Stress, the Hypothalamic- Pituitary-Adrenal Axis, and Vulnerability to Drug Abuse

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In nonlaboratory settings, social users of cocaine are sometimes able to control their drug intake so their patterns of use do not escalate to levels that would increase their risk of dependency and toxicity (Siegel 1984). This suggests that there may be factors in addition to the primary reinforcing properties of cocaine that determine why some individuals can remain casual recreational users while others progress to compulsive drug use. Individual reactivity to anxiety or stress, either mitigated or induced by cocaine, may represent one such factor that could influence the awareness or perception of the reinforcing efficacy of the drug. Clinical evidence supports the concept that anxiety may be involved in the etiology of cocaine use and/or withdrawal. For example, initial cocaine use produces profound subjective feelings of well-being and a decrease in anxiety in humans (Gawin and Ellinwood 1988, 1989). Interestingly, some of the major symptoms observed during withdrawal from chronic cocaine intoxication can also include severe anxiety as well as restlessness, agitation, and depression (Gawin and Ellinwood 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 (Gawin 1986; Khantzian 1985; Kleber and Gawin 1984), especially since increased rates of affective disorders and anxiety are observed in these individuals (Brady and Lydiard 1992; Kilbey et al. 1992; Rounsaville et al. 1991). Cocaine has even 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 a neurobiologically vulnerable individual (Aronson and Craig 1986). Since environmental events can also influence the onset and/or duration of anxiety and depression (Brown et al. 1973; Leff et al. 1970; Lloyd 1980), changes in the amount, severity, or perception of environmental stress may actually predispose sensitive individuals to engage in compulsive drug use.

COCAINE AND BENZODIAZEPINES

Benzodiazepines are among the most widely prescribed drugs for the pharmacological management of anxiety. These drugs are also useful in the emergency room for the treatment of some of the medical compli-cations associated with cocaine intoxication, since convulsions are often apparent following an acute overdose. These seizures can be treated with intravenous (IV) diazepam (Gay 1981; Tarr and Macklin 1987), but not dilantin (Tarr and Macklin 1987). Furthermore, as mentioned earlier, some of the major symptoms associated with cocaine withdrawal often include severe anxiety, restlessness, and agitation (Crowley 1987; Gawin and Ellinwood 1989; Tarr and Macklin 1987). However, even though anxiety appears to be involved in the etiology of cocaine use and withdrawal in humans, and diazepam is clinically useful in the treatment of acute cocaine intoxication, benzodiazepines are not usually recom-mended as the treatment of choice for cocaine withdrawal because of the concern that the use of these drugs might result in a secondary dependence (Wesson and Smith 1985). Nevertheless, data from the author's laboratory have suggested a potential involvement of benzodiazepines in some of the behavioral and neurobiological effects of cocaine.

Chronic cocaine administration (20 or 40 mg/kg, intraperitoneally (IP) for 15 days resulted in differential effects on benzodiazepine receptors in various regions of the rat brain (Goeders 1991; Goeders et al. 1990*b*). In general, cocaine decreased benzodiazepine receptor binding in terminal fields for the mesocorticolimbic dopaminergic system, while increasing labeling in terminal fields for the nigrostriatal system. Statistically significant decreases in benzodiazepine receptor binding in the medial prefrontal cortex and increases in the ventral tegmental area (VTA) were still observed up to 2 weeks following the final injection, suggesting that benzodiazepine receptors in these brain regions may be especially sensitive to the effects of cocaine. However, the results from these experiments do not provide useful information regarding the involve-ment of these receptor systems in cocaine reinforcement since the noncontingent administration of a drug is not, by definition, reinforcing. A reinforcer is an event that increases the probability of the behavior that resulted in its presentation. The following experiments were therefore designed to investigate the effects of self-administered cocaine on benzodiazepine receptor binding (Goeders et al. 1991). Binding was compared between animals that self-administered cocaine and animals that received simultaneous, yoked infusions of cocaine or saline to

determine the potential involvement of these receptor systems in cocaine reinforcement.

Adult male rats originally derived from the Fischer 344 strain and weighing 275 to 325 g at the start of the experiments were used. These rats were divided into seven groups, consisting of three littermates each. The first littermate from each triad was trained to self-administer cocaine (1.0 mg/kg/infusion in 200 L delivered over 5.2 seconds) on a fixed-ratio 2 (FR2) schedule of reinforcement during daily 6-hour sessions. The second rat from each litter received a simultaneous, identical infusion of cocaine, and the third rat received saline each time that the first rat pressed the response lever twice. Sessions were conducted 7 days per week, and the rats were exposed to cocaine or saline for 30 days. The effects of self-administered cocaine on benzodiazepine receptor binding were visualized using [3H]flumazenil under standard autoradiographic conditions (Goeders 1991). The direct pharmacological effects of response-independent cocaine administration were estimated by comparing receptor binding changes in the brains of the yoked-cocaine animals with those from the yoked-saline littermates, while differences between the self-administration and yoked-saline littermates potentially represent a combination of the effects of the general pharmacological as well as the reinforcing actions of cocaine. Benzodiazepine receptor binding was increased in the frontal cortex and decreased in the substantia nigra and VTA in both the self-administration and the yoked-cocaine groups compared to their yoked-saline littermates. Comparisons between the yoked-cocaine and yoked-saline animals also revealed significant reductions in benzodiazepine receptor binding in the hippocampus that were not observed in the self-administration treatment group. However, there were also significant changes in receptor binding between the self-administration and yoked-cocaine treatment groups that may indicate receptor changes specifically related to cocaine reinforcement. Benzodiazepine receptor binding was significantly increased in the medial prefrontal cortex and nucleus accumbens and decreased in the caudate nucleus and globus pallidus of the self-administration rats compared to yoked-cocaine animals. Benzodiazepine receptor binding was also decreased significantly more in the VTA of the self-administration rats compared to yoked-cocaine controls. These data demonstrate that benzodiazepine receptor binding was significantly altered in “reinforcement relevant” brain regions associated with ascending dopaminergic systems (i.e., medial prefrontal cortex, nucleus accumbens), suggesting that these effects may indeed be related to cocaine reinforcement.

In IV self-administration studies, pretreatment with the benzodiazepine receptor agonist chlordiazepoxide significantly decreased drug intake in all rats tested (Goeders et al. 1989). The effects of chlordiazepoxide on self-administration were attenuated when the unit dose of cocaine was increased from 0.5 to 1.0 mg/kg/infusion, suggesting that chlordiaze-poxide may have decreased rather than augmented the reinforcing effects of cocaine. However, since the decreases in drug intake may have resulted from nonspecific effects on the ability of the rats to respond following pretreatment with higher doses of chlordiazepoxide, the next study was initiated. Alprazolam was investigated since this benzo-diazepine receptor agonist has been proven to be clinically effective in the treatment of anxiety and panic attacks (Chouinard et al. 1982) and has been proposed to be useful in the treatment of some types of depression (Dawson et al. 1984; Feighner et al. 1983; Rickels et al. 1985).

Alprazolam was tested in adult male Wistar rats under a multiple schedule of IV cocaine presentation and food reinforcement (Goeders et al. 1993). The rats were implanted with chronic indwelling jugular catheters under pentobarbital anesthesia (50 mg/kg, IP) with methyl-atropine nitrate pretreatment (10 mg/kg, IP) using previously reported procedures (Goeders and Guerin 1994; Koob and Goeders 1989; Roberts and Goeders 1989). Following surgery, the animals were injected with sterile penicillin G procaine suspension (75,000 units intramuscularly (IM)). The swivel and leash assembly was always connected during the experimental sessions, even during training for only the food reinforce-ment component of the schedule. At the end of each session, the leash was disconnected and a dummy cannula inserted into the guide before the rats were returned to their homecages. After at least 4 days' recovery from surgery, the animals were trained to respond under a multiple schedule of IV cocaine presentation and food reinforcement.

Cocaine was available during 1 hour of the session under an FR4 schedule of reinforcement. During the other hour of the schedule, food presentation was available under a discrete-trial, FR10 schedule of reinforcement. A timeout period, during which all stimulus lights were extinguished and responses on the food lever were counted, but had no scheduled consequences, followed each food presentation. This timeout period was individually adjusted so as to be comparable to the average interinfusion interval generated during the cocaine component of the schedule for each rat so that similar temporal patterns of reinforcer presentation were obtained under both components of the multiple schedule. When stable baselines of

responding were obtained under both components of the multiple schedule, the animals were pretreated with alprazolam (0.1, 0.25, 0.5, 1.0, 2.0, and 4.0 mg/kg, IP) or vehicle (1 mL/kg, IP) 30 minutes prior to the start of the behavioral session. Alprazolam was dissolved in a propylene glycol/ethanol (80:20) vehicle. Following initial exposure to alprazolam, responding maintained by both cocaine and food was significantly reduced. However, tolerance quickly developed to the sedative effects of alprazolam on food-maintained responding, while no reduction in the effects of the drug on cocaine self-administration was observed. The results of these experiments demonstrate that alprazolam decreases cocaine self-administration without affecting food-maintained responding, suggesting that these effects may result from specific actions of benzodiazepines on cocaine reinforcement rather than nonspecific effects on the ability of the rats to respond.

The neurobiological effects of cocaine also include actions on other neurotransmitter and neuropeptide systems thought to be involved with stress and anxiety in humans. Chronic cocaine administration increases the synthesis and turnover of gamma-aminobutyric acid (GABA) and decreases [3H]GABA binding in the rat striatum (Gale 1984). Acute, noncontingent cocaine administration increases plasma levels of adrenocorticotropin (ACTH), beta-endorphin, and corticosterone (Forman and Estilow 1988; Moldow and Fischman 1987), possibly through a corticotropin-releasing factor (CRF)-induced mechanism (Rivier and Vale 1987; Sarnyai et al. 1992). Cocaine also stimulates the release of CRF from rat hypothalamic organ culture systems (Calogero et al. 1989) and decreases CRF binding primarily in brain regions associated with the mesocorticolimbic dopaminergic system (Goeders et al. 1990*a*). Since CRF has been reported to be involved in a variety of neuropsychiatric disorders including depression and anxiety (Gold et al. 1984; Nemeroff 1988), the anxiety and depression associated with chronic cocaine use in humans may also be related to the effects of the drug on the release of this endogenous "stress peptide." The effects of benzodiazepines on cocaine self-administration may also be related to the effects of these drugs on corticosterone and other "stress" hormones and peptides. For example, benzodiazepines may decrease plasma corticosterone or may attenuate cocaine-induced increases in plasma concentrations of the hormone to specifically decrease cocaine reinforcement.

COCAINE AND STRESS HORMONES

The acquisition of psychomotor stimulant self-administration in rats is increased by a variety of stressors including social isolation (Schenk et al. 1987), repeated exposure to tailpinch (Piazza et al. 1990*a*) in the adult offspring of female rats exposed to restraint stress during pregnancy (Deminière et al. 1992), and in rats exposed to other rats subjected to electric footshock (Ramsey and Van Ree 1993). It has been reported that rats which exhibit a relatively high response to a novel environment are more likely to self-administer amphetamine than rats which show a lower reaction to novelty (Piazza et al. 1989; 1990*b*), suggesting that behavioral and physiological responses to stress may indicate individual abuse liability. High responding rats exhibit a greater locomotor response to a challenge injection of amphetamine and a prolonged elevation of plasma corticosterone in response to novelty than do low responders (Piazza et al. 1991*a*). High responding rats also display a greater cocaine-induced locomotor response and an increased dopamine (DA) response in the nucleus accumbens than do low responders (Hooks et al. 1991). Environmental conditions (Maccari et al. 1991) or even exogenous infusions of corticosterone (Piazza et al. 1991*a*) can increase the likelihood that a rat will acquire self-administration with low doses of amphetamine, suggesting that changes in activity within the hypo-thalamic-pituitary-adrenal (HPA) axis may be involved in the abuse liability of stimulant drugs.

The effects of exposure to response-contingent (controllable stress) and noncontingent (uncontrollable stress) electric footshock on the acquisition of IV cocaine self-administration in rats have also been investigated (Goeders and Guerin 1994). Adult male Wistar rats were housed singly in an American Association for Accreditation of Laboratory Animal Care (AAALAC) accredited animal care facility on a reversed 12-hour light/dark cycle (lights on at 18:00 hours) with free access to water. Food availability was restricted to maintain the rats at approximately 85 to 90 percent of their free-feeding body weights. The rats were initially screened for their responses to a novel environment as well as the locomotor-stimulating effects of an acute cocaine injection, since other investigators have suggested that the behavioral and neuroendocrine responses of rats to a novel environment can be used to predict vulnerability to self-administer amphetamine (Piazza et al. 1989, 1990*b*). These rats were subsequently divided into six groups of three each based on their similar responses to the novel environment and cocaine to reduce any potential individual variability within the various triads of rats. Each animal was then implanted with a chronic indwelling jugular catheter under pentobarbital anesthesia (50 mg/kg, IP) with methylatropine nitrate pretreatment (10 mg/kg, IP) as described earlier. Following surgery, the animals were injected with sterile penicillin G procaine suspension (75,000 units, IM) and were allowed a minimum of 4 days to recover from surgery.

The groups of three rats were initially trained to respond under a discrete-trial, FR10 schedule of food reinforcement as described previously (Goeders and Guerin 1994). Once stable baselines of responding were obtained, electric footshock was introduced to two of the three rats. The first rat received a random-ratio 15 schedule of shock presentation as described previously (Goeders and Guerin 1994). The second rat in each triad responded on the same schedule of food reinforcement except that shock presentation was yoked to food lever responding by the first rat. The third rat also responded under the same schedule of food reinforcement but was never shocked. Plasma corticosterone was determined (Gwosdow-Cohen et al. 1982) once stable baselines of responding with electric footshock were obtained for all three rats in a triad, but one session prior to the initial exposure to cocaine self-administration. Each rat was anesthetized with methohexital sodium (5 mg, IV) via the IV catheter while still in the behavioral chamber, and 500 L of tail blood was collected into heparinized tubes. The blood was centrifuged, and the plasma was separated and stored frozen at -20% C until needed. Plasma corticosterone was determined following extraction with methylene chloride by radioimmunoassay using the antibody of G. Niswender of Colorado State University. The cocaine component of the multiple schedule was introduced at the start of the next behavioral session. Each triad of rats was initially tested with a very low dose of cocaine (i.e., 0.031 mg/kg/infusion). After approximately 3 to 5 days of exposure to this dose, the unit dose of cocaine was gradually increased, with the concentration doubled every 3 to 5 days so that each triad of rats was tested with 0.031, 0.0625, 0.125, 0.25, and 0.5 mg/kg/infusion cocaine, followed by a saline substitution (cocaine extinction).

There were significant differences in plasma corticosterone among the three treatment groups. Rats exposed to noncontingent shock (0.6 milliampere (mA)) exhibited significantly elevated plasma corticosterone (162.0Å21.2 ng/mL) when compared to the no-shock (68.4Å6.6 ng/mL) control animals ($t = 3.920$, $p < 0.05$). Although plasma corticosterone values for rats exposed to response-contingent footshock (109.0Å18.9 ng/mL) fell between those for rats in the noncontingent and no-shock-treatment groups, the differences were not statistically significant. A two-factor analysis of variance on the average number of infusions self-administered per session indicated a significant interaction between the various cocaine doses and the different treatment conditions [$F(2,12) = 6.04$, $p < 0.0001$]. In every triad of rats, the animals without control over electric footshock presentation (noncontingent shock) were more sensitive to cocaine. Figure 1 is a quantal dose-response curve that depicts the percentage of rats that self-administered cocaine (i.e., 25 or

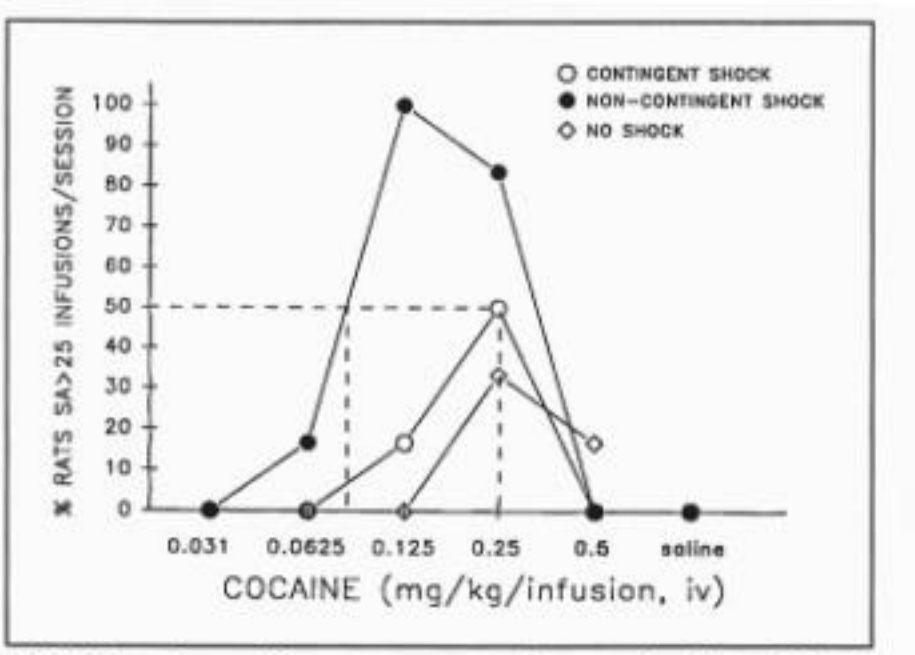

FIGURE 1. *Quantal dose-response curve depicting the effects of the treatment conditions on cocaine self-administration. ED_{50}'s are indicated by the dashed lines.*

more infusions/session) in the three different treatment conditions as a function of cocaine dose. Exposure to noncontingent electric footshock shifted the dose-response curve upward and to the left, indicating that these rats were more sensitive to the reinforcing effects of cocaine at every dose except the highest dose tested (i.e., 0.5 mg/kg/infusion). It is important to note that even though the first and second rats from each triad received the same number of electric footshocks at the same time during each session, only the second rats (without control over stress) consistently appeared more sensitive to cocaine. In general, rats from the other two groups did not self-administer cocaine until the higher concentrations were tested (i.e., 0.25 or 0.5 mg/kg/infusion). These higher concentrations are within the same range of doses used to train experimentally naive rats to self-administer cocaine, indicating a relative lack of effect of the response-contingent or no-shock-treatment conditions on the acquisition of self-administration in these rats. In addition, when the rats from these other treatment groups did self-administer the drug, rates of self-administration were generally lower than observed by rats exposed to noncontingent shock.

Interesting relationships were revealed between plasma corticosterone and cocaine self-administration. There were significant positive

correlations for all three treatment groups ($p < 0.05$) between the number of infusions delivered with the 0.125 mg/kg/infusion dose of cocaine and plasma corticosterone measured before the first exposure to the cocaine self-administration component of the multiple schedule (Goeders and Guerin 1994). These correlations appeared to roughly correspond with the acquisition, or lack thereof, of self-administration with this dose. This relationship between stress-induced elevations in plasma cortico-sterone and cocaine self-administration has now been investigated in an additional 33 triads (i.e., 99 rats). A very small percentage of these rats acquired self-administration with the lowest dose of cocaine tested (i.e., 0.031 mg/kg/infusion, N = 7), while the majority of rats acquired self-administration with the 0.125 mg/kg/infusion dose as previously reported (Goeders and Guerin 1994). There were no differences in plasma corticosterone between the rats that acquired cocaine self-administration with the 0.031 mg/kg/infusion dose compared to those rats from the same triads that did not. However, there were significant differences between these rats in the locomotor response to novelty measured before exposure to electric footshock. These data suggest that individual factors (i.e., response to novelty, see Piazza et al. 1989), which may or may not be associated with the response-contingent versus noncontingent electric footshock paradigm described earlier, were likely involved in this extremely low dose cocaine self-administration for this small percentage (i.e., 7 percent) of the rats tested. On the other hand, plasma corticosterone resulting from the different treatment conditions was significantly different between rats that acquired cocaine self-administration with the 0.125 mg/kg/infusion dose compared to rats from the same triads that did not, although there were no differences in their locomotor responses to novelty. In fact, there was a significant positive correlation between the amount of cocaine self-administered per hour and plasma corticosterone measured prior to exposure to the drug ($r = 0.92$, $p < 0.005$). Although plasma corticosterone ranged from 17 to 220 ng/mL for rats that self-administered no more than 1 mg cocaine/session, plasma corticosterone was always greater than 150 ng/mL for every rat that eventually self-administered 4 or more milligrams of cocaine per hour (i.e., > 32 infusions/session) at the 0.125 mg/kg/infusion dose. These data suggest that plasma corticosterone must be greater than 150 ng/mL for stable self-administration to occur. For example, plasma corticosterone was occasionally higher than usual (i.e., > 150 ng/mL) in rats from the first treatment group, and these rats were more likely to self-administer low doses of cocaine. Conversely, on rare occasions plasma corticosterone was not increased as high as expected (i.e., <

150 ng/mL) in the rats exposed to noncontingent footshock, and these rats were not as likely to self-administer low doses of cocaine as similarly treated rats with greater stress-induced increases in the hormone. Mean plasma corticosterone for rats from the first treatment group was 102.5Å9.8 ng/mL for rats that did not self-administer low doses of cocaine compared to 181.3 Å 10.2 ng/mL for rats that did. On the other hand, mean plasma corticosterone was 215.2Å10.6 ng/mL for rats from the second treatment group that self-administered low doses of cocaine compared to 132Å6.3 ng/mL for those rats that did not. These data suggest that plasma corticosterone measured before exposure to cocaine must be above a critical threshold (e.g., 150 ng/mL) for subsequent low-dose cocaine self-administration to occur.

For some of the triads, plasma corticosterone was also measured following exposure to the cocaine component of the multiple schedule. Plasma corticosterone was significantly elevated in rats from all three treatment groups during cocaine self-administration (259.1Å14.5 ng/mL, response-contingent shock; 237.9Å18.8 ng/mL, noncontingent shock; 271.8Å24.5 ng/mL, no shock) provided that doses of cocaine that would maintain responding were tested. However, when the dose of cocaine was increased to that which would maintain self-administration by all three rats in a triad (e.g., 0.25 or 0.5 mg/kg/infusion), there were no longer any significant correlations between plasma corticosterone measured prior to exposure to cocaine and self-administration, indicating that at these higher concentrations cocaine increased plasma cortico-sterone above a critical threshold, even for rats that had low precocaine corticosterone. In other words, the cocaine injections alone were sufficient to increase plasma corticosterone above the critical threshold necessary for cocaine reinforcement (e.g., 150 ng/mL) regardless of whether the rats had previously been exposed to noncontingent or response-contingent footshock or had never been shocked. When the cocaine dose would not maintain self-administration, plasma cortico-sterone was markedly lower in rats from all three groups. In other experiments when the animals were first trained to self-administer cocaine (0.25 mg/kg/infusion) before the introduction of the food reinforcement/shock component of the multiple schedule, there were no effects of controllable or uncontrollable electric footshock on cocaine maintained responding, further indicating that the cocaine injections alone had already increased plasma corticosterone above a critical threshold for “reinforcement.” In other words, the cocaine-induced increases in plasma corticosterone likely masked any further

increases in the hormone induced by electric footshock since the cocaine injections were by definition already reinforcing.
Since the results from the experiments described earlier suggested that increases in plasma corticosterone resulting from response-contingent and noncontingent electric footshock presentation were related to cocaine self-administration in rats, this experiment was designed to further examine the role of the HPA axis in cocaine reinforcement. Nine bilaterally adrenalectomized (ADX) and six sham-operated control (SHAM) adult male rats (Wistar) were used. A separate group of 11 ADX rats received corticosterone replacement in the drinking water throughout the experiment (CORT). The rats were housed singly in an AAALAC-accredited animal care facility on a reversed 12-hour light/dark cycle (lights on at 18:00 hours) with free access to water (SHAM), 0.9 percent saline (ADX), or 0.9 percent saline with corticosterone (100 g/ mL, CORT). Food availability was restricted to maintain the rats at approximately 85 to 90 percent of their free-feeding body weights. Each animal was implanted with a chronic indwelling jugular catheter under pentobarbital anesthesia (50 mg/kg, IP) with methylatropine nitrate pretreatment (10 mg/kg, IP) as described previously. After at least 4 days' recovery from surgery, the rats were trained to respond under an FR1 schedule of food reinforcement with the catheter and leash assembly attached. When responding stabilized, plasma corticosterone was determined immediately prior to the end of the session. The animals were then allowed access to IV cocaine by depressing a lever on the opposite side of the experimental chamber. Cocaine was available Tuesday through Friday during daily 1-hour sessions. Food (100 presentations) was available each Monday to ensure that the animals could still complete the response requirement. Each rat was initially tested with a very low dose of cocaine (i.e., 0.031 mg/kg/infusion). The cocaine dose was then doubled each week so that each rat was tested with 0.031, 0.0625, 0.125, 0.25, 0.5, and 1.0 mg/kg/infusion cocaine, followed by a saline substitution (cocaine extinction).

Plasma corticosterone was significantly reduced in the ADX rats (8.0Å7.8 ng/mL) compared to the SHAM-operated controls (72.4Å13.5 ng/mL) or the ADX rats with corticosterone replacement (40.5Å11.6 ng/mL). There were no differences among the three groups of rats with respect to responding under the food reinforcement schedule. A typical inverted U-shaped dose-response curve for cocaine self-administration was generated by the control rats. However, the ADX rats did not self-administer cocaine at any dose tested. The dose-response curve for the ADX rats with corticosterone replacement (CORT) fell between the curves for rats

from the other two treatment conditions. These data support the results and conclusions obtained in the experiments described earlier and suggest that plasma corticosterone may be necessary for cocaine reinforcement.

The results of the preceding experiments suggest that plasma corticosterone is important for the acquisition of cocaine self-administration in rats. The following experiments were therefore designed to investigate the effects of a reversible pharmacological adrenalectomy on the maintenance of this behavior using metyrapone. Metyrapone blocks the 11 beta-hydroxylation reaction in the production of corticosterone, thereby resulting in decreases in plasma concentrations of the hormone. Adult male Wistar rats were implanted with chronic indwelling jugular catheters as described previously. After at least 4 days' recovery from surgery, the animals were trained to respond under an FR4 schedule of cocaine reinforcement (0.25 mg/kg/infusion) during daily 1-hour sessions. When stable baselines of self-administration were obtained, the animals were pretreated with metyrapone (5, 25, 50, 100, and 150 mg/kg, IP) or vehicle 1 to 4 hours prior to the start of the behavioral session. Metyrapone pretreatment resulted in significant dose-related decreases in both plasma corticosterone (202.1Å9.1 ng/mL, vehicle versus 103Å7.3 ng/mL, metyrapone) and cocaine self-administration, suggesting that cortico-sterone is important for the maintenance as well as the acquisition of cocaine self-administration. Taken together, the data presented here suggest that drug-induced increases in plasma concentrations of stress hormones (e.g., corticosterone) may be involved in the initiation as well as the maintenance of cocaine self-administration. This relationship between stress hormones and reinforcement is not a new concept. The administration of ACTH or its analogs increases alcohol consumption in rats (Krishnan and Maickel 1991; Krishnan et al. 1991; Nash and Maickel 1988), and corticosterone pretreatment facilitates the acquisition of IV amphetamine self-administration in "nonpredisposed" rats (Piazza et al. 1991*a*). IV infusions of ACTH have even been reported to maintain self-administration in some rats (Jouhaneau-Bowers and Le Magnen 1979), while corticosterone has also recently been reported to maintain oral (Deroche et al. 1993) as well as IV (Piazza et al. 1993) self-administration in rats. Glucocorticoid administration has also been reported to result in euphoria and dependence in humans (Dixon and Christy 1980).

Interestingly, the mesocorticolimbic dopaminergic system appears to be involved in some of the neurobiological effects of both cocaine and

stress. The effects of cocaine include an inhibition of DA uptake, most likely mediated through the binding of the drug to a receptor associated with these uptake sites (Kennedy and Hanbauer 1983; Ritz et al. 1987). IV self-administration studies have implicated the mesocorticolimbic, but not the nigrostriatal, dopaminergic system in cocaine reinforcement in rats since DA depletion within brain regions associated with this system attenuate drug intake (Roberts and Koob 1982; Roberts et al. 1980), and since DA levels in the nucleus accumbens measured using in vivo microdialysis increase during self-administration (Pettit and Justice 1989). The drug is also self-administered directly into the medial prefrontal cortex, but not into the nucleus accumbens or VTA (Goeders and Smith 1983), suggesting that this brain region may also be involved in the initiation of cocaine reinforcement. Discrete response-contingent infusions of cocaine decrease DA turnover at the site of self-injection in the medial prefrontal cortex, while increasing the utilization of the neurotransmitter in the nucleus accumbens (Goeders and Smith 1993). In agreement with these data, rats predisposed to self-administer amphetamine (high responders) also have a lower 3,4-dihydroxyphenyl-acetic acid (DOPAC) to DA ratio (i.e., turnover) in the prefrontal cortex and a higher ratio in the nucleus accumbens and ventral striatum than low responders (Piazza et al. 1991*b*). Stressors have also been reported to affect the mesocortical dopaminergic system. Dopaminergic neuronal activity measured in vitro in the prefrontal cortex is selectively activated following electric footshock in rodents (Deutch et al. 1985; Thierry et al. 1976). In vivo microdialysis studies have demonstrated that footshock stress (Abercrombie et al. 1989), as well as more mildly stressful stimuli such as handling and tailpinch (Cenci et al. 1992), increase DA overflow in the medial prefrontal cortex to a much greater degree than in either the nucleus accumbens or striatum. Restraint stress also increases the release of DA in brain regions associated with the mesocorticolimbic system (Imperato et al. 1989). Adrenalectomy attenuates this response, but exogenous injections of corticosterone can reinstate the DA response in ADX rats (Imperato et al. 1989).

Stress hormones also appear to influence DA neurotransmission. Glucocorticoid receptor binding sites have been identified on DA neurons in the VTA (Harfstrand et al. 1986). Chronic corticosterone administration increases dopaminergic activity (Wolkowitz et al. 1986) and alters normal responses to DA receptor agonists (Faunt and Crocker 1988), although the determination of a facilitating or inhibitory role for adrenocortical hormones depends on the specific behavioral test and conditions. Depletion of glucocorticoids by

adrenalectomy decreases both D_1 and D_2 DA receptor binding in the rat brain, and this effect is reversed following glucocorticoid replacement (Biron et al. 1992), suggesting that these hormones are involved in the modulation of central dopaminergic activity. Since stress and cocaine appear to affect similar neurochemical and neuroendocrine processes in rodents, then stress may sensitize the animals to the behavioral effects of cocaine (Kalivas and Duffy 1989), possibly resulting in changes in the reinforcing properties of the drug. Therefore, brain regions associated with the mesocortico-limbic dopaminergic system may be involved in the stress-induced facilitation of cocaine self-administration.

SUMMARY AND FUTURE DIRECTIONS

In summary, the data presented in this chapter have revealed an interesting relationship between stress-induced activation of the HPA axis and cocaine reinforcement. Benzodiazepines are among the most widely prescribed drugs for the pharmacological management of stress and anxiety. Agonists such as chlordiazepoxide and alprazolam specifically reduced cocaine self-administration in rats, possibly by decreasing the reinforcing efficacy of the drug. Self-administered cocaine increased benzodiazepine receptor binding primarily in discrete brain regions associated with the mesocorticolimbic dopaminergic system (i.e., nucleus accumbens and medial prefrontal cortex). Since these same brain regions have also been implicated in cocaine self-administration, the changes in benzodiazepine receptor binding might be directly relevant to cocaine reinforcement. Noncontingent electric footshock stress facilitated the acquisition of IV cocaine self-administration in rats. Footshock, as well as other stressors, also increase dopaminergic activity within the mesocorticolimbic DA system, suggesting that stress may sensitize rats to cocaine reinforcement. In addition, individual drug intake for these rats was correlated with plasma corticosterone measured before exposure to cocaine, indicating that the hormone must increase above a critical threshold for cocaine infusions to maintain self-administration. Adrenalectomy eliminated the acquisition of cocaine self-administration, and this behavior was reinstated with corticosterone replacement. Metyrapone, a corticosterone synthesis inhibitor, also reduced ongoing cocaine self-administration, suggesting that cortico-sterone may be involved in the maintenance as well as the acquisition of IV cocaine self-administration in rats. Future directions for this research might include investigations of the effects of specific corticosteroid receptor agonists and antagonists on IV cocaine self-administration in rats. These experiments would determine if the effects of stress on cocaine self-administration are actually mediated though the binding of stress hormones to corticosteroid receptors. The effects of

agonists and antagonists for both types of corticosteroid receptors (i.e., mineralo-corticoid and glucocorticoid) should be investigated. Cocaine self-administration may be attenuated by blocking the interaction of stress hormones with corticosteroid binding sites using specific receptor antagonists. On the other hand, corticosteroid receptor agonists might shift the dose-response curve for cocaine self-administration to the left.

The data reported here are potentially of great importance not only to the scientific community but to the general population as well. Some people appear to be able to use cocaine "recreationally" without escalating their patterns of use to levels that pose severe health threats, while other individuals are not able to control their drug intake (Siegel 1984). A better understanding of the behavioral and neurobiological variables potentially involved in why some individuals are able to control their cocaine use while others are not is important for the more efficient and effective treatment of cocaine abuse in humans. The data from these experiments suggest that controllability over environmental stress with resultant effects on the HPA axis may be one such variable. If certain individuals are more sensitive to stress, especially if they find themselves in an environment where they do not feel that they have adequate control over this stress, then these individuals may be more likely to use cocaine and other drugs of abuse. This could occur whether the person is an executive in a high-level stress position or a teenager living in a low-income, inner-city environment with no hope of ever advancing. This hypothesis is in agreement with controlled clinical investigations of the relationship between posttraumatic stress disorder (PTSD) and alcohol and drug abuse disorders. Vietnam theater veterans with PTSD experienced more severe drug and alcohol abuse problems than theater veterans without this disorder and were at greater risk for both forms of substance abuse (McFall et al. 1991; McFall et al. 1992). Other investigators have also reported an increased risk of alcoholism in men exhibiting a hyperreactive response to stress (Finn et al. 1992; Sher and Levenson 1982). Therefore, the continued investigation of the behavioral and neuroendocrinological variables involved in why rats without control over experimental stress are more vulnerable to self-administer cocaine may provide a useful model for understanding the behavioral and biological mechanisms involved in the genesis of cocaine use and dependence. In addition, this model might also be used to test pharmacological and behavioral treatments that may be potentially useful for human users of this and other abused substances.

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