CRH receptor antagonist α -helical CRF₉₋₄₁ (Sarnyai et al., 1992), by the immunoneu-

tralization of CRH with an anti-CRH antibody (Rivier and Vale, 1987; Sarnyai et al., 1992), or by bilateral electrolytic lesions of the PVN (Rivier and Lee, 1994), indicating that these increases are mediated by the cocaine-induced release of CRH from parvocellular neurons in the PVN. In fact, cocaine can even stimulate the release of CRH from rat hypothalamic organ culture systems *in vitro* (Calogero et al., 1989). Acute cocaine administration has also been reported to decrease CRH-like immunoreactivity in the hypothalamus, hippocampus, and frontal cortex, while increasing it in the amygdala (Sarnyai et al., 1993), indicating that cocaine can also affect CRH activity in areas located outside the hypothalamus. Similarly, chronic exposure to cocaine decreases CRH receptor binding in brain regions primarily associated with the mesocorticolimbic dopaminergic system (Goeders et al., 1990). In clinical studies, the intranasal administration of cocaine has been reported to increase cortisol secretion in male volunteers without a history of drug abuse (Heesch et al., 1995). In chronic cocaine users, the acute, intravenous administration of cocaine has also been reported to increase the secretion of cortisol (Baumann et al., 1995) and ACTH (Mendelson et al. 1989, 1992). Interestingly, chronic cocaine use may actually attenuate the ability to release cortisol in response to other stressful stimuli (Vescovi et al., 1992a; Heesch et al., 1995). Plasma cortisol, β -endorphin, and ACTH are elevated in cocaine addicts on the day of admission into treatment centers (Vescovi et al., 1992b), and cocaine-dependent individuals often display abnormal patterns of HPA axis activity (Mendelson et al., 1998). Cocaine appears to produce these HPA axis-related effects by increasing the peak amplitude of secretory pulses of these hormones without altering pulse frequency, which indicates that these increases are likely driven by hypothalamic CRH (Mendelson et al., 1989; Teoh et al., 1994; Sarnyai et al., 1996).

Behaviorally, cocaine use in humans has been reported to produce profound subjective feelings of well being and a decrease in anxiety (Gawin and Ellinwood 1988, 1989). In fact, a subpopulation of chronic cocaine users may actually be self-medicating to regulate “painful feelings” and psychiatric symptoms via their drug use (Kleber and Gawin, 1984; Khantzian, 1985; Gawin, 1986), especially since increased rates of affective disorders and anxiety are observed in these individuals (Rounsaville et al., 1991; Brady and Lydiard, 1992; Kilbey et al., 1992). However, cocaine use, itself, has actually been reported to precipitate episodes of panic attack in some individuals (Anthony et al., 1989; Aronson and Craig, 1986; Washton and Gold, 1984). Since panic disorder only became apparent following chronic cocaine use in many of these cases, the drug may have functioned as a precipitating as well as a causative factor in neurobiologically vulnerable individuals (Aronson and Craig, 1986). Furthermore, some of the major symptoms observed during withdrawal from chronic cocaine intoxication can often include severe anxiety as well as restlessness, agitation and depression (Gawin and Ellinwood, 1989). Interestingly, CRH has been reported to be involved in a variety of neuropsychiatric disorders including depression and anxiety (Gold et al., 1984; Nemeroff, 1988; Musselman and Nemeroff, 1995), suggesting that the anxiety associated with cocaine use and withdrawal may depend, in part, on the effects of the drug on the release of this endogenous “stress peptide” and the resulting activation of the HPA axis.

Cocaine-induced anxiogenic effects have also been observed in non-human animals using a variety of behavioral paradigms. For example, cocaine has been reported to augment the aversion for a white illuminated area in the mouse black and white test box model (Costall et al., 1989), to further reduce punished behavior in rats responding under a conflict schedule (Fontana and Commissaris, 1989), to increase defensive withdrawal in rats (Yang et al., 1992), and to decrease the number of entries into and time spent in the open arms of an elevated plus-maze in mice (Yang et al., 1992) and rats (Rogerio and Takahashi, 1992). Interestingly, even contextual cues previously paired with cocaine delivery can elicit “anxiety-like” responses in drug-free rats tested in the elevated plus-maze (DeVries and Pert, 1998). Withdrawal following repeated cocaine injections has also been reported to induce anxiogenic responses in the elevated plus-maze (Sarnyai et al., 1995), and withdrawal from chronic self-administration enhances startle-induced ultrasonic distress vocalizations (Barros and Miczek, 1996; Mutschler and Miczek, 1998a,b). Cocaine withdrawal-induced anxiogenic responses have also been demonstrated in drug discrimination studies. Pentylenetetrazole (PTZ) is a convulsant drug with discriminative stimulus properties that are related to the production of an anxiogenic response (Lal and Shearman, 1980). Cocaine withdrawal produces PTZ-appropriate responding in rats trained to discriminate PTZ from saline (Wood and Lal, 1987). However, acute cocaine injections also generalize to PTZ in rats trained to discriminate the drug from saline (Shearman and Lal, 1981), suggesting that cocaine itself can be anxiogenic. In fact, it has been demonstrated that the drug can act as a reinforcer while simultaneously producing “aversive” anxiogenic-like effects in rats trained to self-administer cocaine by traversing a straight-arm runway to a goal box (Ettenberg and Geist, 1991). We have also investigated the purported anxiogenic effects of cocaine using the drug discrimination model. In these experiments, rats were trained to discriminate cocaine from saline using a two-lever, food-reinforced responding design. When rats were injected with saline and then exposed to 15 minutes of restraint stress (Mantsch and Goeders, 1998) or electric footshock (Mantsch and Goeders, 1999), significant cocaine-appropriate responding was observed, indicating that a component of cocaine’s subjective effects may actually be associated with stress or anxiety. The finding that cocaine and stressors produce similar discriminative stimulus effects suggests that these two stimuli activate one or more common pharmacological effector systems, which may provide useful information regarding how stressors interact with cocaine-seeking behavior.

3. Drug self-administration

During the last several years, our research program has focused on the involvement of stress and the subsequent activation of the HPA axis in cocaine reinforcement. Behaviorally, there are at least three general phases in the etiology of drug self-administration to consider, and knowledge of the interactions between stress and cocaine during each of these is essential for understanding the complex interplay through which stress alters vulnerability to cocaine seeking. The first of these is the

acquisition phase, when an animal first comes into contact with cocaine and its rewarding effects. This is also when the animal learns to make the response that leads to cocaine delivery, thereby producing reinforcement. The type of response that is required can vary, ranging from the animal poking its nose through a designated opening, depressing a response lever or pressing the appropriate response key in an operant chamber. Environmental events (e.g., pharmacological treatments, exposure to physical stimuli) 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. A better understanding of how these environmental events alter the acquisition of self-administration may help to identify populations at risk for developing cocaine addiction and may suggest interventions that could attenuate increased vulnerability.

During the second phase in the etiology of drug self-administration (i.e., maintenance), the animal has already learned that the drug is a reinforcer and what responses are required for its subsequent presentation. Maintenance studies can provide useful information regarding the direct neurobehavioral interactions between environmental events and drug reinforcement. Understanding how environmental events can reduce drug reward during ongoing self-administration may lead to the development of therapies designed to decrease the effectiveness of the drug if the addict does come into contact with the substance and chooses to use it. Although treatment-seeking addicts housed in inpatient facilities are generally cocaine free, those treated through outpatient services can and do come into contact with the drug on the street.

The third phase involves the extinction and reinstatement of drug seeking, which is considered to be an animal model of relapse (Gerber and Stretch, 1975; Stewart and De Wit, 1987; Markou et al., 1993). With reinstatement, an animal is first trained to self-administer a drug. When self-administration stabilizes, the animal is placed into extinction so that responding no longer results in the delivery of the drug. Once responding drops below a specified level indicating that successful extinction has been reached, the ability of environmental events to increase or reinstate responding during subsequent extinction testing is determined. Knowledge of the events that increase extinguished drug-seeking behavior in animals may provide insight into the factors that promote relapse in humans and may lead to the development of therapies to reduce or prevent this from occurring. Our research program has investigated the role for the HPA axis in each of these three phases of cocaine self-administration, and the results of these studies are presented below.

4. Acquisition

The ability of stressors to alter the acquisition of psychomotor stimulant self-administration has received considerable attention during the last several years. The acquisition of amphetamine and cocaine self-administration is enhanced in rats

exposed to social isolation (Schenk et al., 1987) or tail pinch (Piazza et al., 1990), in rats witnessing other rats being subjected to electric footshock (Ramsey and Van Ree, 1993) and in rats born of female rats exposed to restraint during pregnancy (Deminière et al., 1992). Housing with female rats also increases psychomotor stimulant self-administration by male rats (Lemaire et al., 1994), as do other forms of “social stress” including female rats exposed to an attack by a lactating female rat (Haney et al., 1995) or male rats exposed to an attack by an aggressive male (Haney et al., 1995), exposed to the threat of attack following several defeats (Tidey and Miczek, 1997) or exposed to only the threat of attack (Miczek and Mutschler, 1996).

We first investigated the effects of exposure to response-contingent (“controllable stress”) and non-contingent (“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 were in some control over whether or not 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 or not it had pressed its food response lever at all (non-contingent 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. When responding under this food reinforcement/electric footshock schedule stabilized for all three rats, tail blood was collected for the determination of plasma corticosterone and testing for the acquisition of cocaine self-administration commenced. These rats were initially tested with an extremely low dose of cocaine (i.e., 0.031 mg/kg/infusion) for one week, and this concentration was subsequently doubled weekly through 0.5 mg/kg/infusion, a dose that is readily self-administered by rats. Doses were tested in an ascending order in all of our acquisition experiments since exposure to higher doses of psychomotor stimulants can sensitize rats to lower doses (Schenk and Partridge, 1997), resulting in the acquisition of self-administration at doses of these drugs that would not otherwise maintain responding. In this experiment, animals without control over electric footshock presentation (non-contingent shock) were more sensitive to cocaine. Exposure to non-contingent footshock shifted the ascending limb of the cocaine dose-response curve upward and to the left, indicating that these rats were more sensitive to the reinforcing effects of low doses of cocaine (i.e., 0.125 mg/kg/infusion or lower) than rats exposed to response-contingent or no shock (Fig. 1). In general, rats from these other two groups did not self-administer cocaine until higher concentrations were tested (i.e., 0.25 or 0.5 mg/kg/infusion). In addition, when the rats from these other treatment groups did self-administer the drug, rates of self-administration were generally lower than observed in rats exposed to non-contingent 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). Electric footshock did not affect responding

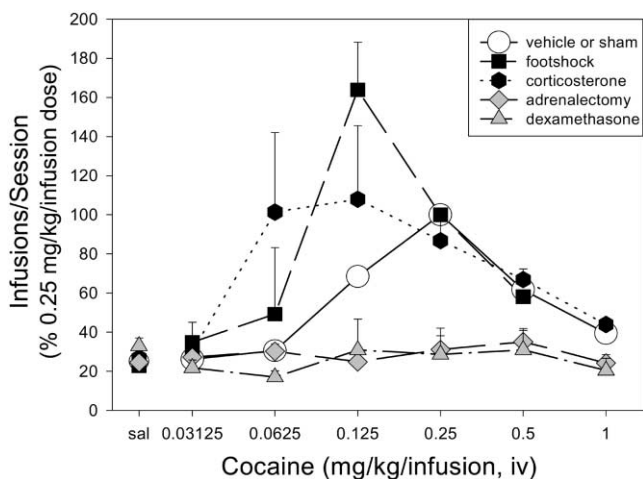


Fig. 1. Effects of environmental events on the acquisition of intravenous cocaine self-administration in rats. The infusion/session data from the different experiments are all plotted as the percentage of responding maintained by the 0.25 mg/kg/infusion dose of cocaine in sham- or vehicle-treated controls for each particular experiment to fit all data onto a single graph. In control animals, a typical inverted “U-shaped” dose-response curve was generated during acquisition. Exposure to footshock or exogenous injections of corticosterone shifted the ascending limb of the acquisition dose-response curve upwards and to the left without affecting the descending limb. Adrenalectomy or chronic injections of dexamethasone prevented the acquisition of cocaine self-administration across all doses tested.

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 (Fig. 2). This phenomenon appears to be relatively specific for the acquisition phase 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 during the maintenance phase. Thus, it appears that once this “reward threshold” is crossed, further stress-induced increases in plasma corticosterone are without additional effects on drug intake.

Stress-induced increases in plasma corticosterone were positively associated with the ability of non-contingent electric footshock to shift the ascending limb of the acquisition dose-response curve upwards and to the left. The following experiment was therefore designed to determine the effects of exogenous injections of corticosterone on the acquisition of cocaine self-administration (Mantsch et al., 1998). As reviewed above, corticosterone (cortisol in humans) is the last hormone in the cascade of HPA axis activation, so we hypothesized that the stress-induced increase in corticosterone secretion above a critical threshold may have mediated the increased sensitivity to cocaine we observed in rats exposed to non-contingent electric footshock. In these experiments, adult male Wistar rats were treated daily, 15 min prior to each self-administration session, with corticosterone (2.0 mg/kg, IP, suspended in saline) or saline. These injections began two weeks prior to the start of self-adminis-

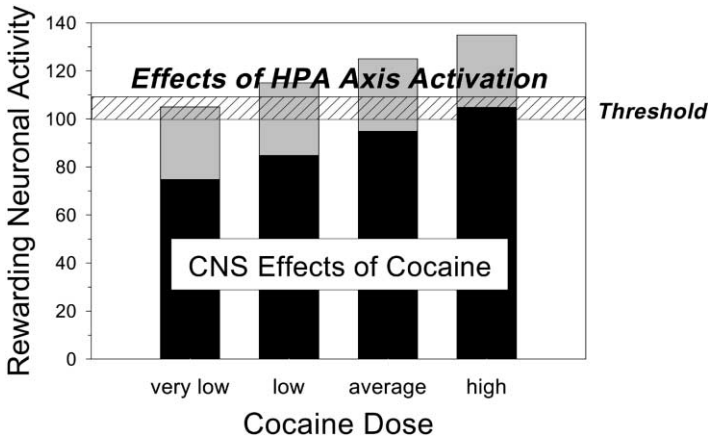


Fig. 2. We hypothesize that cocaine reward results from a combination of the direct effects of the drug in the central nervous system (black shaded areas) and its effects on the HPA axis (gray shaded areas). The central actions of cocaine are dose related. With very low doses of cocaine, a threshold critical for reward (striped horizontal bar) is not crossed unless the HPA axis is also activated. As the cocaine dose is increased, the influence of HPA axis activation is less and less pronounced, as the central effects of the drug become sufficient to initiate rewarding neuronal activity above this threshold. Therefore, if the HPA axis is activated during acquisition, cocaine doses that would not otherwise be perceived as being different from saline begin to generate rewarding neuronal activity as the threshold is crossed. Conversely, if self-administration is maintained by low to moderate doses of cocaine, inhibiting corticosterone secretion can decrease neuronal activation below the reward threshold and drug intake decreases to levels observed during extinction. If the cocaine dose is subsequently increased, this inhibition of self-administration can be reversed.

tration testing to mimic the stress experiment described above as closely as possible since exposure to electric footshock also began approximately two weeks before self-administration testing began (Goeders and Guerin, 1994). 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 (Fig. 1), indicating that corticosterone-treated rats were more sensitive to the reinforcing effects of low doses of cocaine. All of the corticosterone-treated rats acquired self-administration at the 0.0625 mg/kg/infusion dose or lower, whereas none of the saline-treated rats acquired this behavior until the 0.125 mg/kg/infusion dose or higher.

The results from the experiments described above suggest that increasing plasma corticosterone, either through exposure to stress or via exogenous injections of the hormone, can influence the acquisition of intravenous cocaine self-administration in rats. The following experiments were therefore designed to further examine the role for the HPA axis in cocaine reinforcement by investigating the effects of adrenalectomy on the acquisition of cocaine self-administration in rats (Goeders and Guerin, 1996b). Plasma corticosterone was significantly reduced in adrenalectomized rats compared to sham-operated controls, but there were no differences between these rats with respect to responding under a food reinforcement schedule, indicating that

adrenalectomized rats could still learn to make the response necessary for the delivery of a food reinforcer. However, while a typical inverted U-shaped dose-response curve for cocaine self-administration was generated by the sham rats, adrenalectomized rats did not learn to self-administer cocaine at any dose tested (Fig. 1). These data support the results and conclusions obtained in the experiments described above and suggest that plasma corticosterone is necessary for the acquisition of cocaine self-administration to occur in rats.

To distinguish between the potential roles for mineralocorticoid or glucocorticoid receptors in the effects of corticosterone on the acquisition of cocaine self-administration, separate groups of rats were pretreated daily with the mineralocorticoid receptor agonist, aldosterone (0.1 mg/kg, IP, 15 min), or the glucocorticoid receptor agonist, dexamethasone (0.1 mg/kg, IP, 60 min) as described above for corticosterone (Mantsch et al., 1998). While aldosterone treatment had little or no effect on the acquisition of self-administration, dexamethasone-treated rats did not acquire cocaine self-administration at any dose tested (Fig. 1). This was surprising in light of the results we obtained with corticosterone since we had anticipated a similar facilitation of self-administration with dexamethasone. However, at this relatively high dose, dexamethasone pretreatment completely inhibited the corticosterone response to either IP injections of cocaine or to a single self-administered infusion of the drug 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 essentially a pharmacological adrenalectomy, the failure of these animals to acquire cocaine self-administration functionally replicated the results from our surgical adrenalectomy experiments (Goeders and Guerin, 1996b).

In summary (see Fig. 1), exposure to uncontrollable electric footshock facilitates the acquisition of cocaine self-administration, most likely through the activation of the HPA axis since this increased sensitivity was positively correlated with stress-induced elevations in plasma corticosterone. In fact, similar effects were also seen in rats injected chronically with corticosterone. Electric footshock or exogenous injections of corticosterone each selectively shift the ascending limb for the acquisition of cocaine self-administration upwards and to the left, which indicates that animals receiving such treatments are more sensitive to low doses of the drug. Neither stress nor corticosterone pretreatment affects the descending limb of the acquisition dose-response curve, suggesting that low cocaine doses are especially sensitive to the influence of the HPA axis. Reductions in plasma corticosterone, either pharmacologically or surgically induced, prevent the acquisition of cocaine self-administration over a wide range of doses, further suggesting that the HPA axis is critical to this process.

5. Maintenance

In our earliest work in this area, we reported that pretreatment with the benzodiazepine receptor agonist, chlordiazepoxide, significantly decreased intravenous

cocaine self-administration in rats (Goeders et al., 1989). This effect was attenuated when the unit dose of cocaine was increased, suggesting that chlordiazepoxide decreased the efficacy of cocaine as a reinforcer. In pilot experiments, diazepam also attenuated intravenous cocaine self-administration maintained under a progressive-ratio schedule of reinforcement in rats (Dworkin et al., 1989). However, since these decreases in drug-intake may have resulted from a non-specific disruption of the ability of the rats to respond, an additional study was conducted. Alprazolam was tested in adult male Wistar rats responding under a multiple schedule of intravenous cocaine presentation and food reinforcement, with cocaine available during one hour of the session and food presentations available during the other (Goeders et al., 1993). Food reinforcement was used to generate a control performance to evaluate whether or not the effects of alprazolam were specific for cocaine-maintained responding. Initially, responding maintained by both food and cocaine was reduced following exposure to alprazolam. However, tolerance quickly developed to the sedative effects of alprazolam on food-maintained responding during subsequent testing. On the other hand, no tolerance was observed in the ability of alprazolam to reduce cocaine self-administration (Fig. 3). The results of these experiments demonstrate that upon repeated administration, alprazolam could decrease cocaine self-administration without affecting food-maintained responding. This outcome suggests that these effects may result from specific actions on cocaine reinforcement rather than non-specific effects on the ability of the rats to respond.

The ability of benzodiazepines to decrease cocaine self-administration may actually have been related to the effects of these drugs on corticosterone and other

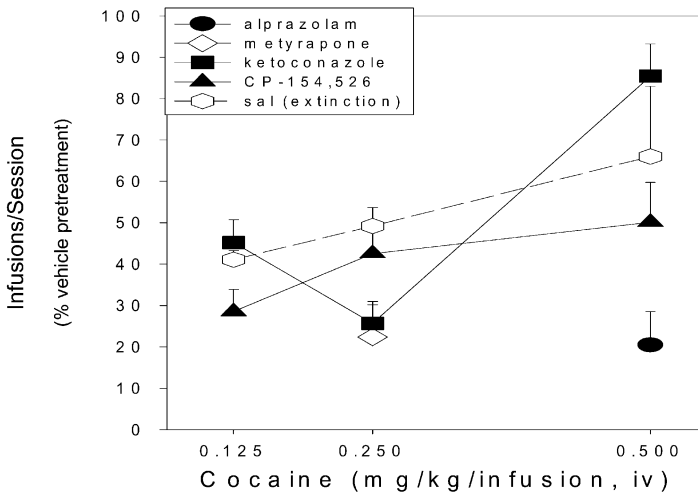


Fig. 3. Effects of the different treatments on ongoing cocaine self-administration. Data are presented as the percentage of responding maintained by the various doses of cocaine following pretreatment with vehicle. Alprazolam was only tested against 0.5 mg/kg/infusion cocaine and metyrapone was only tested against the 0.25 mg/kg/infusion dose of cocaine. The effects of substituting saline for cocaine during self-administration (i.e., extinction) are also plotted.

“stress” hormones and peptides. These drugs can decrease plasma corticosterone (Keim and Sigg, 1977), cortisol and ACTH (Meador-Woodruff and Greden, 1988; Torpy et al., 1993) or they can attenuate cocaine-induced increases in plasma corticosterone (Yang et al., 1992) to decrease cocaine reinforcement. Therefore, the following experiments were designed to investigate the effects of a reversible “pharmacological adrenalectomy” on the maintenance of cocaine self-administration using metyrapone (Goeders and Guerin, 1996b) and ketoconazole (Goeders et al., 1998).

Metyrapone blocks the 11β -hydroxylation reaction in the production of corticosterone, thereby resulting in decreases in plasma concentrations of the hormone (Haleem et al., 1988; Haynes, 1990). Pretreatment with metyrapone resulted in significant dose-related decreases in both plasma corticosterone and ongoing cocaine self-administration (Fig. 3), suggesting that corticosterone is involved in the maintenance as well as the acquisition of cocaine self-administration (Goeders and Guerin, 1996b). However, it was not clear whether these effects were specific for cocaine reinforcement or were the result of nonspecific effects on the ability of the rats to respond. An additional experiment was designed to address this problem through the use of a multiple, alternating schedule of food presentation and cocaine self-administration.

Ketoconazole is an oral antimycotic agent with a broad spectrum of activity and low toxicity that is used in the treatment of fungal disease (Sonino, 1987; Thienpont et al., 1979). This drug also inhibits the 11β -hydroxylation and 18-hydroxylation steps in the synthesis of adrenocorticosteroids (Engelhardt et al., 1985) and may also function as a glucocorticoid receptor antagonist (Loose et al., 1983), which makes it a useful drug with which to study the effects of corticosterone in cocaine reinforcement. Furthermore, clinical trials have suggested that ketoconazole is effective in the treatment of hypercortisolemic depression that is resistant to standard antidepressant therapy (Ghadirian et al., 1995; Murphy et al., 1991; Wolkowitz et al., 1993). Since depression and anxiety are often manifested during cocaine withdrawal in humans (Gawin and Ellinwood, 1989) and since corticosterone has been implicated in cocaine reinforcement (Goeders, 1997), the following experiments were therefore designed to investigate the effects of ketoconazole on intravenous cocaine self-administration in rats (Goeders et al., 1998). In these experiments, adult male Wistar rats were allowed alternating 15-min periods of access to food reinforcement and cocaine self-administration during daily 2-hour sessions. Pretreatment with ketoconazole reduced low dose (i.e., 0.125–0.25 mg/kg/infusion) cocaine self-administration (Fig. 3) without affecting food-reinforced responding. In fact, pretreatment with ketoconazole resulted in rates and patterns of self-administration at these doses of cocaine that were indistinguishable from those observed during cocaine extinction, when responding only resulted in infusions of saline. However, these effects were attenuated when the highest dose of cocaine tested was self-administered (i.e., 0.5 mg/kg/infusion). Although basal levels were not altered, ketoconazole also reduced plasma corticosterone in rats trained with the lower doses of cocaine but did not significantly affect the hormone when the highest dose was self-administered. These data suggest that ketoconazole may have reduced drug-intake, at least in part, through its effects on corticosterone. These data also imply that the use of more effective

and/or efficient corticosterone synthesis inhibitors might potentially decrease plasma corticosterone and reduce the self-administration of higher doses of cocaine without producing nonspecific effects.

However, in other experiments neither exogenous injections of corticosterone (Goeders and Guerin, 1999) nor exposure to electric footshock (Goeders and Guerin, 1996a) significantly altered the maintenance phase of cocaine self-administration. This inability to affect ongoing drug taking is likely 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 (Fig. 2). In the experiment described above, the effects of cocaine on plasma corticosterone remained dose related even though ketoconazole reduced cocaine-induced increases in the hormone (Goeders et al., 1998). Thus, ketoconazole may be more effective against lower unit doses of cocaine since at these lower doses, ketoconazole is able to decrease the cocaine-induced secretion of corticosterone below the threshold critical for reward. When higher doses of cocaine are self-administered, this threshold is still reached despite the reduction in corticosterone synthesis (Fig. 2).

In our earlier experiments, exposure to uncontrollable electric footshock shifted the ascending limb of the cocaine acquisition dose-response curve upwards and to the left without affecting the descending limb (Goeders and Guerin, 1994). In other words, electric footshock-induced elevations in plasma corticosterone increased low dose cocaine self-administration, but had little or no effect on responding maintained by higher doses of the drug (Goeders and Guerin, 1994; Goeders and Guerin, 1996a). Likewise, exogenous injections of corticosterone also shifted the ascending limb of the acquisition curve for cocaine self-administration to the left without affecting the descending limb (Mantsch et al., 1998). This is a critical distinction since the ascending limb of the cocaine dose-response curve is believed to be more involved with the reinforcing effects of the drug, while the descending limb is also affected by the rate-decreasing effects resulting from higher doses of the drug (Woods et al., 1987). Interestingly, ketoconazole only reduced low dose cocaine self-administration, indicating that the ascending limb of the dose-response curve was specifically affected. These data suggest a potential role for corticosterone in the maintenance of cocaine reinforcement. These data further suggest that the anxiety and depression associated with chronic cocaine use and withdrawal in humans may be related to changes in HPA axis responsiveness resulting from the prolonged and repeated stimulation of ACTH and cortisol secretion.

Although the experiments described above suggested an important role for corticosterone in cocaine self-administration, cocaine-induced increases in plasma corticosterone ultimately result from the effects of the drug on CRH secretion from the hypothalamus (Rivier and Vale, 1987; Sarnyai et al., 1992). Therefore, the following experiment was designed to determine the effects of pretreatment with CP-154,526, a centrally active, small molecule CRH1 receptor antagonist, on intravenous cocaine self-administration in rats (Goeders and Guerin, 2000). Adult male Wistar rats were trained to respond under the same multiple, alternating schedule of food reinforcement and cocaine self-administration described above. Prior to testing, these rats

were also exposed to multiple cocaine extinction probes (i.e., saline substitutions) until reproducible decreases in responding during extinction were observed (Goeders et al., 1997). Pretreatment with CP-154,526 did not affect food-maintained responding. However, cocaine self-administration was significantly attenuated, and in some cases completely eliminated, following pretreatment with CP-154,526 (Fig. 3). Drug intake was decreased across all doses of cocaine tested, with the dose-response curve for cocaine self-administration effectively shifted downward and flattened, suggesting that CP-154,526 decreased cocaine reinforcement. Furthermore, responding on the cocaine lever following CP-154,526 pretreatment was significantly suppressed even during the first 15 minutes of the session, a time when rats typically sample the cocaine lever during extinction (Goeders et al., 1998), suggesting that CRH may be involved in the conditioned effects of cocaine as well (DeVries and Pert, 1998; Goeders et al., 1999). These data underscore a potential role for CRH in cocaine reinforcement and further suggest a role for the HPA axis in cocaine addiction and withdrawal.

In summary (Fig. 3), ongoing cocaine self-administration can be attenuated by drugs that reduce corticosterone secretion (i.e., benzodiazepines, ketoconazole, metyrapone), but 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 a threshold critical for reward and cocaine self-administration is significantly attenuated (Fig. 2). If the dose of cocaine is sufficiently increased, plasma corticosterone can still reach this threshold even though synthesis is suppressed, and drug taking is not affected. Once this threshold has been crossed, however, further increases in plasma corticosterone do not affect ongoing self-administration. Finally, cocaine self-administration can also be decreased by drugs that inhibit HPA axis activity through the blockade of central CRH receptors (e.g., by pretreatment with CP-154,526). In this case, however, increasing the cocaine dose does not overcome the attenuation of self-administration and the dose-response curve is effectively shifted downward and flattened, which further underscores an important role for the HPA axis in the maintenance phase of cocaine self-administration.

6. Reinstatement

Understanding the factors that contribute to the precipitation of relapse is integral to the development of more effective and efficient strategies for the treatment of addiction. Since these factors are often difficult if not impossible to study in human addicts, the development of animal models that reflect many of the salient features of relapse in humans has recently received considerable attention (Markou et al., 1993). One well-studied animal model of relapse involves a reinstatement procedure (Gerber and Stretch, 1975; Stewart and De Wit, 1987). Using this model, rats are trained to self-administer a given drug. Once stable self-administration is observed, the rats are subjected to repeated extinction whereby responding is no longer reinforced by the delivery of the drug. Once extinction has been successful, the rats

are exposed to various events in an attempt to reinstate drug-seeking behavior. In both humans and non-humans, the acute re-exposure to the self-administered drug itself is a potent event for provoking relapse to drug seeking (Stewart and De Wit, 1987; De Wit, 1996). This drug-induced reinstatement has been observed for both stimulant (Gerber and Stretch, 1975; De Wit and Stewart, 1981; Slikker et al., 1984) and opiate (Davis and Smith, 1976; De Wit and Stewart, 1983) self-administration. Exposure to stress (Shiffman and Wills, 1985), or simply the presentation of stress-related imagery (Sinha et al., 1999), is another event long thought to be important for relapse in humans. In this regard, exposure to stress in the form of intermittent electric footshock has been reported to reinstate heroin- (Shaham and Stewart, 1995) and cocaine-seeking behavior (Erb et al., 1996; Ahmed and Koob, 1997) in rats without affecting food-seeking behavior (Ahmed and Koob, 1997). We have conducted experiments in which adult male Wistar rats were trained to self-administer cocaine during daily 2-hour sessions (Mantsch and Goeders, 1999). After 15 sessions of stable self-administration, this behavior was extinguished over the course of 10 consecutive sessions. The ability of electric footshock to reinstate extinguished cocaine-seeking behavior was then determined by exposing rats to intermittent footshock (15 min) immediately prior to the reinstatement test session, which was otherwise identical to extinction conditions. Electric footshock significantly increased responding on the cocaine lever compared to that observed during the previous extinction sessions (Fig. 4). However, electric footshock did not affect responding in animals pretreated with ketoconazole prior to exposure to the stressor. Although



Fig. 4. Effects of the different treatments on the reinstatement of extinguished cocaine-seeking behavior induced by exposure to electric footshock (shock induced) or to the response-contingent presentation of cues associated with cocaine during self-administration (cue induced). Data are presented as the percentage of responding that occurred during baseline cocaine self-administration. Ketoconazole (Keto) reduced the electric footshock- and conditioned cue-induced reinstatement (Rein) of drug seeking to levels seen during extinction (Ext). CP-154,526 (CP) produced similar effects on conditioned cue-induced reinstatement.

plasma corticosterone was still slightly elevated above basal levels, ketoconazole pretreatment significantly decreased the plasma corticosterone response to electric footshock, suggesting an important role for corticosterone in the ability of this stressor to reinstate cocaine-seeking behavior in rats. These data also imply that corticosteroids may be involved in stress-induced cocaine craving in humans as well.

Finally, we have also investigated the ability of a cue previously paired with cocaine self-administration to reinstate extinguished cocaine-seeking behavior (Meil and See, 1996; Goeders et al., 1999; Clampitt et al., 2000). In these experiments, adult male Wistar rats were trained to self-administer cocaine during daily 2-hour sessions. A light above the response lever indicated the availability of cocaine. A separate house light and tone stimulus complex was paired with each cocaine injection and the subsequent 20-s timeout period that followed each injection. When stable self-administration was observed, extinction training began whereby responding resulted in no programmed consequences. Extinction training continued for 10 sessions or until responding decreased below 20% of baseline self-administration. Reinstatement was then tested in two ways. During non-contingent reinstatement, the tone and house light stimulus complex was presented for 30 s every 15 min regardless of responding. During response-contingent reinstatement, responding resulted in the contingent presentation of the tone and house light. The response-contingent presentation of a light and tone previously paired with cocaine during self-administration reliably reinstated extinguished cocaine-seeking behavior (Fig. 4). However, the non-contingent presentation of the same stimulus complex did not. Conditioned increases in plasma corticosterone were evident during cocaine extinction as well as during reinstatement, with plasma corticosterone increased 15 min into the sessions to levels as high as those observed during cocaine self-administration. However, while 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 a potential relationship between HPA axis activation and cue-induced cocaine seeking. Pretreatment with ketoconazole reversed the conditioned cue-induced reinstatement of extinguished cocaine-seeking behavior (Fig. 4) and also attenuated the conditioned increases in plasma corticosterone observed during reinstatement (Goeders et al., 1999), which further underscores a role for corticosterone in this behavior. In other studies (Clampitt et al., 2000), pretreatment with the CRH receptor antagonist CP-154,526 also attenuated the ability of conditioned cues to reinstate extinguished cocaine seeking (Fig. 4). These data demonstrate an important role for corticosterone and CRH receptors in the ability of environmental cues to stimulate cocaine-seeking behavior in rats, suggesting that the HPA axis may also be involved in cocaine craving induced by exposure to cocaine-associated cues in humans. Improved treatment for relapse in former cocaine addicts may therefore result from the development of therapies that reduce the activation of the HPA axis induced by environmental cues previously associated with cocaine use.

7. Conclusions

To summarize, our data demonstrate that the HPA axis is involved in all three phases of cocaine self-administration to some degree. Corticosterone is necessary for the acquisition of drug taking, and self-administration does not occur unless this stress hormone is increased above a threshold critical for reward (Fig. 2). Increasing circulating levels of corticosterone augments sensitivity to low doses of cocaine falling on the ascending limb of the acquisition dose-response curve. Similar treatments do not affect responding maintained by higher doses, suggesting that once this threshold is reached, further increases in plasma corticosterone are without observable effects. In this regard, ongoing, low-dose cocaine self-administration can be decreased by drugs affecting the synthesis and/or secretion of corticosterone. 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. Finally, corticosterone is also critical for the stress- and cue-induced reinstatement of extinguished cocaine-seeking behavior, demonstrating an involvement of the HPA axis in the relapse to cocaine use.

At first glance, these data may appear somewhat counterintuitive since cocaine can induce anxiety and panic in humans and anxiogenic-like responses in animals through its effects on CRH release. Accordingly, one would expect that augmenting HPA axis activity would therefore increase the “aversive” anxiety-like effects of cocaine and reduce motivation for the drug, while inhibiting the HPA axis would be expected to increase cocaine reward, which is exactly the opposite of what we found. However, it is important to remember that an essential 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 animal. This is a fundamentally germane consideration since the controllability and predictability of a stressor significantly decrease its aversive effects (Levine, 2000). Therefore, an integral part of our hypothesized reward threshold involves HPA axis activation that is under the direct control of the animal via the cocaine it self-administers (Fig. 2). Rather than producing an aversive anxiogenic response, 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 animal. 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; Deltu et al., 1996). Cocaine self-administration may represent, in part, an attempt by the animal 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. Therefore, continued investigations into how stress and the subsequent activation of the HPA axis affect all three phases of 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 promoting abstinence in individuals seeking treatment for cocaine addiction.

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