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Cocaine's Effects on Neuroendocrine Systems: Clinical and Preclinical Studies

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MELLO, N. K. AND J. H. MENDELSON. *Cocaine's effects on neuroendocrine systems: Clinical and preclinical studies.* PHARMACOL BIOCHEM BEHAV **57**(3) 571–599, 1997.—This review examines the effects of cocaine on the neuroendocrine system and summarizes findings from clinical studies of cocaine abusers and preclinical studies in rodents and rhesus monkeys. The effects of acute and chronic cocaine administration on anterior pituitary, gonadal, and adrenal hormones are described, and the functional consequences of chronic cocaine exposure are discussed. Many of cocaine's acute effects on the endocrine system are consistent with its actions as a monoamine reuptake inhibitor. Acute cocaine administration stimulates release of gonadotropins, ACTH, and cortisol or corticosterone and suppresses prolactin levels. It has been difficult to detect changes in basal levels of most hormones or alterations in hormone responsiveness to a challenge dose of cocaine or other agents after chronic cocaine treatment. Interpretation of clinical data is often complicated by polydrug abuse involving opiates and alcohol as well as cocaine. However, preclinical studies of the effects of chronic cocaine exposure on integrated neuroendocrine function have revealed disruptions of the estrous cycle in rats and the menstrual cycle in rhesus monkeys. Furthermore, the menstrual cycle disorders observed in rhesus monkeys parallel those reported in women who abuse cocaine. Much remains to be learned about cocaine's interactions with the endocrine system and the consequences of cocaine abuse for reproductive function. © 1997 Elsevier Science Inc.

Cocaine Prolactin Luteinizing hormone Follicle stimulating hormone Adrenocorticotropic hormone Cortisol Corticosterone Estrous cycle Menstrual cycle

COCAINE abuse and dependence continues to be one of the nation's most serious drug abuse problems (2), and the associated social and economic costs include a number of adverse effects on health (135). Emergency room statistics indicate a high incidence of cocaine-related cardiovascular, cerebrovascular, and gastrointestinal illnesses (30,70,78). Cocaine and other abused drugs have direct suppressive effects on immune function (24,39,155,163), and immunosuppression, in combination with needle use and needle sharing, increases the risk for HIV infection and for other infectious disorders (1,51). In pregnant women, cocaine's vasoconstrictive and hypertensive actions may result in spontaneous abortion and premature labor as well as teratogenic effects (25,157,242). Moreover, it is important to recognize that cocaine abuse is not restricted to a small group of polydrug abusers but also affects the general population. In 1993, The National Institute on Drug Abuse's National Household Survey on Drug Abuse estimated that over 4.5 million people had used cocaine during the previous year and 1.3 million used it at least once a month. A major federal program to develop medications for cocaine abuse treatment is under way, but thus far the available pharmacotherapies have not been as effective as methadone, l-acetyl-methadone (LAAM), and buprenorphine for the treatment of opioid dependence (136,162,218).

Cocaine's effects on the neuroendocrine system are the focus of this review. Cocaine's interactions with prolactin and with the hypothalamic–pituitary–gonadal axis and the hypothalamic–pituitary–adrenal axis are poorly understood. However, cocaine-related changes in these hormones have broad implications for normal reproductive function as well as immune function. In addition, there is emerging evidence that cocaine's perturbation of anterior pituitary hormones may be related to its reinforcing properties (138,140). Illustrative clinical and preclinical studies of the effects of cocaine on anterior pituitary, gonadal, and adrenal hormones are described in the remainder of this review. We have emphasized findings from preclinical investigations, in part because of the relatively limited number of clinical studies. Also, animal models permit examination of the effects of cocaine alone, whereas in clinical studies of cocaine abusers, polydrug abuse often complicates interpretation of cocaine's effects on the endocrine system. The interactions of cocaine with other pituitary hormones (e.g., growth hormone, oxytocin, somatostatin) have been reviewed recently elsewhere (104,182) and will not be considered here.

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The first three sections of this review describe the effects of cocaine on the following endpoint measures: a) prolactin; b) adrenocorticotropic hormone (ACTH) and cortisol or corticosterone; and c) the gonadotropins and gonadal steroid hormones. In each of these sections, the acute and chronic effects of cocaine are considered separately. The disruptive effects of chronic cocaine exposure on reproductive function are described in the fourth section of this review. Some of the ways in which cocaine's effects on anterior pituitary and gonadal steroid hormones may interact to disrupt the menstrual cycle and impair reproductive function are discussed. At present, relatively little is known about the mechanisms by which cocaine and other abused drugs disrupt the menstrual cycle in women and compromise reproductive function in men. However, an improved understanding of the interactions between the neuroendocrine system and cocaine use and abuse may clarify some aspects of the neurobiology of substance abuse.

COCAINE'S EFFECTS ON PROLACTIN REGULATION

Background

Prolactin exists in all vertebrates, and one of its primary physiological functions is the stimulation of milk production and the maintenance of lactation after pregnancy. Prolactin also has a number of other behavioral and physiologic effects in humans and other species (112,147,163,250). For example, in addition to its effect on the mammary glands, prolactin also influences migration in birds, parenting behavior in birds and mammals, and the maintenance of water and electrolyte balance (147). Prolactin levels increase in response to diverse stimuli such as suckling, nipple stimulation, coitus, exercise, and stress. Sleep is also associated with increases in pulsatile prolactin release, and basal prolactin levels are highest between 4 and 6 a.m. (112) Prolactin is secreted from the lactotrope cells, which account for 40–50% of all cells in the anterior pituitary (250). During late pregnancy, the lactotropes nearly double in size, and prolactin secretory activity increases (250). Two subtypes of lactotropes have been identified, and these are sensitive to dopamine or to TRH. The dopamine-sensitive lactotropes, which have primarily D_2 dopamine receptors, secrete significantly more prolactin than TRH-sensitive lactotropes (250). In in vitro models, dopamine occupancy of the D_2 receptors on the lactotropes is correlated with inhibition of prolactin release, and following dissociation of dopamine from the D_2 receptors there is an increase in prolactin release (114). The regulation of prolactin release is complex and appears to involve both neuroendocrine and paracrine mechanisms (248–250). Unlike the pituitary gonadotropins, prolactin is not regulated by negative feedback from peripheral target sites. Rather, prolactin appears to control its own secretion by feedback regulation of hypothalamic dopamine (248–250). This regulatory system is further complicated by the fact that dopamine release from the tuberoinfundibular dopamine neurons is autoregulated by dopamine itself (178).

Dopamine inhibits prolactin release in humans, rhesus monkeys, and rodents (11,49,146,149,248–250). Cocaine acts as an indirect dopamine agonist because it binds to the dopamine transporter and blocks the reuptake of dopamine (96,97,168). Cocaine also inhibits prolactin after acute administration, probably as a result of increasing dopamine levels (64,124,132). Other dopamine agonists such as apomorphine and bromocriptine, which have a high affinity for D_2 receptors, also inhibit prolactin release (250). Conversely, D_2 receptor antagonists (e.g., domperidone, haloperidol, metoclopromide) stimulate prolactin release by antagonizing endogenous dopaminergic inhibition (250). However, clinical and preclinical studies suggest that cocaine changes prolactin levels in different ways during acute and chronic administration. It appears that chronic cocaine abuse may impair the sensitive regulatory feedback relationship between hypothalamic dopamine and prolactin to culminate in disregulation and abnormally high levels of prolactin or hyperprolactinemia (32,139,243,244). Thus, an acute cocaine-induced suppression of prolactin levels appears to be inconsistent with the hyperprolactinemia sometimes seen clinically. It is generally believed that cocaine's blockade of dopamine reuptake may eventually result in downregulation of dopamine receptors and decreased dopaminergic tone, a phenomenon often described as dopamine depletion (32, 243,244). This concept is consistent with decreases in D_1 and D_2 dopamine receptors observed in several brain regions after cocaine exposure in animal models (43,76,90,151,244). Clinical studies have also shown a decreased density of dopamine D_2 receptors associated with reduced brain glucose metabolism in the frontal lobe regions of abstinent cocaine abusers (232).

The clinical consequences of cocaine-induced prolactin disregulation and hyperprolactinemia include compromised reproductive function and immune function (122,155,163,193,206). Because IV drug abusers are already at high risk for HIV infection (1,188,201), cocaine-induced prolactin disregulation may enhance vulnerability to infection. Disorders of reproductive function such as amenorrhea (the failure to menstruate) have also been associated with hyperprolactinemia, although each condition can occur independently. Clinical evidence suggests that hyperprolactinemia may be an index of the severity of cocaine dependence and may predict relapse to cocaine abuse (209,236). However, in addition to chronic cocaine abuse, a variety of other pathological conditions such as renal failure, pituitary tumors (prolactinomas), transection of the pituitary stalk, hypothyroidism, and Laennecs's cirrhosis may also result in hyperprolactinemia (112).

The acute and chronic effects of cocaine on prolactin in clinical and preclinical studies will be reviewed in the remainder of this section. It is well known that a number of abused drugs may have different effects on neuroendocrine hormones if intoxication occurs occasionally or repeatedly through time, and cocaine's effects on prolactin are one of the most dramatic examples of this phenomenon (126,130). The disparities between the acute and chronic effects of cocaine on basal levels of prolactin indicate the importance of examining both exposure conditions in an effort to clarify how cocaine may disrupt prolactin regulation.

Preclinical Studies of Acute Effects of Cocaine on Prolactin

In rodent models, the acute effects of cocaine on prolactin have been inconsistent. Both suppression of prolactin (10,105,161,202) and no change in prolactin levels have been reported (156). Vast differences in cocaine doses and routes of administration and in the frequency and duration of sample collection limit meaningful comparisons among studies. In rhesus monkeys, prolactin levels decreased after acute administration of either cocaine, an indirect dopamine agonist, or dopamine itself (49,124–126,132,146). In drug-naive female rhesus monkeys, cocaine administration was followed by a significant decrease in basal prolactin levels (124,132). All females were studied during the early follicular phase of the menstrual cycle, 4–7 days after the onset of menstruation (124). In this study, as well as our subsequent studies, cocaine

doses (0.4 or 0.8 mg/kg IV) were selected to be comparable to those shown to produce subjective and physiological effects in humans (e.g., 32–64 mg/70 kg) (48). Moreover, previous studies had shown that a cocaine dose of 1 mg/kg IV is safe in rhesus monkeys, whereas 3–8 mg/kg IV is in the convulsant dose range (116,117,144).

Figure 1 summarizes data from the first study conducted in our laboratory on the acute effects of cocaine on prolactin levels in female rhesus monkeys. Prolactin levels decreased gradually and reached a nadir within 40–80 min after cocaine administration (124). The generality of this cocaine-related decrease in basal prolactin levels in rhesus monkeys was subsequently established in males and in mid-luteal phase rhesus females (132). The duration of prolactin suppression after cocaine administration corresponded to the estimated half-life of IV cocaine (1 mg/kg) in rhesus monkey plasma (144). Prolactin began to increase within 80–90 min and returned to or exceeded baseline in 10 of 18 studies. In some monkeys, there was a gradual rebound elevation of prolactin, whereas in others, prolactin increased very rapidly. Illustrative data from individual monkeys are shown in Fig. 2. These postcocaine increases in prolactin are reminiscent of the rebound increases in prolactin observed after cessation of exogenous dopamine infusions in rhesus monkeys (49) and after cessation of both dopamine and L-dopa infusions in humans (98,101,102). In rhesus monkeys, prolactin levels increased rapidly within 10–20 min after brief interruptions (2.5, 5.0, and 7.5 min) of a continuous infusion of dopamine and remained elevated for 35–110 min (49). Taken together, these findings suggested that recurrent episodes of acute cocaine intoxication may be associated with biphasic effects on prolactin similar to those observed after cocaine or dopamine administration (49,124). In behavioral studies in rats, cocaine self-administration was associated with rapid increases in extracellular dopamine (measured by microdialysis in the nucleus accumbens), and peak increases in dopamine were measured within 3 min after IV

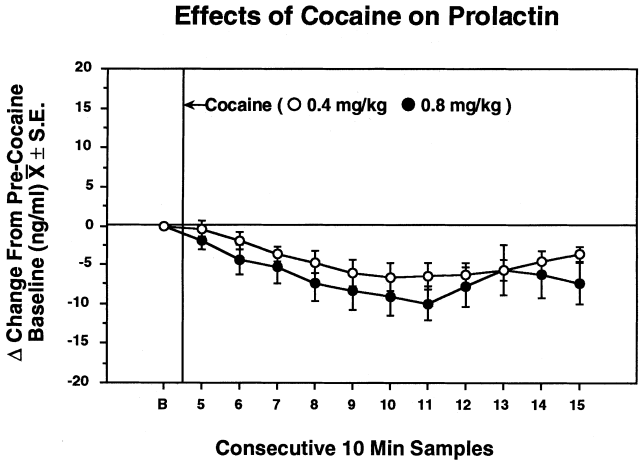

FIG. 1. Effects of cocaine on basal prolactin levels in female rhesus monkeys. Integrated plasma samples were collected at 10-min intervals over 150 min. Cocaine (0.4 or 0.8 mg/kg IV) was administered after sample 4, as indicated by the vertical line. Data are expressed as change scores (open triangles) from baseline levels. Each prolactin data point (closed circles) represents the mean (± SE) of seven follicular phase female rhesus monkeys. (Adapted from Mello et al., *J. Pharmacol. Exp. Ther.* 254(3):815–823; 1990. Reprinted with permission.)

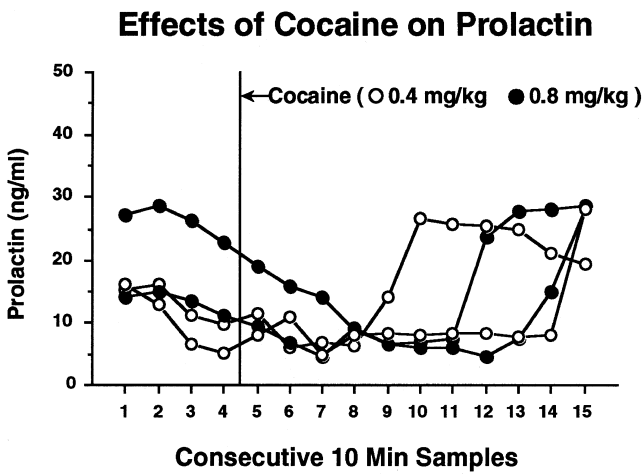

FIG. 2. Effects of cocaine on prolactin levels in individual female rhesus monkeys. Prolactin after administration of 0.4 mg/kg IV cocaine is shown as open circles; prolactin after administration of 0.8 mg/kg IV cocaine is shown as closed circles. All other details of sample collection are identical to those described for Fig. 1. (Adapted from Mello et al., *J. Pharmacol. Exp. Ther.* 254(3):815–823; 1990. Reprinted with permission.)

cocaine injections (240). The average interinjection interval was 10 min, and dopamine decreased before the next injection (240). It is reasonable to postulate that similar fluctuations in dopamine levels may accompany cocaine self-administration by humans, and that changes in dopamine levels may result in biphasic decreases and increases in prolactin. Thus, chronic cocaine use may impair the sensitive regulatory cycle of prolactin and hypothalamic dopamine release to culminate in disregulation and sustained hyperprolactinemia (124,126). Preclinical and clinical data consistent with this hypothesis are described below in the section on the effects of chronic cocaine exposure on prolactin (126,139).

Cocaine's suppression of prolactin in rhesus monkeys is consistent with evidence that prolactin is under inhibitory dopaminergic control in rhesus monkeys, humans, and rodents (11,49,146,149,249,250,253). Moreover, the time course of prolactin suppression (within 40–60 min after IV cocaine administration) was consistent with that following infusion of dopamine in rhesus monkeys (149) and normal women (101). However, cocaine influences many endocrine and neurotransmitter systems in addition to its blockade of dopamine reuptake, and the contribution of these effects to prolactin suppression is unclear. Interestingly, ovariectomized rhesus females are one exception to the general finding that cocaine significantly suppresses prolactin levels in rhesus monkeys (133). Administration of the same doses of cocaine (0.4 and 0.8 mg/kg IV) under identical conditions had no effect on basal prolactin levels in ovariectomized females. Whether this lack of effect was due to low precocaine baseline prolactin levels (3.6 and 5.5 ng/ml) or the absence of gonadal steroid hormones in ovariectomized females is unknown and is currently under investigation in our laboratory.

Clinical Studies of Acute Effects of Cocaine on Prolactin

In human cocaine abusers, acute cocaine administration did not decrease prolactin levels significantly. The effects of an acute dose of cocaine (30 mg IV) on prolactin release were

examined in 18 men who met DSM-III-R criteria for dependence on both cocaine and opioids (142). All men had low normal prolactin levels under drug-free conditions, and prolactin decreased significantly after both cocaine and placebo administration (142). Similarly, in men who reported occasional cocaine use (at least three times per month), cocaine (40 mg IV) did not change prolactin levels significantly (9). The reason for these discrepancies between men and rhesus monkeys is unclear but may reflect differences in the history of cocaine exposure. This interpretation is supported by the finding that in cocaine-naive men, intranasal cocaine (2 mg/kg) significantly decreased plasma prolactin levels (64). Prolactin decreased after both placebo and cocaine administration, but prolactin levels were significantly lower at 60 and 90 min after cocaine administration than at 60 and 90 min after placebo administration (64). The time course of decreases in prolactin levels after intranasal cocaine was somewhat slower than after intravenous cocaine in rhesus monkeys (64,124). Prolactin levels reached a nadir after 90 min in humans (64) and after 60–70 min in rhesus monkeys (124). These differences probably reflect the differences in the pharmacokinetic profiles of intranasal and intravenous cocaine.

Preclinical Studies of Chronic Effects of Cocaine on Prolactin

Cocaine's acute suppression of prolactin contrasts sharply with the development of hyperprolactinemia after chronic use, but little is known about the determinants or the time course of this transition and whether or not it can be detected in animal models. The duration of persistence of cocaine-related abnormalities in prolactin after cocaine abstinence is also unclear, and findings are inconsistent across studies. These questions are part of the larger issue of the extent to which chronic cocaine may produce enduring changes in brain function as reflected in neuroendocrine measures.

One approach to this question is to examine changes in prolactin regulation during chronic cocaine exposure using a provocative test of prolactin release. In clinical endocrinology, dopamine agonists are often used to study relative resistance to prolactin suppression in hyperprolactinemic patients (7,57,66,190). An increase in prolactin after discontinuation of an exogenous dopamine infusion has been consistently observed in humans (83,101,248) and rhesus monkeys (146,149), and the magnitude of the increase provides another index of prolactin regulation. For example, in normal intact female rhesus monkeys, the postdopamine prolactin increase usually does not exceed baseline levels, but in hyperprolactinemic females, prolactin may increase significantly above baseline levels after dopamine suppression (49,146). Even brief interruptions of a continuous infusion of dopamine can result in rapid (within 10–20 min) increases in prolactin in rhesus monkeys made hyperprolactinemic by surgical transection of the hypophyseal stalk and estrogen replacement (49). These data suggested to us that a similar paradigm could be used to evaluate changes in dopamine regulation of prolactin during chronic cocaine exposure (126). Although exogenously administered dopamine does not cross the blood–brain barrier, it does act at the median eminence and the anterior pituitary to regulate prolactin secretion (248).

We examined the effects of dopamine perturbation on prolactin levels in drug-naive rhesus females before cocaine self-administration and again at repeated intervals for up to 2.7 years of daily cocaine self-administration (126). The primate model of drug self-administration simulates human drug abuse insofar as monkeys self-administer cocaine at levels comparable to those often reported clinically. One advantage of this model is that it permits examination of the contribution of cocaine alone to any changes in prolactin regulation without the confounding influence of polydrug use often seen in human cocaine abusers (28,41,54,94,95,189). Operant behavioral procedures were used to maintain chronic cocaine and food self-administration. Monkeys were surgically implanted with intravenous catheters under aseptic conditions to permit response-contingent IV cocaine self-administration (126). Cocaine (0.10 mg/kg/injection) and food (1-g banana pellets) were available under a second-order schedule of reinforcement that required an average of 64 responses for each drug injection or food pellet. Cocaine and food were available during four daily sessions that lasted for 1 h or until 25 pellets or 20 injections were delivered. Cocaine injections were limited to 80 per day (8 mg/kg/day) to minimize the possibility of adverse drug effects (126). Under these conditions of self-regulated cocaine access, monkeys controlled the number and frequency of cocaine injections, remained healthy, and continued to self-administer cocaine for 2 years or more.

During the course of training, monkeys were adapted to placement in a standard restraining chair and to routine venipuncture procedures. On each endocrine study day, a catheter was implanted into the saphenous vein and monkeys were placed in a restraining chair during blood sample collection. Three successive 80-min dopamine infusions (10 μg/kg/min IV) were alternated with 20-min interruptions of the dopamine infusion to assess the degree of prolactin suppression and the magnitude of rebound increases in prolactin. The dose of dopamine selected for study produces plasma dopamine concentrations equivalent to those measured in hypophyseal stalk blood of rhesus monkeys (146). This dose of dopamine produced maximal suppression of prolactin in both intact and pituitary stalk-sectioned female rhesus monkeys, whereas higher doses (20–40 μg/kg/min) did not produce significantly greater decreases in prolactin and a lower dose (6 μg/kg/min) had no effect (149).

Dopamine significantly reduced prolactin levels below baseline levels within 60–80 min in drug-naive and in cocaine-experienced female rhesus monkeys (126). In four drug-naive follicular phase females, the prolactin increases after dopamine suppression never exceeded predopamine baseline levels of 6.2 ng/ml (Fig. 3, top panel). This finding is consistent with previous studies of normal rhesus females (146,149). During chronic cocaine self-administration, basal prolactin levels were 227% to over 350% higher than before cocaine exposure. Moreover, the rebound increases in prolactin after dopamine infusions exceeded these high baseline levels. For example, after an average of 74 days of cocaine self-administration at an average dose of 3.7 mg/kg/day, the postdopamine infusion increases in prolactin were significantly higher than under drug-free control conditions and reached hyperprolactinemic levels of 57.6 ng/ml (Fig. 3, middle panel). These prolactin levels exceeded the clinical criteria for hyperprolactinemia, i.e., daytime prolactin levels above 25 ng/ml (112). After an average of 300 days of cocaine self-administration (6.5 mg/kg/day), rebound increases in prolactin peaked at 339% above predopamine basal levels (Fig. 3, lower panel) (126). A similar pattern of postdopamine prolactin increases to hyperprolactinemic levels (ranging from 44.5 to 141.2 ng/ml) was also measured in two other females studied after 19–20 months of chronic cocaine self-administration. The dramatic prolactin rebound to 141.2 ng/ml shown in Fig. 4 (top panel) anticipated the subsequent development of hyperprolactinemia. After 2.7

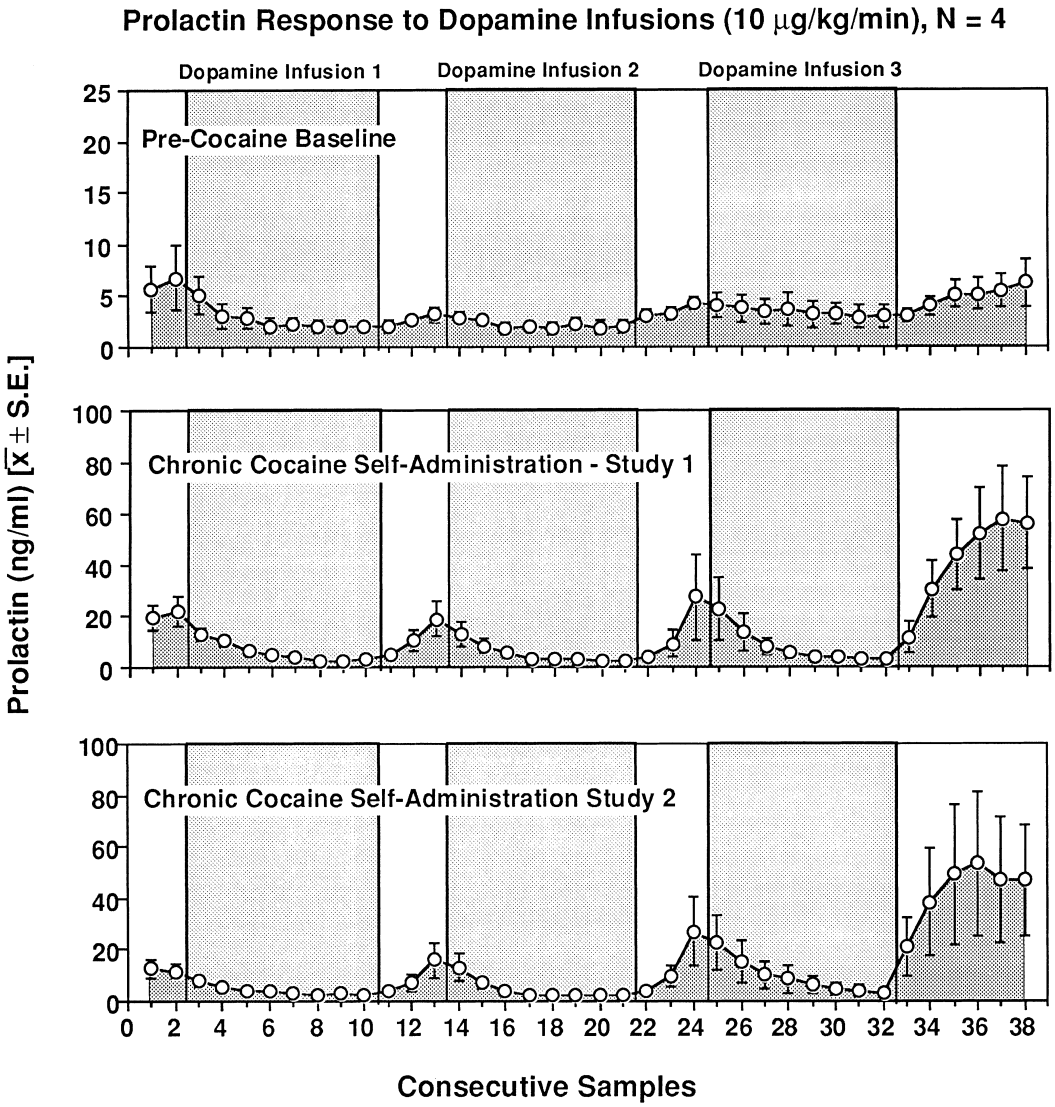

FIG. 3. Effects of dopamine infusions and interruptions on prolactin before and after chronic cocaine self-administration. A continuous infusion of dopamine (10 μg/kg/min) was started immediately after collection of samples 2, 13, and 24. Each dopamine infusion continued for 80 min and stopped abruptly after collection of samples 10, 21, and 32. Bolus samples for prolactin analysis were collected at 10-min intervals except during the first two interruptions of the dopamine infusion, when the first two samples were collected at 5-min intervals. Prolactin levels (nanograms per milliliter) are shown on the left ordinate, and consecutive samples are shown on the abscissa. Each data point represents the mean (± SE) of the four female rhesus monkeys. (Adapted from Mello et al., *J. Pharmacol. Exp. Ther.* 270(3):1110–1120; 1994. Reprinted with permission.)

years of cocaine self-administration, one monkey developed persistent hyperprolactinemia during cocaine withdrawal, and prolactin levels averaged 326 ng/ml after 89 days of cocaine abstinence (Fig. 4, lower panel).

In summary, we observed a biphasic prolactin response to dopamine perturbation. Dopamine induced a prompt suppression of prolactin before and during cocaine self-administration. In drug-naive females, prolactin returned to baseline levels after dopamine suppression. However, during chronic cocaine self-administration, prolactin increased significantly above baseline levels during interruptions of dopamine infusions, and basal (predopamine) prolactin levels also increased significantly. These data suggest that exogenous dopamine infusions may be a sensitive procedure for monitoring changes in regulation of prolactin secretion during chronic cocaine self-administration and withdrawal. These findings are consistent with clinical evidence that chronic cocaine abuse can produce persistent derangements in prolactin regulation, as described in the next section.

In rodent models, the effects of an acute cocaine challenge after chronic cocaine maintenance have been evaluated, and there is general agreement that acute administration of cocaine is followed by a decrease in prolactin after chronic cocaine exposure (10,14,105,156). For example, chronic treatment with cocaine (15 mg/kg IP) for 3 or 7 days (10,14) or for 14 days (105) did not alter the prolactin response to an acute

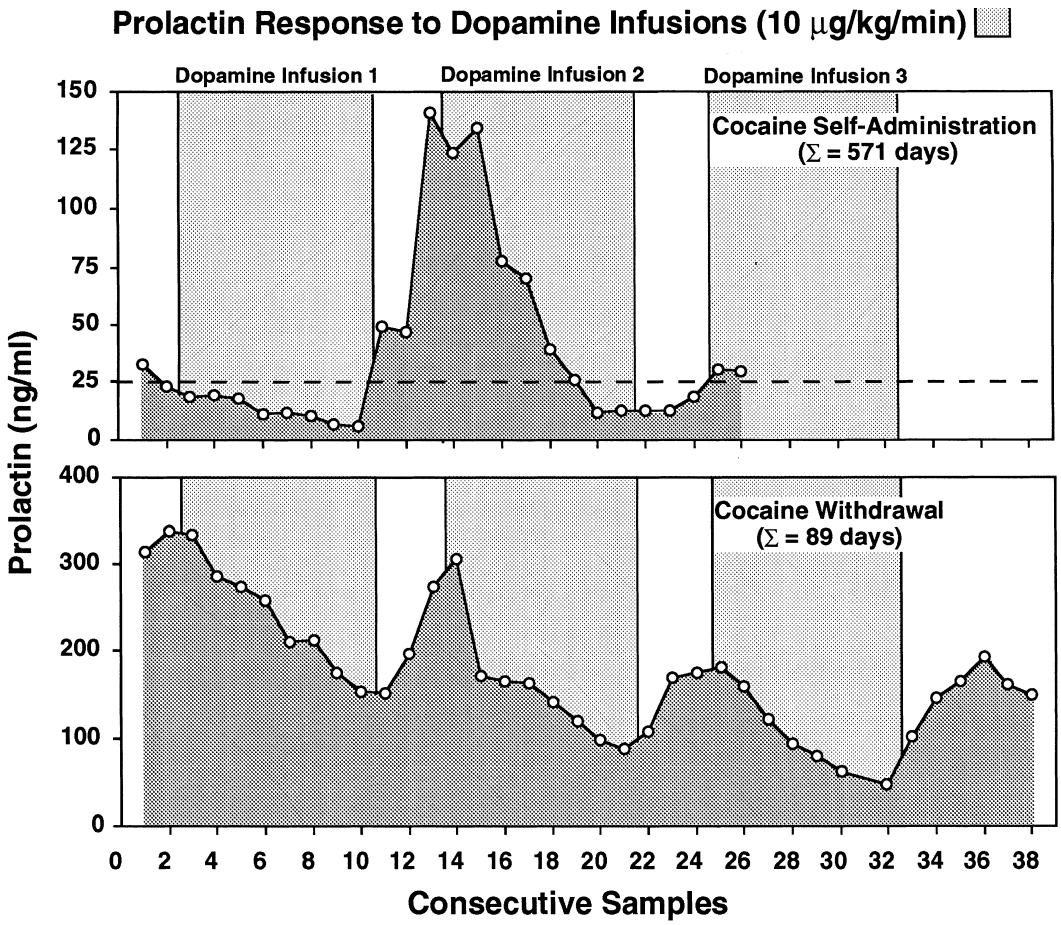

FIG. 4. Effects of dopamine infusions and interruptions on prolactin levels in one female rhesus monkey during cocaine self-administration and after cocaine withdrawal. Dopamine infusion and sample collection procedures were the same as described for Fig. 3. (Adapted from Mello et al., *J. Pharmacol. Exp. Ther.* 270(3):1110–1120; 1994. Reprinted with permission.)

cocaine challenge. In addition, maintenance on a lower dose of cocaine (10 mg/kg, administered in 10 divided doses of 1 mg/kg over 2 h) for 10 days resulted in a cocaine dose-dependent decrease in prolactin, whereas acute administration of cocaine (1, 3, and 10 mg/kg) did not (156). The duration of chronic exposure in these studies (3–14 days) was not sufficient to alter prolactin regulation as measured by cocaine-induced suppression of prolactin.

Clinical Studies of Chronic Effects of Cocaine on Prolactin

Chronic cocaine abuse is sometimes associated with hyperprolactinemia during and following periods of active cocaine abuse (27,32,55,139). However, not all cocaine abusers develop clinically significant hyperprolactinemia, and low to normal prolactin levels have been reported during active cocaine use as well as during cocaine withdrawal (56,103,186,204). After cocaine abuse for 8 years, persistent elevations in prolactin associated with galactorrhea (abnormal secretion of breast milk) were observed during cocaine abstinence (27).

The factors that determine relative vulnerability to (or protection from) cocaine-related disruption of prolactin regulation are unclear. In a sample of 42 patients admitted for cocaine abuse treatment, five had high prolactin levels (20.7–39 ng/ml) and reported using less cocaine (6 vs. 9.9 g/week) for a shorter period of time (5.6 vs. 7.2 years) than patients with normal prolactin levels (236). In another clinical sample, four hyperprolactinemic male cocaine abusers reported using cocaine for 2–7 years, whereas the normoprolactinemic cocaine abusers reported using equivalent amounts of cocaine for 1–10 years (139). Years of cocaine abuse, but not reported cocaine dose, was correlated with decreased dopamine D_2 receptor density in human cocaine abusers (232).

Pituitary enlargement in male cocaine abusers. There is recent evidence from brain imaging studies that the pituitary gland is larger in men who abuse cocaine chronically than in controls (211). An increase in pituitary size could reflect generalized hyperplasia of the lactotropes (the cells that release prolactin). Pituitary enlargement is also observed during late pregnancy, when prolactin levels are high (112). However, a comparable increase in pituitary volume has not been observed in women after an equivalent history of cocaine abuse: cocaine-abusing women did not differ from normal control women in pituitary volume measures (210). These data suggest that men may be somewhat more vulnerable to cocaine-related changes in pituitary volume than women, and indeed a

higher incidence of hyperprolactinemia has been detected in men (four of five) in our clinical sample (236). However, pituitary volume has not been measured in hyperprolactinemic cocaine abusers, and the extent to which pituitary enlargement may covary with vulnerability for development of hyperprolactinemia is unknown.

Pulsatile release of prolactin in chronic cocaine abusers. Prolactin release is pulsatile, and the release patterns have been well characterized in human males (228). We examined prolactin pulsatile release patterns to determine whether the abnormally high levels of prolactin observed in some chronic cocaine abusers reflect aberrant patterns of release (139). The pulsatile release patterns of prolactin in chronic cocaine abusers with high prolactin levels (22–44 μg/liter) and in chronic cocaine abusers with normal prolactin levels were compared with those of normal control men (139). The cocaine abusers all had positive urine screens for cocaine and/or cocaine metabolites at the time of the study. The reported duration and doses of cocaine used did not distinguish the cocaine abusers with hyperprolactinemia from those with normal prolactin levels. Blood samples for prolactin analysis were collected at 10-min intervals for 6 h, and prolactin release patterns were analyzed with the cluster analysis program developed by Veldhuis and Johnson (227). The amplitude rather than the frequency of prolactin pulses distinguished the cocaine abusers from the normal controls. The hyperprolactinemic cocaine abusers had higher average prolactin peak heights than did controls or normoprolactinemic cocaine abusers, and also had higher average prolactin levels between peaks than the other groups. Examples of pulsatile prolactin release patterns in a hyperprolactinemic cocaine abuser and a normoprolactinemic cocaine abuser are shown in Fig. 5. We interpreted these data to suggest that hyperprolactinemia may be due to a cocaine-induced derangement of dopaminergic inhibition of basal prolactin secretion (139). These findings are consistent with the escalating prolactin levels after dopamine suppression observed in rhesus monkeys chronically exposed to cocaine shown in Figs. 3 and 4 (126).

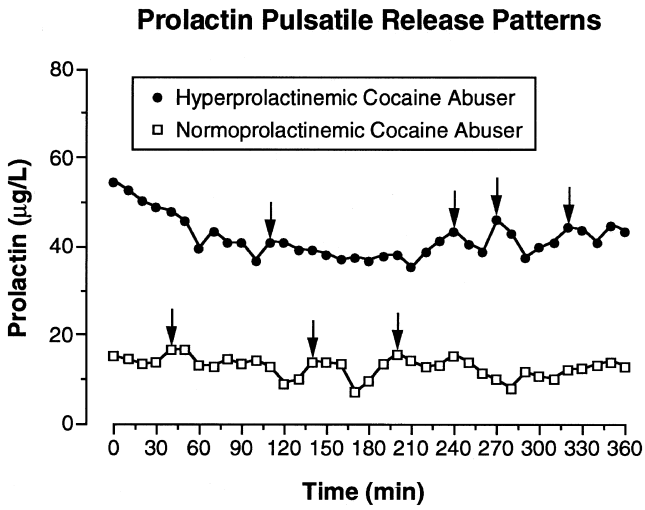

FIG. 5. Effects of chronic cocaine abuse on pulsatile release of prolactin in men: prolactin pulsatile release patterns in a cocaine abuser with hyperprolactinemia and a cocaine abuser with normal prolactin levels. Samples for prolactin analysis were collected at 10-min intervals over 6 h and evaluated with cluster analysis procedures. Each arrow indicates a pulse detected by the cluster analysis program. These individuals were part of the group of subjects described by Mendelson et al. (139).

Effects of dopamine agonists on prolactin in chronic cocaine abusers. It has been difficult to interpret variations in hormone levels measured during cocaine withdrawal because the amount and duration of cocaine use are unknown and subjects are often polydrug abusers. McDougle and coworkers (119) studied cocaine-dependent men who reported using only cocaine (at least 1 g of cocaine each week with periodic cocaine binges of 3 g within 5 days). After admission to a clinical research ward, three doses of oral cocaine (1.0 mg/kg) were administered each day for 3 days, then placebo-cocaine capsules were administered for 9 days. The effects of a dopamine agonist challenge on prolactin and growth hormone levels were studied to determine if there were detectable changes in dopamine function during early and late cocaine withdrawal. Homovanillic acid (HVA) and 3-methoxy-4-hydroxyphenethyleneglycol (MHPG), the principal metabolites of dopamine and norepinephrine, were also measured. The effects of a dopamine agonist, Sinemet® (L-dopa 250 mg/carbidopa 25 mg), and placebo-Sinemet were compared 1 and 2 days and 15 and 16 days after the period of controlled cocaine exposure.

Basal prolactin levels were equivalent during early and late cocaine withdrawal, and there were no differences in the effects of Sinemet on prolactin. Prolactin decreased to a nadir within 180 min after Sinemet administration and remained low throughout the remainder of the sampling period (240 min). Placebo-Sinemet had no effect on any measure. After a Sinemet challenge, increases in growth hormone and HVA were significantly greater during early withdrawal than during late withdrawal. There were no significant differences in MHPG. These data were interpreted as evidence for a compensatory response of dopamine neurons to an acute deficiency of synaptic dopamine after cocaine exposure that normalized through time (119). The normal hormonal levels observed 2 weeks after cessation of cocaine use are consistent with findings from previous studies of cocaine abusers during withdrawal (186). Similarly, when the prolactin response to an apomorphine challenge was studied at various intervals after street cocaine use, low doses of apomorphine (0.01 mg/kg SC) did not change prolactin levels significantly in comparison to levels in control subjects (103). A higher dose of apomorphine (0.75 mg SC) was followed by a decrease from normal to low prolactin levels (8 ± 2.1 ng/ml to 5.7 ± 1.6 ng/ml) during cocaine withdrawal (69).

An alternative approach to the question of changes in dopaminergic responsivity as a function of cocaine exposure is to examine the effects of a dopamine agonist on both the degree of prolactin suppression and the subsequent rebound increase in prolactin [cf. (126)]. In ongoing studies, we are examining the effects of Sinemet on prolactin levels in cocaine- and opioid-dependent men in comparison to normal control men. Cocaine- and opioid-dependent men were studied after 6–8 days of abstinence under controlled research ward conditions. Samples for prolactin analysis were collected for 480 min after Sinemet administration. Oral administration of Sinemet produced a rapid suppression of prolactin within 30–45 min in both groups. However, the degree of suppression was significantly greater in control subjects than in the chronic cocaine and opioid abusers (70% vs. 45%). The post-Sinemet increase in prolactin was equivalent in both groups (J. H. Mendelson, pers. comm., 1996). These findings differ from our previous observations in rhesus monkeys, where the post-dopamine prolactin increase was greater after chronic cocaine exposure than in naive monkeys (126).

COCAINE'S EFFECTS ON ACTH AND CORTISOL

Background

The hypothalamic–pituitary–adrenal (HPA) axis is the major endogenous hormonal system that activates the integrative physiological response to stress. Corticotropin-releasing hormone (CRH) regulates the pulsatile release of ACTH from the anterior pituitary. CRH is secreted by neurons in the basal hypothalamus, and CRH and ACTH secretion are under negative feedback control by cortisol, which is released from the adrenal cortex. A number of neuronal systems are involved in the regulation of CRH secretion. Noradrenergic and adrenergic neuronal modulation may increase the pulsatile release of CRH. Serotonergic and dopaminergic systems may be involved in both stimulation and inhibition of CRH secretion, and endogenous opioid systems have been shown to inhibit CRH secretion (251).

It has been long known that CRH activation of ACTH release and the subsequent increase of cortisol secretion from the adrenal are essential for prompt responses of the cardiovascular, respiratory, gastrointestinal, and immune systems to stress. Cocaine-induced modulation of the HPA axis may result in disruption of normal immune–neuroendocrine interactions and immune function [see (12,163) for review]. Consequently, intravenous cocaine abuse may amplify risk for HIV infection (1,188,201). It is known that ACTH may inhibit macrophage activation and synthesis of IgG and interferony(163) and that CRH may have a stimulatory effect on lymphocyte and monocyte proliferation and activation (163). Corticotropin, acting through the adrenal cortex and the secretion of glucocorticoids, may suppress proliferation of lymphocytes and the secretion of inflammatory mediators (79, 153,163). Glucocorticoids directly stimulate the transcription of the HIV virus in vitro (111,195) and therefore may increase susceptibility to AIDS (153). These data converge to suggest that persons who abuse cocaine may be at enhanced risk for HIV infection (24) due to immunosuppression consequent to activation of the HPA axis. In addition to CRH secretion in the basal hypothalamus, there is also evidence that corticotropin-releasing hormones are widely distributed throughout the central nervous system. These multiple corticotropin-releasing hormone systems in the brain appear to regulate processes associated with pain perception, affective states, learning, arousal, and motivation (251).

There is general agreement that cocaine stimulates ACTH and cortisol secretion in humans (9,65,140,212), rhesus monkeys (183), and rats (13,106,145,156,170,181,214–216). Cocaine also stimulates CRH release from hypothalamic tissue in vitro (20) and alters CRH levels in different brain structures in vivo (179). Antagonism of CRH release prevents cocaine stimulation of ACTH (170,180). Taken together, these studies suggest that the cocaine-induced stimulation of the HPA axis is mediated by hypothalamic CRH. The exact mechanisms underlying cocaine's effects on the HPA axis remain to be clarified, but it is increasingly apparent that cocaine-related stimulation of ACTH (and by inference CRH) is modulated by several interacting neurotransmitter systems. CRH release is regulated by dopamine and serotonin, and antagonists that are selective for dopamine receptors or for 5-HT receptors attenuate cocaine-induced stimulation of ACTH (13, 106). Moreover, both dopamine and 5-HT receptor agonists stimulate ACTH release in rats (8,13,104,220). The complex relationships among cocaine, dopamine, serotonin, and the HPA axis have been reviewed recently (104). The stimulatory effects of cocaine on ACTH and cortisol/corticosterone appear to be related primarily to its acute effects. Peak levels of ACTH coincide with peak levels of plasma cocaine, and ACTH remains elevated for 30–45 min. In contrast, chronic cocaine exposure usually does not alter basal levels of ACTH and cortisol/corticosterone or the hormonal response to acute stimulation with cocaine or synthetic corticotropin-releasing factor (CRF) (14,100,105,156,215,216,220). Moreover, ACTH and cortisol pulsatile release patterns were equivalent in cocaine-abusing men and normal men studied under similar conditions (77, 139,212). Some illustrative studies of the acute and chronic effects of cocaine on ACTH and cortisol in humans and rhesus monkeys and on ACTH and corticosterone in rats are described below.

Preclinical Studies of Acute Effects of Cocaine on ACTH and Cortisol

Acute effects of cocaine on ACTH and corticosterone in rodent models. There is an extensive literature indicating that acute administration of cocaine increases levels of ACTH and corticosterone in rats (13,106,145,156,170,177,180,214–216). Cocaine's effects on ACTH and corticosterone appear to be centrally mediated because intracerebroventricular (ICV) injections of cocaine (50, 200, 500, and 1000 μg/kg) result in dose-dependent increases in ACTH and corticosterone levels (106). These ICV doses of cocaine were approximately 300 times lower than IP doses required to produce equivalent increases in ACTH and corticosterone (106). The observed difference in potency of ICV or systemic cocaine administration is consistent with the fact that cocaine is rapidly degraded by tissue and plasma cholinesterases.

There is considerable evidence that the stimulatory effects of cocaine on ACTH and corticosterone are mediated by CRF. Cocaine-induced increases in ACTH release were prevented by passive immunization against CRF (170,180). Moreover, pretreatment with a CRF receptor antagonist prevented the cocaine-induced increase in corticosteroids in rats (180). In in vitro models, cocaine stimulated CRF release from hypothalamic tissue (20) but had no effect on ACTH secretion from dispersed pituitary cells (170). More recently, it was found that acute cocaine administration increased levels of CRF mRNA in the paraventricular nucleus of the hypothalamus, suggesting that cocaine stimulated CRF synthesis and release in this region (169). Moreover, bilateral lesions of the paraventricular nuclei attenuated cocaine stimulation of ACTH release (169).

The effects of repeated acute administration of cocaine on ACTH and corticosterone have also been examined in rats (214). Three doses of cocaine (5 mg/kg IV) or vehicle control were administered at intervals of 1, 2, 4, and 6 h. Samples for ACTH and corticosterone analysis were collected before and 10 min after IV cocaine administration. Cocaine stimulated a significant increase in ACTH at all treatment intervals, but there was a significant decrease in the magnitude of the ACTH response over time in the 1-, 2-, and 4-h-interval treatment paradigms. In contrast, corticosterone increases were equivalent after each cocaine injection at all interinjection intervals. Subsequently, cocaine was administered to adrenalectomized rats to evaluate the contribution of negative corticoid feedback to the time-related diminution in the ACTH response to cocaine. Despite elevated basal ACTH levels (over 1000 pg/ml in comparison to 40–50 pg/ml in intact rats), cocaine administration was followed by a significant increase in ACTH at each 2-h time interval. However, when cocaine was

administered at 1-h intervals, the ACTH levels were not significantly different from control levels after the second cocaine injection, and ACTH levels were significantly lower after the third cocaine injection than after the first cocaine injection. Because adrenalectomy attenuated the time-dependent decrease in ACTH after cocaine administration, these data suggest that negative corticosteroid feedback may mediate these effects in intact rats. It is unlikely that depletion of ACTH reserves could account for the attenuated ACTH response observed in intact rats, because cocaine stimulated significant ACTH increases even when basal levels were elevated after adrenalectomy (214).

Cocaine blocks the reuptake of dopamine, serotonin, and norepinephrine (167), and there has been considerable interest in determining the extent to which dopamine and serotonin modulate cocaine's effects on ACTH and corticosterone (13,15,104,106). It now appears that dopamine and serotonin are important mediators of cocaine-induced ACTH and corticosterone release (13,15,106). It was found that antagonists selective for dopamine D_1 receptors (SCH 23390) and dopamine D_2 receptors (sulpiride) each attenuated cocaine-induced increases in ACTH (13,106). Subsequent studies showed that dopamine receptor agonists, as well as a dopamine reuptake inhibitor (GRB 12909), acted like cocaine in stimulating ACTH and corticosterone release (13,15). For example, dopamine agonists selective for D_1 receptors (SKF 38393; 5–20 mg/kg) and D_2 receptors (quinpirole; 0.05–1 mg/kg) each stimulated a dose-dependent increase in ACTH and corticosterone release (15). The relative receptor selectivity of these effects was evaluated by administration of antagonists selective for D_1 and D_2 receptors. D_1 agonist stimulation of ACTH release was blocked by a D_1 antagonist, SCH 23390, but not by a D_2 antagonist, sulpiride. D_2 agonist stimulation of ACTH release was blocked by a D_2 antagonist, sulpiride, and slightly attenuated by a D_1 antagonist, SCH 23390. When submaximal doses of these D_1 and D_2 agonists were administered concurrently, the increase in ACTH was additive, suggesting that both dopamine receptor subtypes contribute to regulation of the HPA axis (15). It is interesting that dopamine agonists (which act at postsynaptic sites) and cocaine and other dopamine reuptake blockers (which act at presynaptic sites) each stimulate ACTH and corticosterone release and act as reinforcers in behavioral studies of drug self-administration (71,192, 199,234,235). We have suggested elsewhere that activation of CRH neuronal activity, inferred from increases in ACTH, may covary with and contribute to the reinforcing effects of cocaine (138,140).

Evidence that serotonin also mediates cocaine-induced increases in ACTH and corticosterone in rats is based on studies of the effects of serotonin antagonists and of serotonergic neuron lesions (13,104,106). A 5-HT_2 receptor antagonist, ketanserin, and a 5-HT_2/5-HT_1C antagonist, ritanserin, each significantly attenuated cocaine's stimulation of ACTH and corticosterone (13,106). Lesions of 5-HT neurons and 5-HT depletion with *p*-chlorophenylalanine (PCPA) prevented cocaine stimulation of ACTH and corticosterone release in rats (106). These findings are consistent with anatomical evidence that CRH neurons in the paraventricular nucleus synapse with serotonergic neurons (108). Moreover, there is accumulating evidence that a number of 5-HT receptor subtypes stimulate ACTH and corticosterone release (165,219). There is extensive literature on the behavioral (anxiolytic/antidepressive) effects of 5-HT agonists (33), but drugs that stimulate 5-HT neurotransmission do not appear to be reinforcing in animal models of drug self-administration (222,241).

Basal patterns of ACTH and cortisol release in male rhesus monkeys. Clinical studies have shown that ACTH is released at an average frequency of 3.3 pulses/h (77). Before we examined the effects of cocaine on ACTH and cortisol in rhesus monkeys, we developed procedures to study micropulsatile hormone secretory patterns under basal (nonstimulated) conditions (185). On each endocrine study day, male rhesus monkeys were placed in a standard monkey chair for 3 h before sample collection began to reduce any possible stress reaction associated with the catheter implantation procedure. Pilot studies indicated that ACTH returned to normal baseline levels within 2–3 h after acute saphenous vein catheterization. Blood samples for ACTH and cortisol analysis were collected at 2-min intervals for 120 min. Plasma ACTH concentrations were measured with a sensitive (0.2 μg/dl) and specific radioimmunoassay (IRMA). An objective pulse detection algorithm (cluster analysis) was used to assess the pulsatility of ACTH and cortisol secretion (227). The temporally coincident release of ACTH and cortisol was also examined with cross-correlation analyses (226).

The pulsatile release patterns of ACTH in rhesus monkeys (185) were very similar to those measured in humans using similar procedures (77). The number of ACTH peaks (3.2 peaks/h), the duration of interpulse intervals (18.5 ± 2.4 min), and the amplitude of ACTH pulses (44.8 ± 7.1 pg/ml) in rhesus monkeys were consistent with ACTH release patterns measured in humans [3.3 peaks/h, interpulse intervals 18 ± 0.8 min, and pulse amplitudes 21.3 ± 4.6 pg/ml (77)]. Moreover, these findings were concordant with previous studies in rhesus monkeys in which blood samples were collected at 1-min intervals and analyzed with the pulsar program (22) and with studies in rats using 2-min samples and cluster analysis (23). This convergence of data across species suggests that ACTH micropulses occur about three times per hour.

Cortisol was released at an average frequency of 2.3 peaks/h with an interpulse interval of 26.4 ± 8.6 min in rhesus monkeys. There was a 32% exact concordance of ACTH with cortisol peaks (11 out of 34; $p < 0.001$). Fifty-six percent of ACTH peaks (19 out of 34) were followed by a cortisol peak within 10 min, and there was a significant correlation between the ACTH and coincident cortisol pulse amplitudes. The amplitude of ACTH peaks coincident with cortisol peaks at 0 min time lag was significantly higher than when ACTH peaks were not temporally coupled with cortisol peaks. These data suggest that an adequate incremental ACTH pulse amplitude may elicit concurrent release of cortisol from the adrenal cortex. Thus, in addition to its autonomous cortisol secretory rhythm (68), the adrenal cortex may be sensitive to a relative increase in blood ACTH levels. These findings are consistent with earlier studies that suggest cortisol is modulated by the amplitude and not the frequency of ACTH pulsatile release (23,226). Once basal patterns of ACTH and cortisol secretion were determined under these conditions (185), we examined the effects of cocaine on ACTH and cortisol secretory patterns in male rhesus monkeys.

Effects of acute cocaine administration on pulsatile ACTH and cortisol release in male rhesus monkeys. There is little information about the acute effects of cocaine on the HPA axis in rhesus monkeys. In our initial studies, we examined the effects of cocaine on basal levels of ACTH and cortisol in males using procedures identical to those described above (183). Cocaine induced a dose-dependent increase in ACTH and cortisol release in some male rhesus monkeys (183). Cocaine (0.4 mg/kg) increased ACTH peak duration, peak amplitude, and mean peak area in comparison to placebo control. A

higher dose of cocaine (0.8 mg/kg) increased all peak and valley characteristics, including peak duration, peak amplitude, percent increase in peak amplitude, mean peak area, incremental height, valley level, and nadir. Cortisol peak amplitude and incremental peak height increased significantly after a high dose of cocaine (0.8 mg/kg) but not after a low cocaine dose or placebo. ACTH and cortisol pulse frequencies were unchanged by cocaine treatment in all monkeys. The cocaine-related increase in ACTH pulse amplitude, but not pulse frequency, in these male rhesus monkeys is consistent with previous studies suggesting that endogenous CRH may regulate the amplitude, but not the frequency, of the micropulsatile ACTH release episodes (23). This interpretation is also supported by findings that cocaine's stimulation of the HPA axis in rats is inhibited by the blockade of endogenous CRH (170,181). It is important to note that cocaine stimulated an increase in ACTH and cortisol only in those male rhesus monkeys that subsequently showed signs of behavioral activation (struggling) (183). However, struggling did not appear to induce the observed increases in ACTH, because struggling occurred after the ACTH increases were measured. Latency to the first struggling episodes averaged 14 min, and latencies to the first significant increase in ACTH averaged 4.6 min.

Acute effects of cocaine and CRF on ACTH and cortisol in ovariectomized rhesus monkeys. We also compared the effects of cocaine and CRF on the pulsatile release of ACTH and cortisol in ovariectomized females (184). ACTH and cortisol pulsatile release patterns in ovariectomized rhesus females (184) were similar to those measured in human and rhesus males under comparable conditions (77,139,185). However, cocaine (0.4 and 0.8 mg/kg) had no significant effect on pulsatile ACTH and cortisol secretion (184). These data are consistent with our earlier observation that cocaine had no effect on gonadotropins in ovariectomized females (133). In contrast to cocaine, a low dose of synthetic CRF (1.0 μg/kg IV) significantly increased the ACTH incremental peak height in comparison to pre-CRF values. All other peak and valley characteristics were slightly, but not significantly, increased. A high dose of CRF (10.0 μg/kg IV) significantly increased the ACTH peak amplitude, area under the peak, incremental peak height, valley level, and nadir. CRF also increased the amplitude of cortisol pulses. Cortisol valley levels also increased after high-dose (10 μg/kg) CRF administration. These data in ovariectomized monkeys indicate that the pituitary was responsive to stimulation by CRF but not cocaine. Basal levels of ACTH before cocaine or placebo administration were in the low normal range, so it is unlikely that abnormal baseline values contributed to these findings. One major difference between intact and ovariectomized monkeys is the absence of gonadal steroid feedback, and the role of gonadal steroid hormones in modulating ACTH release remains to be determined.

Clinical Studies of Acute Effects of Cocaine on ACTH and Cortisol

Cocaine administration is usually followed by an increase in ACTH and a subsequent increase in cortisol in human males. However, the route of cocaine administration and the rate of increase in plasma cocaine levels appear to be critical determinants of the ACTH response. Intravenous cocaine administration consistently results in rapid increases in ACTH levels (134,135,206). However, when Heesch et al. (65) administered cocaine intranasally, a change in ACTH was not detected, but there was a significant increase in cortisol levels, which were maximal 60 min after cocaine administration. Clinical studies of cocaine's effects on basal levels of ACTH and cortisol and on pulsatile release patterns of ACTH are described below.

Acute effects of cocaine on basal levels of ACTH and cortisol. Cocaine's acute effects on ACTH were studied in 18 men who met DSM-III-R criteria for cocaine and opioid dependence (142). Subjects resided on a clinical research ward and were drug-free for 6 days before the study. ACTH levels were measured before and after IV administration of cocaine (30 mg over 1 min) or placebo; cortisol was not measured. Each subject served as his own control during the IV placebo and cocaine administration conditions. ACTH levels before and after IV cocaine or placebo administration are shown in Fig. 6 (top panel). Baseline levels of ACTH were equivalent under both conditions. No significant changes in plasma ACTH levels were observed following placebo administration. However, within 5 min after IV cocaine administration, ACTH levels increased significantly and remained significantly above baseline levels for 45 min. These findings are consistent with preclinical reports that cocaine administration is followed by a rapid and sustained increase in ACTH. In related studies, we evaluated the effects of chronic treatment with buprenorphine on cocaine-related stimulation of ACTH (141). Buprenorphine is an opioid mixed agonist–antagonist that may be useful for the treatment of opioid abuse and dual dependence on cocaine and opioid drugs (123,129). After at least 10 days of buprenorphine maintenance (4 mg/day sublingually), six cocaine- and opioid-dependent men were given an IV challenge dose of cocaine (30 mg) and samples for ACTH analysis were collected for 120 min. In comparison to prebuprenorphine conditions, the ACTH response to cocaine was significantly decreased (Fig. 6, lower panel), even though plasma cocaine levels and cardiovascular responses to cocaine were equivalent before and during buprenorphine treatment. Moreover, basal ACTH levels were not significantly different before and after buprenorphine treatment (141). This reduction in the ACTH response to cocaine after chronic buprenorphine treatment is consistent with preclinical reports that opioids attenuate CRF-stimulated ACTH release (5,166). Interestingly, subjective ratings of euphoria, measured when subjects were certain they had received cocaine, were also significantly lower during buprenorphine treatment than during prebuprenorphine control conditions (141).

We have also examined the relationship between cocaine pharmacokinetics and release of ACTH in men with a history of cocaine abuse. Figure 7 shows plasma cocaine levels and plasma ACTH levels for one man before and after IV cocaine administration (0.4 mg/kg over 1 min). Peak plasma cocaine levels were coincident with the peak increase in plasma ACTH levels, which occurred 8 min after cocaine administration. The reported intensity of euphoric effects was greatest at the time of peak cocaine and ACTH levels. A regression analysis revealed a highly significant relationship between the rate of decrease in plasma cocaine levels and plasma ACTH levels ($r = 0.95$; $p = 0.0001$). Decrements in cocaine-induced euphoria also were significantly related to the decrease in plasma cocaine and ACTH levels from peak values. Taken together, these data are consistent with the hypothesis that the reinforcing properties of cocaine may be related to cocaine-induced stimulation of endogenous CRH in the brain (138,140).

Cocaine stimulates cortisol release in human males (9,65,237). A significant increase in plasma cortisol levels was found in cocaine-dependent men following IV infusion of 40 mg of cocaine (9). However, the magnitude and duration of cortisol increases were not cocaine dose dependent when the

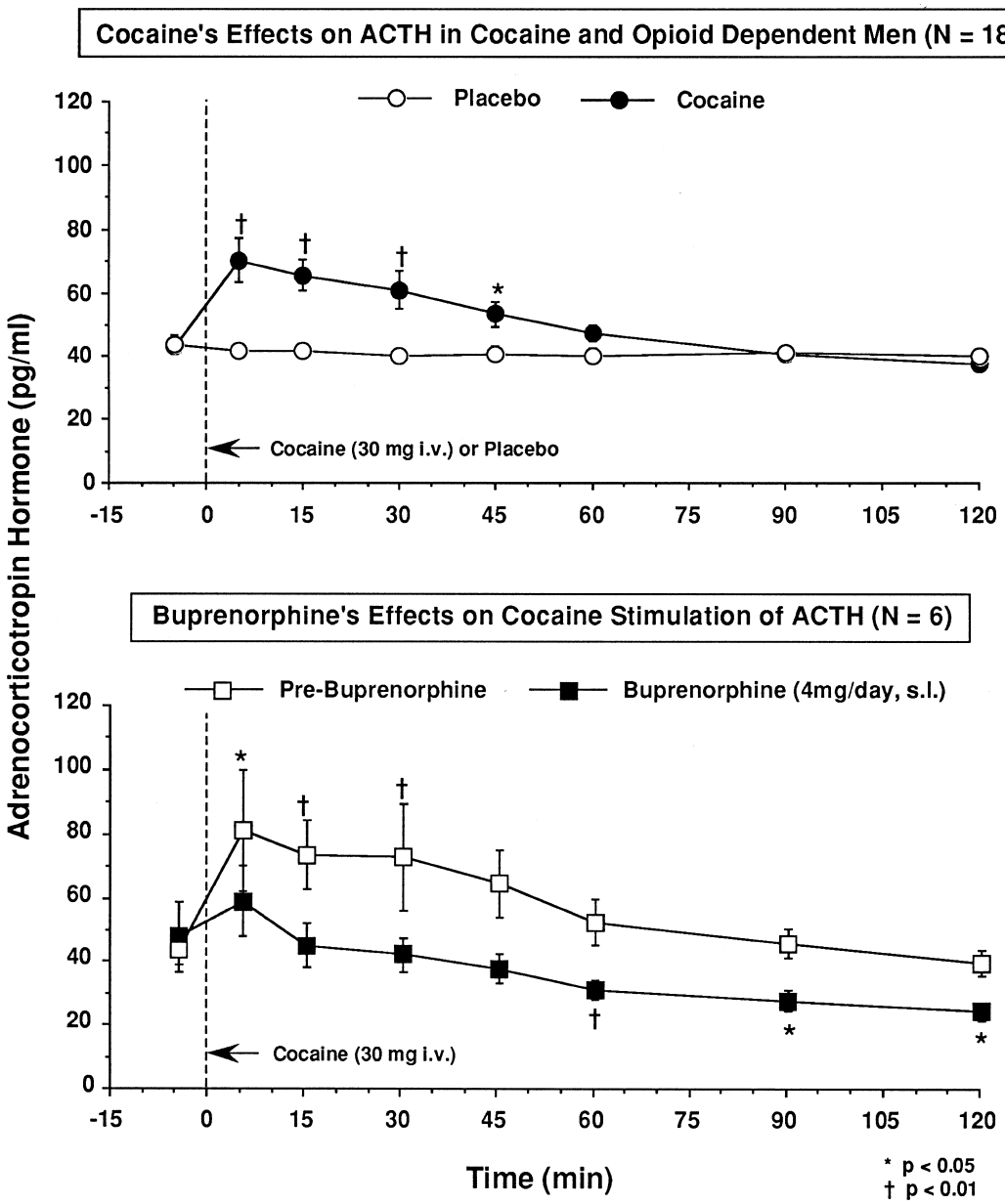

FIG. 6. Effects of cocaine on ACTH levels in men. (Top panel) Mean plasma ACTH levels (± SE) for 18 men before and after IV injection of cocaine (30 mg) (closed circles) or placebo (open circles). The vertical line indicates the end of a cocaine or placebo injection. These men met DSM-III-R criteria for concurrent cocaine and opiate dependence and had been drug-free for at least 6 days at the time of the study. (Adapted from Mendelson et al., *J. Pharmacol. Exp. Ther.* 263(2):505–509; 1992. Reprinted with permission.) (Bottom panel) Mean plasma ACTH levels for six men before and after IV injection of cocaine (30 mg) before (open circles) and during (closed circles) at least 10 days of treatment with buprenorphine (4 mg/day sublingually). (Adapted from Mendelson et al., *Neuropsychopharmacology* 17:157–162; 1992. Reprinted with permission.)

effects of 10 or 90 mg of IV cocaine were examined in male cocaine abusers (237). Cocaine also increased plasma cortisol levels in cocaine-naive men (65). Following intranasal cocaine administration (2 mg/kg), cortisol levels were significantly elevated in comparison to levels with intranasal saline. However, the increase in plasma cortisol levels after administration of intranasal cocaine to cocaine-naive men (65) was not as great as the increment in plasma cortisol levels observed following IV cocaine administration to drug-free cocaine abusers (9). These differences in the cocaine-induced increase in plasma cortisol levels may have been due to differences in the past history of cocaine use or to the dose and mode of cocaine administration. A slow, continuous infusion of cocaine did not stimulate secretion of ACTH in rats (216), which suggests that a rapid increase in cocaine levels may be necessary to increase ACTH secretion.

Acute effects of cocaine on pulsatile release of ACTH. We studied the effects of cocaine on pulsatile secretion of ACTH

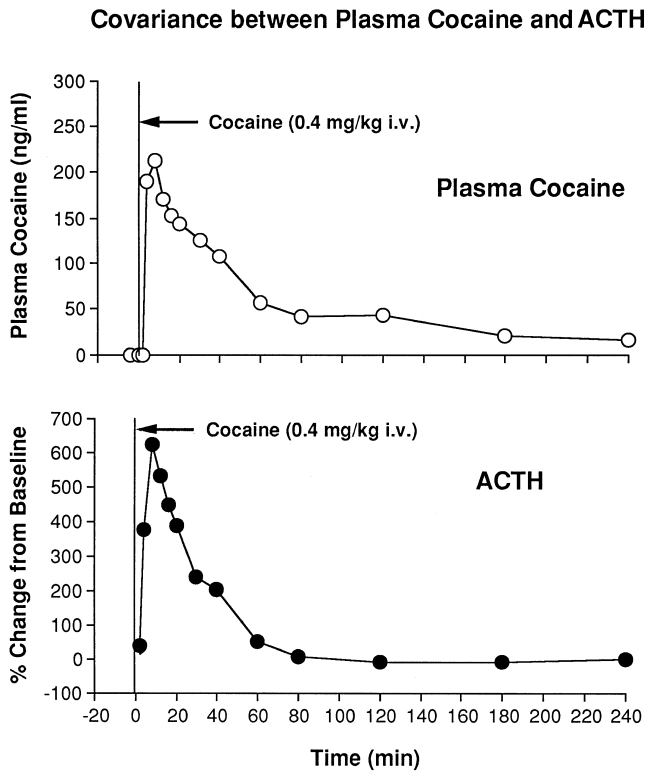

FIG. 7. Covariance between ACTH and plasma cocaine levels. Plasma cocaine level (nanograms per milliliter) is shown on the left ordinate of the top panel, and percent change in ACTH level from baseline is shown on the left ordinate of the lower panel. The time of sample collection is shown on the abscissa. The time of cocaine injection (0.4 mg/kg IV) is indicated by a vertical line in each panel. These data were collected from a man with a history of cocaine abuse.

in men under controlled clinical research ward conditions (212). Eight men with a DSM III-R diagnosis of concurrent cocaine and opioid dependence provided informed consent for participation and were drug-free for at least 6 days before the study was conducted. Following an overnight fast, a challenge dose of cocaine (30 mg IV) or placebo was administered under single blind conditions in a randomized order on two study days. Blood samples were collected at 2-min intervals for 76 min for establishment of a baseline and for an additional 76 min following IV cocaine or placebo administration. Peak plasma cocaine levels of 313.8 ± 46.5 ng/ml were detected within 2 min after cocaine administration. ACTH pulsatile release patterns in two representative subjects are shown in Fig. 8. There was a rapid increase in ACTH that reached peak levels within 8 min after cocaine administration (Fig. 8), a time course identical to that shown earlier in Fig. 7. The cluster analysis program originally described by Veldhuis and Johnson (227) was used to characterize ACTH pulsatile release patterns. Acute cocaine administration (30 mg IV) significantly increased ACTH mean peak amplitude, mean percent increase in peak amplitude, mean peak area, total peak area, and incremental peak height. Mean ACTH valley level and mean valley nadir were also significantly increased following cocaine administration. We postulate that cocaine stimulates CRF release and that cocaine-induced CRF secretion increases the *amplitude* of ACTH pulses, because ACTH pulse frequency was not altered by cocaine (212). These data in cocaine- and opioid-dependent men are concordant with our findings in drug-naive rhesus monkeys (183).

Data obtained in this clinical study (212) appear to reflect the acute effects of cocaine rather than the consequences of chronic drug abuse, because baseline data collected before placebo and cocaine administration are comparable to pulsatile properties of ACTH measured in normal men (77). Our methods were similar to those of Iranmanesh and coworkers (77) and confirm the feasibility of using intensive blood sampling procedures (2-min intervals) for identification of ACTH pulse frequency by the cluster analysis program. We also used the same radioimmunoassay techniques (IRMA, Nichols Institute) and achieved similar assay sensitivities in our studies (0.15 pmol/liter vs. 0.22 pmol/liter). An ACTH interpulse interval of 18 ± 0.8 min was reported in normal men (77); this was similar to our baseline preplacebo and precocaine interpulse intervals of 15.9 ± 1.3 and 20.1 ± 1.7 min. The ACTH mean peak amplitude in normal men was 4.7 ± 1.0 pmol/liter with 79.3 ± 12.6% as the fractional increment and approximately 3.3 ± 0.9 pmol/liter as the mean valley level (77). We found a mean ACTH peak amplitude of 6.8 ± 0.7 pmol/liter with 106.8% as a fractional increment and a mean valley level of 5.4 ± 0.5 pmol/liter. These values are slightly higher than those reported in normal controls by Iranmanesh and coworkers (77), but the small differences may be due to prolonged antecedent opioid and cocaine dependence by our subjects (212).

The men who participated in this study (212) served as their own controls prior to and following cocaine or placebo administration. It is unlikely that expectancy accounted for alteration of ACTH pulsatile release patterns following cocaine administration, because placebo administration was not associated with any significant changes in ACTH. We have previously reported that an acute intravenous injection of 30 mg cocaine induced significant changes in heart rate and systolic and diastolic blood pressure within 20 min of cocaine injection (208). In this study (212), cocaine-induced increases in ACTH peak amplitude persisted for the duration of the study (76 min), although physiological parameters returned to baseline. We have suggested elsewhere that it is possible that cocaine's rapid reinforcing effects in humans may be mediated, in part, by CRF activation of ACTH secretion (140). It is interesting that adrenalectomy completely eliminated cocaine self-administration in preclinical studies (59). These data converge to suggest a role for the hypothalamic–pituitary–adrenal axis in cocaine reinforcement (59).

At present, the precise mechanism(s) of action of cocaine on ACTH are unknown. Carnes and coworkers (23) have reported that CRF immunoneutralization had no effect on the frequency of ACTH micropulses in rats, but it significantly reduced micropulse amplitude. These findings suggest that endogenous hypothalamic CRH regulates the amplitude modulation of micropulsatile ACTH secretion, but the frequency of ACTH micropulses may reflect an intrinsic secretory rhythm of corticotroph cells in the anterior pituitary. In macaque monkeys, in vitro studies in isolated hypothalamic tissue indicate that CRH is released in a pulsatile manner at intervals of 9.0 min (143). Intrinsic pulsatility of ACTH release from isolated human pituitary has also been demonstrated in vitro (53). In human males, cocaine increased the amplitude (a CRH-dependent component), but not the frequency (a CRH-independent component) of pulsatile ACTH release (207). Immunoneutralization and receptor blockade of CRH completely abolished the effects of cocaine on ACTH and corticosterone in rats (170,180). Acute cocaine administration has been shown to

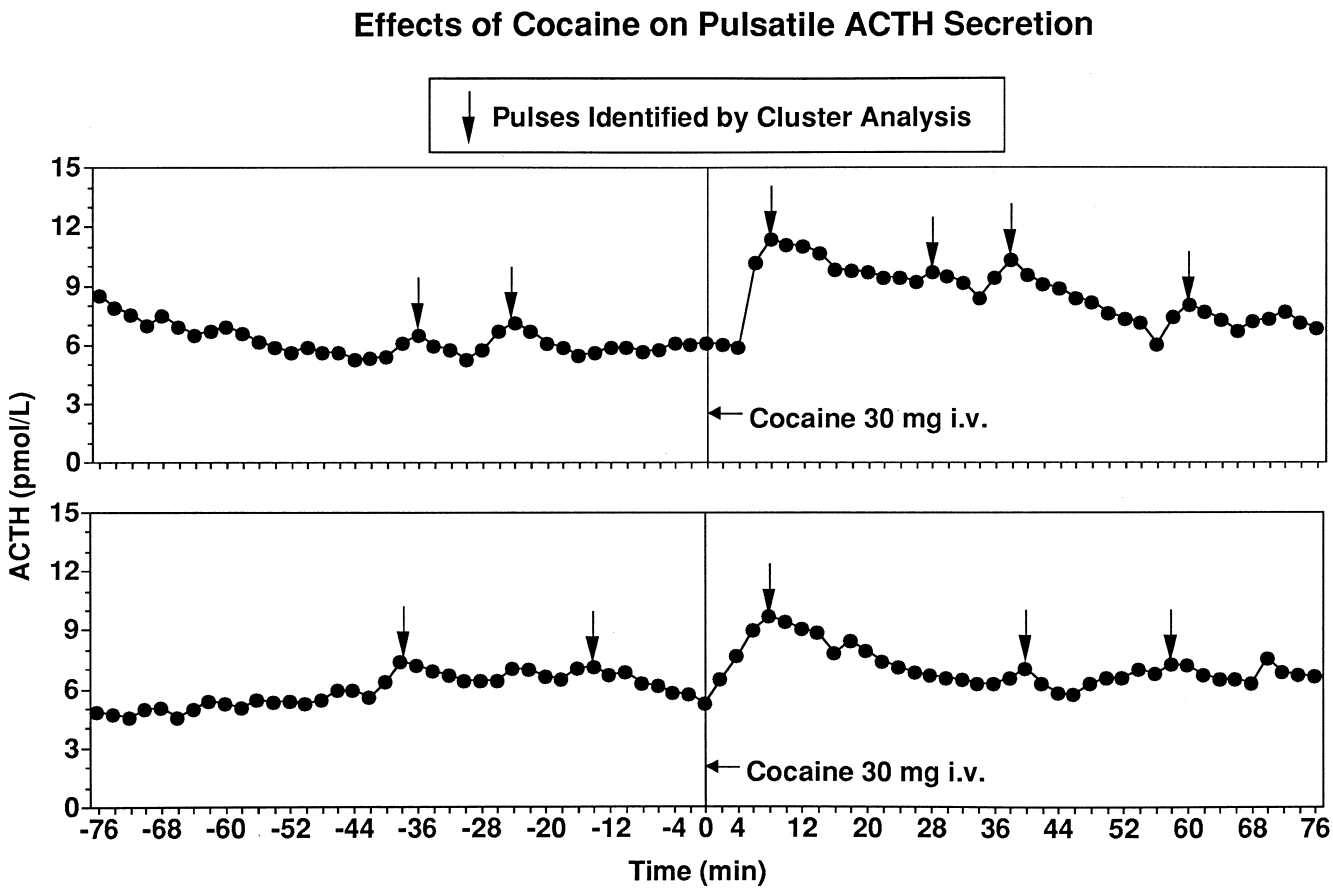

FIG. 8. Effects of cocaine on pulsatile release of ACTH in men. Pulsatile release patterns of ACTH before and after cocaine administration (30 mg IV) are shown for men who met DSM-III-R criteria for concurrent cocaine and opioid dependence. These studies were conducted on a clinical research ward after each man had been detoxified and was drug-free for at least 6 days. Samples for ACTH analysis were collected at 2-min intervals for 76 min before and 76 min after cocaine administration (indicated by vertical line). Pulsatile ACTH release patterns were evaluated with cluster analysis procedures, and each arrow indicates an ACTH pulse detected by the analysis program. These individuals were part of a group of subjects described by Teoh et al. (212).

stimulate CRH secretion directly from the hypothalamus in vitro (20) and to increase in vivo hypothalamic immunoreactive CRH levels (179). We interpret our findings as evidence that cocaine increases ACTH pulse amplitude by stimulation of CRF release from the hypothalamus in men with a history of cocaine and opioid dependence (212).

Chronic Effects of Cocaine on ACTH and Cortisol/Corticosterone

Preclinical studies of chronic cocaine effects on ACTH and corticosterone. In the rodent model, the duration of "chronic" cocaine exposure usually ranged from 3 days to 2 weeks, and cocaine doses were administered by the investigator, not self-administered by the animal. Under these conditions of limited cocaine exposure, ACTH and corticosterone levels did not change appreciably, although decreases in CRH receptors have been reported. For example, 15 days of cocaine injections (20 mg/kg IP) were followed by significant decreases in CRH receptors in the mesolimbic/mesocortico-dopaminergic system measured by quantitative autoradiography (58). However, it was not clear whether the reductions in CRH binding reflected changes in receptor density or in binding affinity (58). Because stimulation of CRH neurons appears to result in ACTH release (170), a cocaine-induced reduction in CRH receptors might be followed by a lower ACTH response to cocaine. It has been difficult to demonstrate that chronic cocaine treatment alters basal levels of ACTH or corticosterone or reduces the stimulatory effects of a challenge dose of cocaine. For example, basal levels of ACTH and corticosterone did not change significantly from pretreatment levels after 10 days of cocaine treatment (10 mg/kg/day, delivered in ten 1-mg/kg injections over 2 h) (156). Even after 30 days of cocaine treatment (1, 5, 10, and 15 mg/kg IP, b.i.d), no changes in basal levels of ACTH and corticosterone were detected (220). It has been suggested that the regimen of cocaine administration influences basal levels of ACTH and corticosterone during cocaine treatment (216). Daily intravenous cocaine injections (5 mg/kg) resulted in significant increases in ACTH and corticosterone on days 2, 4, and 6 of treatment, and ACTH and corticosterone remained elevated during a 30-min sampling period. However, because samples for ACTH and corticosterone analysis were collected 10 and 30 min after cocaine injections, these elevations probably reflected acute rather than chronic cocaine effects. Continuous infusion of cocaine (5 or 100 mg/kg/day) was associated with relatively low

levels of ACTH and corticosterone on days 2, 4, and 6 during 30-min sampling periods. There were no differences in ACTH and corticosterone levels between saline-infused and cocaine-infused rats (215). Although a cocaine dose of 100 mg/kg per day is considerably higher than doses shown to produce convulsions in other studies [e.g., 20 mg/kg; (156,202)], no exaggerated motor activity or convulsions were detected during treatment (215).

Results from studies of the effects of chronic cocaine treatment on ACTH and corticosterone after a cocaine challenge are consistent with results from studies of basal levels of ACTH and cortisol after chronic treatment described above. For example, when rats were chronically treated with cocaine (15 mg/kg IP) for 14 days, then challenged with an acute dose of cocaine (1, 3.75, 7.5, or 15 mg/kg IP) 18 h or 7 days after the last chronic cocaine treatment, the ACTH and corticosterone responses did not differ from those under control treatment conditions (107). Similarly, rats given two daily doses of cocaine (15 mg/kg IP) for 3 or 7 days had normal ACTH and corticosterone responses to a cocaine challenge (15 mg/kg IP) 24 h after the last chronic treatment dose (14). In contrast, behavioral measures of cocaine-induced locomotor activity were significantly enhanced after the same chronic cocaine treatment regime (14). These data were interpreted to suggest that chronic cocaine exposure has different effects on hypothalamic dopamine systems, which modulate ACTH release, and forebrain dopamine systems, which are thought to mediate locomotor activity in rats. These findings were confirmed and extended to periadolescent rats (100). After 4 days of placebo or cocaine administration (0, 10, or 20 mg/kg IP) a challenge dose of cocaine (10 mg/kg IP) had equivalent effects on ACTH and corticosterone in the placebo- and cocaine-treated groups (100). In contrast, a variety of behavioral measures increased in frequency after chronic cocaine treatment in comparison to placebo control treatment (100). Chronic cocaine exposure also did not change the ACTH response to a synthetic CRF challenge (216). After 6 days of continuous cocaine infusion (5 or 25 mg/kg/day), CRF (0.2, 1 or 5 mg/kg) stimulated a dose-dependent increase in ACTH that was identical to the ACTH response in vehicle-treated control rats (216). Together, these data indicate that chronic cocaine exposure does not result in tolerance or sensitization of the HPA axis to stimulation by cocaine or synthetic CRF.

The effects of chronic cocaine exposure on the capacity of serotonin agonists to stimulate ACTH and cortisol have also been examined (8,220). A 5-HT releaser, *p*-chloroamphetamine, was significantly less effective in stimulating ACTH and corticosterone release after 7 and 30 days of chronic treatment with cocaine (15 mg/kg, IP) than after 1 day of treatment (220). However, after 7 days of chronic cocaine treatment, acute administration of 5-HT 1 agonists (RU 24969; 0.2–5.0 mg/kg IP; or *m*-CPP, 1.0–20.0 mg/kg IP) resulted in dose-dependent increases in ACTH and cortisol equivalent to those observed in chronic saline-treated controls (220). These data were interpreted as evidence that chronic cocaine exposure alters 5-HT neurons and impairs presynaptic serotonergic function but not postsynaptic serotonergic receptors (220). In related studies, the plasma corticosterone response to a series of 5-HT receptor agonists was examined at 42 h and 8 days after chronic saline or cocaine (15 mg/kg IP, b.i.d.) treatment for 7 days. At 42 h after cocaine exposure, corticosterone increased in response to all the 5-HT receptor agonists, but the response to fenfluramine was significantly attenuated (8). Eight days after cocaine treatment, the corticosterone response to fenfluramine was lower than in control animals, but the differences were not statistically significant. There were no differences in the corticosterone response to 8-OH-DPAT (50 μg/kg), DOI (100 μg/kg), or saline at any time period.

Clinical studies of chronic cocaine effects on ACTH and cortisol. Although there have been several reports that chronic cocaine abuse may cause persistent alterations of HPA axis function in humans (110,230), we found no significant differences in the pulsatile release of cortisol in male cocaine abusers in comparison to normal controls (139). Pulsatile release of ACTH in men with a past history of cocaine abuse who were studied under controlled drug-free research ward conditions (212) also did not differ from data obtained in normal controls (77). One clinical study reported significantly higher diurnal plasma ACTH concentrations of 19.8 pmol/liter (or 90 pg/ml) in cocaine-dependent men prior to abstinence compared with normal controls (230). However, normal diurnal secretory rhythms were not disrupted (230). After 15 days of cocaine withdrawal, normalization of circulating ACTH patterns was observed (230). In our study, the baseline mean ACTH after six drug-free days averaged 5.8 pmol/liter (or 26 pg/ml). These basal ACTH levels were lower than those reported for chronic cocaine abusers (230), and this difference may reflect the fact that our subjects abused both opioids and cocaine. Opioid agonists alter basal and CRF-induced ACTH secretion in experimental animals (217) and in humans (5,166). Blunted ACTH and cortisol responses to CRF (1 μg/kg) injection have been observed following subcutaneous morphine (0.14 mg/kg) pretreatment in subjects who were not drug dependent (166). Other ACTH-releasing factors, such as vasopressin and oxytocin, may also be involved in drug-induced disruption of pituitary ACTH secretion, and these neurohormones may be altered by chronic opioid and cocaine administration (182).

COCAINE'S EFFECTS ON GONADOTROPINS AND GONADAL STEROID HORMONES

Background

The gonadotropin hormones, luteinizing hormone (LH) and follicle stimulating hormone (FSH), are released from cells called gonadotropes located in the anterior pituitary. Although most gonadotropes (60%) contain both LH and FSH, a number of small gonadotropes contain LH or FSH alone. The release of both LH and FSH is stimulated by a hypothalamic peptide hormone, luteinizing-hormone releasing-hormone (LHRH), also known as gonadotropin-releasing hormone (GnRH). LH and FSH release is pulsatile and covaries with the episodic secretory release of hypothalamic LHRH (251, 252). LH and FSH regulate (and are regulated by) gonadal steroid hormone levels in men and women. The ovaries are the primary source of the steroid hormones estradiol and progesterone in women, and the testes are the primary source of testosterone and estradiol in men. In males, estradiol is produced by the Sertoli cells and testosterone by the Leydig cells of the testes; however, testosterone and androstenedione may be converted to estradiol under some conditions. In females, estradiol is produced by the ovarian follicles, and maximal estradiol production precedes the onset of the LH surge. Progesterone is secreted from the ovarian follicle and from the corpus luteum after ovulation.

Changes in gonadotropin and gonadal steroid hormone levels across the menstrual cycle. Changes in basal levels of gonadotropins and gonadal steroid hormones define the functionally distinct phases of the menstrual cycle: the follicular phase, the ovulatory phase, and the luteal phase (252). The patterns of

hormonal changes across a typical menstrual cycle are shown schematically in Fig. 9. The follicular phase of the cycle begins on the first day of menstruation and lasts for about 13 days until the periovulatory phase at midcycle. During the follicular phase, adequate FSH levels are necessary for normal development and maturation of the ovarian follicles (60,174). Studies of folliculogenesis in the primate ovarian cycle indicate that the recruitment of the dominant follicle occurs during days 1–4 of the menstrual cycle, a single follicle is selected to ovulate during days 5–7, and the selected follicle achieves dominance during cycle days 8–12 (36,60,62,67). The dominant follicle selected for ovulation presumably inhibits development of other competing follicles, but the factors that determine selection and dominance of a single ovulatory follicle are unclear (62). A preovulatory surge in LH results in maturation of the dominant ovarian follicle and is essential for ovulation to occur. Rupture of the oocyte from the dominant follicle occurs approximately 36 h after the preovulatory LH surge begins. After ovulation, the site of the dominant follicle becomes highly vascularized and forms the corpus luteum, which lasts for approximately 14 days and then spontaneously regresses unless pregnancy occurs. The development of ovarian follicles for the next menstrual cycle is dependent upon the regression of the corpus luteum. The end of the luteal phase, when FSH levels rise and initiate follicle recruitment, is often referred to as the luteal–follicular transition (252).

Interactions between gonadotropin and gonadal steroid hormones. Gonadotropin and ovarian steroid hormone levels are controlled by a complex and changing pattern of reciprocal stimulation and inhibition across the menstrual cycle. Both estradiol and progesterone may have inhibitory or stimulatory effects on gonadotropin release at different phases of the menstrual cycle. Changes in gonadotropin levels also reflect changes in pulsatile release patterns, as described below. Abnormally high or low hormone levels can have a variety of functional consequences. For example, during the follicular phase, FSH is one important determinant of follicle development, and low levels of FSH may delay follicle maturation and ovulation or may result in luteal phase dysfunction after timely ovulation (37,38,60,238). FSH levels also are influenced by estradiol and by LH. An increase in estradiol levels during the early follicular phase suppresses FSH, inhibits preovulatory follicular growth, and prolongs the follicular phase (34,35,75). Clinical evidence suggests that high levels of LH during the early follicular phase may also impair normal folliculogenesis and lead to luteal phase defects (120,196,197).

During the periovulatory phase, the preovulatory LH and FSH surge is stimulated by increases in estradiol levels, which occur over 2–3 days, and an abrupt increase in progesterone about 12 h before the onset of the LH surge (see Fig. 9) (252). LH levels decrease after ovulation, and the luteal phase of the menstrual cycle begins (148,198). Progesterone levels gradually increase and remain elevated until the postovulatory corpus luteum regresses. The inhibitory feedback actions of estradiol on the gonadotropins presumably occur at the level of the anterior pituitary, because estradiol administration after destruction of the arcuate nucleus in the hypothalamus or transection of the pituitary stalk still resulted in a decrease in pulsatile LH release and LH levels (46,92). The comodulatory interactions between ovarian steroid hormones and the gonadotropins also are illustrated by the fact that after ovariectomy or natural menopause, when the inhibitory influence of ovarian steroids is removed, LH and FSH levels remain elevated at levels comparable to the periovulatory period. Similarly, in males, the gonadal steroid hormones testosterone and estrogen modulate LH release, and disruption of the hypothalamic–pituitary–testicular axis results in elevated LH levels (224). LH stimulates increased secretion of testosterone, and testosterone in turn inhibits LH secretion. Acute administration of testosterone decreases the frequency of LH pulsatile release, whereas acute administration of estradiol decreases the amplitude of LH pulses in men (224).

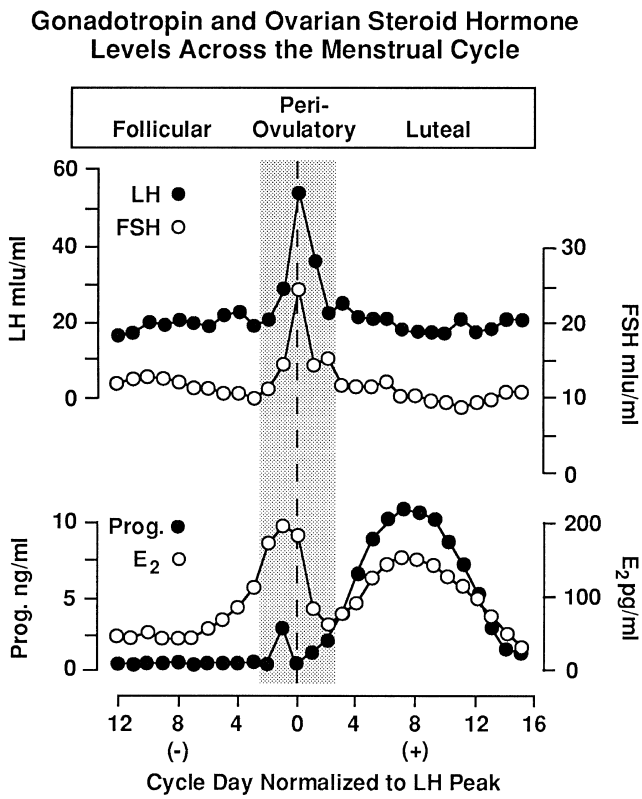

FIG. 9. Schematic diagram of the pattern of changes in the gonadotropins (LH and FSH) and the ovarian steroid hormones (estradiol and progesterone) across a typical menstrual cycle in rhesus monkeys and human females. The successive phases of the menstrual cycle are labeled at the top of the diagram. Menstruation, shown as a shaded rectangle, defines the beginning of a cycle. Hormone levels are shown as days from the LH peak. This schematic was constructed from data on the human menstrual cycle (252) and the rhesus monkey menstrual cycle (92,93).

Regulation of gonadotropin pulsatile release patterns. The changing levels of gonadotropins across the menstrual cycle reflect changes in pulsatile release patterns. These patterns are controlled by ovarian steroid hormones and by hypothalamic release of LHRH. Current understanding of the neuroendocrine regulation of the menstrual cycle is based on the fundamental discovery that pulsatile gonadotropin release is essential for normal reproductive function (91–93). When hypothalamic release of endogenous LHRH was disrupted by lesions of the arcuate nucleus and the median eminence in ovariectomized rhesus monkeys, LH and FSH secretory activity was abolished. Pulsatile administration of synthetic LHRH restored the pulsatile release patterns of LH and FSH, whereas continuous administration of LHRH did not (91–93). These important findings in the rhesus monkey model were rapidly translated into clinical treatment for infertility disorders in

women. It was discovered that suppression of gonadotropin pulsatile release was often associated with amenorrhea (a failure to menstruate) and that normal ovulatory function could be restored by the pulsatile infusion of synthetic LHRH (29,31, 72,109,175,176).

Recognition of the importance of pulsatile gonadotropin release for normal reproduction (91,92) led to studies of how gonadotropin release patterns changed across the menstrual cycle (225). LH pulse frequency increases across the follicular phase of the menstrual cycle from one to two pulses per hour. During the midcycle LH surge, there is an increase in LH pulse amplitude but no change in the frequency of LH pulsatile release (4). The observed increase in LH pulse amplitude may reflect an increase in pituitary sensitivity to LHRH release (4). After ovulation, LH pulse frequency decreases to approximately one pulse every 4 h during the luteal phase (44,198,223). Although LH pulsatile release is slower during the luteal phase, the amplitude of LH pulses is almost double that measured during the early follicular phase in rhesus monkeys (46).

Several lines of evidence indicate that the pulsatile release of LHRH from the hypothalamus is under inhibitory control by endogenous opioid peptides, but the role of norepinephrine and dopamine in primates is unclear (252). Although LHRH cannot be measured directly in peripheral blood, LH release mirrors LHRH release in preparations where LHRH is measured in cerebrospinal fluid (245). Administration of opioid drugs decreases circulating levels of LH (44,46). Levels of the endogenous opioid beta endorphin measured in pituitary stalk blood increased from the onset of menstruation through the follicular phase and were highest in the luteal phase (46). The administration of an opioid antagonist, such as naloxone or naltrexone, is followed by an increase in LH release during the luteal phase of the menstrual cycle. Opioid antagonist administration can be used as a provocative test of hypothalamic–pituitary function (137,254). However, opioid antagonists do not change gonadotropin release patterns after menopause (164), and these findings are usually interpreted to suggest that gonadal steroids as well as opioid peptides are important in the inhibitory regulation of LHRH release (252,254). Both beta endorphin and dopamine neurons in the medial basal hypothalamus synapse with LHRH neurons. Axons from cells containing beta endorphin, dopamine, and LHRH terminate in the median eminence. Ovarian steroids are thought to influence LHRH release through the estrogen and progesterone receptors on beta endorphin and dopamine neurons, rather than by directly affecting LHRH neurons, but the basis for these comodulatory interactions remains to be clarified (252).

In the remainder of this section, the acute effects of cocaine on gonadotropin release in humans and in animal models will be described. Some possible consequences of cocaine's effects on the interactions between gonadal steroid hormones and gonadotropins are discussed later in the section on reproductive function. One of the most consistent findings to emerge from both clinical and preclinical studies is that acute cocaine administration is followed by a rapid increase in LH release. This effect was not predictable from the pharmacology of cocaine or from the clinical literature on dopamine–gonadotropin interactions. The functional implications of a cocaine-related increase in LH are unclear, but repeated episodes of cocaine intoxication accompanied by elevated LH levels could compromise folliculogenesis and prompt early ovulation. There has been relatively little attention to cocaine's effects on gonadal steroid hormones despite their obvious importance in the control of gonadotropin release.

Preclinical Studies of Acute Cocaine Effects on Gonadotropin Hormones

Acute effects of cocaine on LH in rhesus monkeys. An acute dose of cocaine stimulated a significant increase in LH release in follicular phase female rhesus monkeys (124). LH increased within 20 min after cocaine administration (0.4 and 0.8 mg/kg IV) and remained above baseline levels for 40–50 min. We also examined the acute effects of cocaine on LH levels in six mid-luteal phase females (menstrual cycle days 20–23) to determine if cocaine also stimulated LH release when endogenous opioid inhibition of LH was greatest (45,254). In addition, we studied the acute effects of cocaine on LH and testosterone levels in male rhesus monkeys. These studies were conducted under the same conditions as our previous studies in early follicular phase females (124,132). The mid-luteal phase of the menstrual cycle was confirmed by elevated progesterone levels (above 8 ng/ml). There were no obvious gender differences in cocaine's stimulatory effects on LH in rhesus monkeys (132). Cocaine administration (0.8 mg/kg IV) was followed by a significant LH increase in both male and midluteal female rhesus monkeys, and the overall time course of cocaine's effects on LH was similar. LH increased significantly within 10–20 min after cocaine administration and remained elevated for 50 min in males and midluteal females. Peak LH increases occurred within 30 min after cocaine administration. FSH levels were unchanged in midluteal females. These findings in rhesus monkeys were unexpected because cocaine acts centrally as an indirect dopamine agonist, and exogenous dopamine administration suppresses LH in women (82,173, 250) and men (83,115). However, in rhesus monkeys, exogenous dopamine administration did not decrease basal LH levels or pulsatile LH release in response to LHRH stimulation (152,200). The acute effects of cocaine on LH are consistent with evidence that dopamine may stimulate LH release under some conditions (80,159,231).

The effects of cocaine and placebo-cocaine on LHRH (100 μg IV)-stimulated LH were compared in follicular phase rhesus females (126). Cocaine (0.4 mg/kg IV) significantly enhanced synthetic LHRH stimulation of LH, whereas placebo-cocaine and a higher dose of cocaine (0.8 mg/kg IV) did not. A deconvolution analysis was subsequently conducted on LH data collected after cocaine or placebo administration and LHRH stimulation (125). This analysis was carried out in collaboration with Dr. Johannes Veldhuis, using computer algorithms for deconvolution based assessment of in vivo neuroendocrine secretory events (229). This analysis indicated that cocaine's stimulation of LH probably reflected a burst of hypothalamic LHRH and not a change in LH disposition. As shown in Table 1, there were no statistically significant differences for LH half-life or peak position. The mass of LH secreted was significantly greater after cocaine than after placebo administration. These data indicate that cocaine significantly increases the mass of LH secreted without altering LH half-life. The mechanisms underlying the large increment in mass of LH secreted following cocaine and LHRH in contrast to placebo and LHRH administration to female rhesus monkey remains to be determined. LH is excreted by the kidney, and cocaine may alter renal blood flow because it is a potent vasoconstrictor (81,134), but any transient cocaine-induced alteration in renal blood flow also does not appear to significantly affect LH half-life.

Acute effects of cocaine on gonadotropin hormones in ovariectomized rhesus monkeys. We extended our studies of the acute effects of cocaine on anterior pituitary hormones in in-

TABLE 1
DECONVOLUTION ANALYSIS OF COCAINE'S EFFECTS ON LH

	Half-Life (min)	Peak Position (min after LHRH injection)	Mass of LH Secreted (ng/ml)
LH + placebo	65 ± 1.5 (65)	10.0 ± 0.54 (10.1)	2.6 ± 0.37 (2.6)
LH + cocaine	75 ± 11 (68)	8.2 ± 1.2 (9.4)	6.5 ± 1.5* (6.1)

Data are the mean ± SEM (median). *$p = 0.028$ by the Wilcoxon paired nonparametric test.

tact rhesus males and females (124,125,132) to ovariectomized females to evaluate the generality of these findings (133). Cocaine was administered to ovariectomized rhesus females under conditions identical to those previously studied in intact females and males (124,125,132). We examined cocaine's effects on gonadotropins under two conditions: basal (nonstimulated) and after synthetic LHRH stimulation (100 μg IV). In contrast to our previous observations in rhesus and human males and in early follicular and mid-luteal phase rhesus females, cocaine did not change basal levels of gonadotropins in long-term ovariectomized females. This could not be attributed to impaired pituitary function because LHRH alone stimulated a significant and sustained increase in LH within 20 min and FSH within 40 min in these ovariectomized females. When cocaine (0.8 mg/kg IV) was administered before LHRH, significant increases in LH and FSH were measured 10 min sooner than after placebo-cocaine, but cocaine did not significantly enhance or attenuate the magnitude or duration of LHRH-stimulated increases in gonadotropins as it did in follicular phase females (125). Thus, although pituitary responsiveness to LHRH stimulation was adequate in these ovariectomized females, cocaine did not have a stimulatory effect on LH release (133). The differences observed in cocaine's effects in intact (124,125,132) and ovariectomized rhesus females (133) suggest that a normal gonadal steroid milieu may be important for cocaine-induced release of gonadotropins. However, the complex feedback relationships between ovarian steroid and anterior pituitary hormones (84) preclude any simple explanation of cocaine's interactions within this regulatory system. Studies to evaluate the effects of estrogen replacement on cocaine's effects on anterior pituitary hormones in ovariectomized rhesus females are now ongoing in our laboratory.

The lack of effect of cocaine (0.4 and 0.8 mg/kg) on LH and FSH in ovariectomized rhesus females (133) is at variance with a study in which high doses of cocaine (2–4 mg/kg IV) decreased LH and FSH levels in ovariectomized cynomolgus females (*Macaca fascicularis*) (21). In addition to species differences, a number of procedural differences complicate comparisons between these studies in ovariectomized monkeys (21,133). However, the most important factors contributing to these discordant findings are the differences in the doses of cocaine used and the duration of sampling. We limited our cocaine dose to less than 1 mg/kg (132,133) because the convulsant threshold for intravenous cocaine is 3–8 mg/kg (116,117,144) and because this dose range is comparable to that used in clinical studies (48). In contrast, Canez and coworkers (21) administered an IV bolus of 2–4 mg/kg of cocaine, i.e., doses fivefold higher than used in our study. We collected samples for 110 min after cocaine administration (132,133), because this corresponds to the period of maximal cocaine concentrations in plasma (144). Canez and coworkers (21) collected blood samples for 6 or 7 h after cocaine administration, and significant decreases in LH and FSH were not measured until 2–6 h post-cocaine, when cocaine and benzoylecgonine were no longer detectable (21). The factors accounting for these delayed decreases in gonadotropin levels are unclear.

Acute effects of cocaine in rodent models. There has been relatively little attention to the acute effects of cocaine on neuroendocrine function in rats, and the results are often inconsistent. Many of the discrepant findings in the literature can be attributed to differences in dosage regimens and the use of high cocaine doses that induced convulsions. The effects of cocaine (5–20 mg/kg) on gonadotropins were measured in ovariectomized female rats (202). LH increased significantly after acute administration of 10 and 20 mg/kg cocaine IP, but there was no systematic relationship with cocaine dose. FSH was somewhat higher after 5 and 10 mg/kg of cocaine than after 20–40 mg/kg cocaine, but these values were not significantly different from controls (202). However, interpretation of these results is qualified by the fact that high doses of cocaine (20–40 mg) produced convulsant activity and occasionally death.

Testosterone levels were measured in male rats after administration of 15 mg of cocaine (61). Testosterone levels increased significantly at 90 and 120 min after cocaine administration in comparison to vehicle controls, then fell significantly below normal levels at 180 min after cocaine administration. Unfortunately, LH was not measured, so it is not clear whether an antecedent stimulation in LH was followed by increased testosterone levels or if these data reflect a direct, albeit delayed, effect of cocaine on the testes. The cocaine dose used in these studies was below the convulsant threshold, although hyperventilation was observed (61). In other studies, relatively low doses of cocaine (0.5 mg/kg administered over 5 h) were followed by significant increases in testosterone within 30 min after the last cocaine dose (172). High doses of cocaine (10 mg/kg over 5 h) did not change testosterone levels, and LH was equivalent to controls in both the low- and high-dose cocaine groups (172). Cocaine treatment was followed by disruption of spermatogenesis and significant structural and ultrastructural alterations in the Sertoli and germ cells in the rat testes, but the Leydig cells were unaffected (172).

Clinical Studies of Acute Cocaine Effects on Gonadotropin Hormones

Acute effects of cocaine on LH in men. The finding that cocaine stimulates LH in gonadally intact rhesus monkeys (124, 125,132) was confirmed and extended in human male cocaine abusers (140) and cocaine-naive men (64). Eighteen men who reported more than 10 years of cocaine and opioid abuse were studied on a clinical research ward after detoxification (142). Each man met DSM-III-R diagnostic criteria for concurrent dependence on cocaine and opioids. These men had been drug-free for at least 6 days when the acute effects of cocaine on anterior pituitary hormones were evaluated. The time course of the LH increase paralleled the initial rise in plasma cocaine levels. Acute administration of 30 mg of cocaine IV was followed by a significant increase in LH within 5 min, when plasma cocaine levels averaged 260 ng/ml. LH levels were maximal at 15 min, a time course comparable to that observed in rhesus monkeys. There were no changes in LH after placebo-cocaine administration (142). These cocaine-related changes in LH did not appear to be a function of cocaine experience, because similar findings were reported in cocaine-naive men (64). After administration of intranasal cocaine (2 mg/kg), LH increased significantly within 30 min and reached

peak levels within 60 min. Plasma cocaine levels averaged 102 ng/ml within 40 min after intranasal cocaine and reached peak levels of 142 ng/ml at 80 min (64).

Although these findings in men were consistent with studies in rhesus monkeys, the data were surprising because of cocaine's indirect dopamine agonist actions. Clinical studies have consistently shown that administration of exogenous dopamine inhibits LH in women (82,173,248,249) and in men (83,115). The basis for the rapid cocaine-related increase in LH is unknown. In ongoing studies in rhesus monkeys, we have observed that the acute administration of exogenous dopamine does not increase or decrease LH (127). However, this does not preclude the possibility that cocaine's central dopaminergic effects may influence LH release. Because LH release is influenced by many neuromodulators in the brain (85,213,250), cocaine's stimulation of LH could be due to its effects on endogenous opioid peptides, norepinephrine, and serotonin or interactions between several neurotransmitter systems.

We subsequently reanalyzed LH data from the 18 cocaine- and heroin-dependent men described previously (142) to determine if subgroups could be identified that had high or low LH responses to cocaine. Using a criterion of a 20% or greater increase in LH to define responders and less than 20% to define nonresponders, we identified two subgroups of subjects (Fig. 10, top panel). After cocaine administration, LH increased rapidly to a maximum of 40% above baseline levels in 10 men and did not change appreciably in 8 men. One factor that contributed to these differences was the precocaine baseline LH levels. Baseline LH levels were significantly lower in the LH responders than in the nonresponders (12.9 $\pm$ 0.9 vs. 16.3 $\pm$ 1 IU/liter; $p < 0.02$).

As described earlier, the peak ACTH response to cocaine occurs within 5–8 min (see Figs. 6–8), whereas the peak LH response occurs later, within 15 or 20 min after IV cocaine administration. We reexamined the time course of changes in ACTH in each group of subjects to determine whether differences in the time course or magnitude of the ACTH response to cocaine covaried with relative LH responsiveness to cocaine. As shown in the lower panel of Fig. 10, there were no differences in the time course of the ACTH response in the two groups. However, ACTH levels were higher after cocaine in the LH nonresponders than in the LH responders (Fig. 10, lower panel). Preclinical studies have shown that administration of synthetic CRF, which stimulates ACTH, decreases LH levels (150,247), and this appears to be a central rather than an adrenal effect (239,246). These findings suggest that both lower LH baseline levels and lower ACTH levels after cocaine combined to facilitate the observed cocaine-related increase in LH in human males.

The physiological and/or clinical significance of cocaine-related increases in LH remains to be determined. In women, high levels of LH during the follicular phase can impair folliculogenesis (120,196,197), and recurrent episodes of cocaine intoxication could have a similar effect. Cumulative increases in LH could also trigger early ovulation. Increases in LH could also interact with some of cocaine's purported subjective effects. Clinical studies indicate that increases in LH levels were significantly related to the degree of sexual arousal reported by young men during an erotic film in comparison to a neutral control film (99). Measures of penile tumescence also were correlated with reports of sexual arousal (99). Clinical descriptions of cocaine's acute effects often include increased sexual feelings and energy as well as intense euphoria (55,191,194,221). Consequently, it is interesting to speculate that the cocaine-related increase in LH may covary with sexual arousal. However, it is unlikely that there is a simple relationship between increased LH levels and sexual arousal or sexual behavior, and the possible behavioral significance of these findings is unknown.

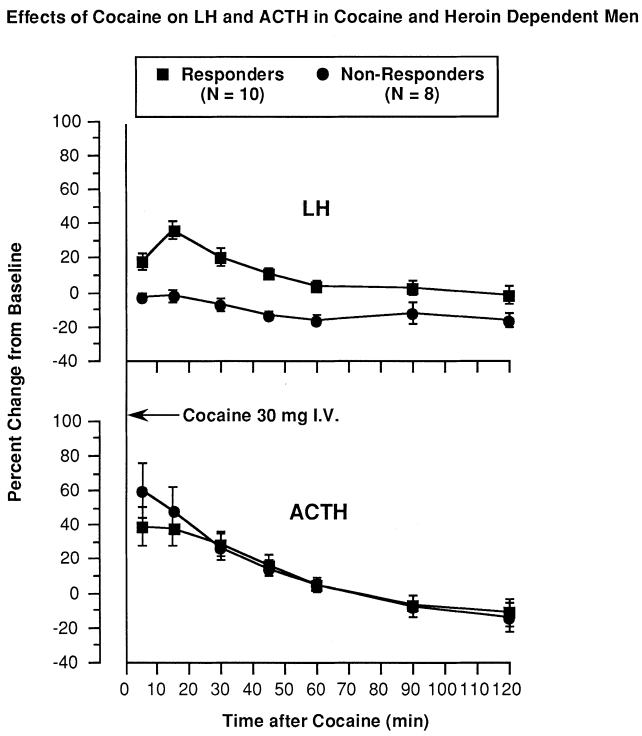

FIG. 10. LH and ACTH levels in cocaine- and opiate-dependent men. Samples were collected at 5, 10, 15, 20, 30, 45, 60, 90, and 120 min after IV cocaine (30 mg) administration. The 18 subjects were divided into two groups on the basis of the magnitude of the postcocaine increase in LH using a criterion of greater or less than 20% above baseline levels. LH levels for the 10 men classified as LH responders and the 8 men classified as nonresponders are shown in the upper panel. ACTH levels after cocaine for the same subgroups of subjects are shown in the lower panel. Data are presented as percent change from the precocaine baseline level (left ordinate). Time after cocaine administration is shown on the abscissa. Data were abstracted from group data described by Mendelson et al. (142).

Clinical Studies of Chronic Cocaine Effects on LH

As noted earlier, it has been difficult to conduct clinical studies in individuals who abuse only cocaine, and multiple drug use has an undetermined effect on the endocrine variables measured. Despite this caveat, a history of cocaine abuse was not associated with abnormal LH and testosterone pulsatile release patterns in men. The pulsatile release patterns of LH and testosterone were examined in eight men who met DSM-III-R diagnostic criteria for cocaine abuse (139). These men reported 1–7 years of cocaine abuse and use of 1–14 g of cocaine per week. No opioid use was reported, but all subjects used marijuana and alcohol. Although subjects were cocaine abstinent during the sample collection period, all had used cocaine recently; urine samples were positive for cocaine and cocaine metabolites on the day of the study. Subjects were admitted to a clinical research ward and, after an overnight fast, samples for hormone analyses were collected at 10-min intervals over 6 consecutive hours. LH

and testosterone pulsatile release patterns were analyzed with the cluster analysis program developed by Veldhuis and Johnson (227). There was no significant difference in LH pulse frequency or peak duration between cocaine abusers and eight control subjects. These data indicate that chronic cocaine abuse had no demonstrable effects on pulsatile release patterns of LH or testosterone during a period of relative cocaine abstinence in men (139). To the best of our knowledge, similar studies have not been conducted in women who abuse cocaine.

COCAINE'S EFFECTS ON REPRODUCTIVE FUNCTION

Background

We have seen that acute cocaine administration changes anterior pituitary and gonadal hormone levels but, with the exception of prolactin, it has been difficult to detect changes in basal hormone levels after chronic cocaine abuse or short-term cocaine exposure in animal models. We infer that chronic changes in neuroendocrine function do occur, on the basis of clinical and experimental evidence of cocaine-related disruptions in reproductive function (27,122,191,193,206). However, the ways in which cocaine interacts with gonadotropin and gonadal steroid hormones to disrupt the menstrual cycle in women and compromise reproductive function in men are unclear. Anterior pituitary and gonadal steroid hormones have both positive and negative feedback effects on each other, and disruption of these feedback relationships affects the functional integration and regulation of the neuroendocrine system. It is apparent that integrative neurobiologic studies in humans and in whole animal models are necessary to analyze these complex interrelationships between the hypothalamic–pituitary–gonadal axis and the hypothalamic–pituitary–adrenal axis.

The hormonal changes that define the phases of the menstrual cycle are one of the most fundamental biological rhythms. The patterns of gonadotropins and ovarian steroid hormones during the normal menstrual cycle were shown earlier (Fig. 9). In women and in higher primates, a menstrual cycle occurs approximately every 28 days from menarche until menopause. The onset of menstruation defines the beginning of a cycle, the follicular phase, and heralds the development of the ovarian follicle, which culminates in ovulation at midcycle. Subsequently, during the luteal phase, the ovarian follicle becomes the corpus luteum, and there is a concomitant increase in progesterone. This postovulatory rise in progesterone is essential for maintaining the fertilized ovum when pregnancy occurs. In the nonfertile cycle, the demise of the corpus luteum is followed by menstruation and the beginning of the next menstrual cycle.

The adverse effects of cocaine on reproductive function include disorders of menstrual cycle duration, which in turn may reflect impairments in folliculogenesis, ovulation, and luteal phase adequacy in otherwise normal women (122, 205,206). Such impairments may result in a series of clinical syndromes that include amenorrhea, anovulation, and luteal phase dysfunction. The complete cessation of menses for periods of months or years is called amenorrhea. Anovulation is a failure to ovulate. Luteal phase dysfunction is defined as either a short luteal phase of 8 days or less from ovulation to menses or an inadequate luteal phase in which progesterone levels are abnormally low but the interval from ovulation to menstruation is of normal length. Both anovulation and luteal phase dysfunction may occur in women who continue to menstruate. Cocaine abuse also may result in disorders of prolactin regulation that are expressed clinically as abnormally high prolactin levels or hyperprolactinemia. This is sometimes associated with abnormal secretion of breast milk, a condition called galactorrhea (27). Cocaine abuse also may increase the risk for spontaneous abortion once pregnancy occurs (30).

Understanding the basis for the most commonly observed disorders (amenorrhea, luteal phase dysfunction, anovulation) is complicated by the fact that each may result from events that occurred earlier in the menstrual cycle. For example, although FSH is only one determinant of normal folliculogenesis, adequate FSH levels during the late luteal and the follicular phases are necessary for normal follicle development and maturation (36,60). Suppression of FSH may delay follicle maturation and subsequent ovulation or may result in luteal phase dysfunction after timely ovulation. Cocaine stimulates LH release, and abnormally high levels of LH and/or estradiol during the follicular phase may suppress FSH and result in anovulation and/or luteal phase dysfunction (34,255). If estrogen levels are high during the early luteal phase, this may shorten the menstrual cycle by 5 or 6 days, resulting in a short luteal phase (74). Acute cocaine administration suppresses prolactin levels, and abnormally low or high prolactin levels may also be associated with luteal phase dysfunction (120). The continuing controversies and unresolved issues concerning the prevalence, differential diagnosis, and pathogenesis of luteal phase dysfunction have been critically examined elsewhere (120,203). Chronic cocaine abuse is sometimes associated with abnormal elevations in prolactin, and hyperprolactinemia may be a concomitant of amenorrhea. However, both amenorrhea and hyperprolactinemia can occur independently (187). A number of medical disorders, malnutrition or fasting, and strenuous exercise may also result in amenorrhea (17,52,233).

In addition to the direct and indirect effects on the gonadotropins and prolactin, cocaine abuse also may disrupt reproductive function by stimulation of the HPA axis. The considerable evidence that cocaine stimulates ACTH and cortisol/corticosterone and, by inference, CRH was described earlier in this review. Although the contribution of cocaine-related increases in CRH to menstrual cycle abnormalities is unclear, it is well established that administration of synthetic CRF inhibited pulsatile release of LH and FSH in ovariectomized rhesus females (150), whereas ACTH infusions did not (246). Synthetic CRF administration also suppressed endogenous LHRH levels measured in rat portal blood (154). Because synthetic CRF also reduced LH and FSH levels in adrenalectomized ovariectomized rhesus females (247), this appears to be a central effect mediated through the hypothalamic–pituitary axis rather than through adrenal activation (246). Subsequent studies have confirmed that administration of CRF (200 μg IV) decreased LH levels as well as electrophysiological activity in the mediobasal hypothalamus in rhesus monkeys (239). The inhibitory effects of CRF on electrophysiological volley frequency (but not duration) were prevented by a continuous infusion of naloxone (8.0 ml/h), suggesting that endogenous opioids may mediate the inhibitory effects of CRF (239).

Clinical evaluation of cocaine's effects on reproductive function has been complicated by the fact that many cocaine abusers also use a number of other drugs, including opioids, alcohol, and marijuana (122,205,206). Moreover, cocaine, opioids, alcohol, and marijuana appear to disrupt the menstrual cycle in very similar ways, although perhaps by different mechanisms (122,130,193,206). Consequently, it is impossible to attribute disorders of the menstrual cycle to cocaine alone in clinical studies. Fortunately, the neuroendocrine control of the menstrual cycle is very similar in female rhesus monkeys and in women and, as a result, the rhesus monkey is a model of choice in reproductive biology. As noted earlier, studies in

the rhesus monkey model have clarified the basis for some clinical disorders of endocrine function and have led to new approaches to the treatment of infertility. For example, after the discovery of the importance of pulsatile gonadotropin release in neuroendocrine control of the menstrual cycle in rhesus monkeys (91,92), it was found that many infertility disorders in women are associated with infrequent LH pulses of low amplitude throughout the menstrual cycle or no LH pulses at all (31,175). These abnormal LH pulsatile release patterns are associated with amenorrhea, the failure to menstruate. In ovariectomized rhesus monkeys with lesions of the arcuate nuclei and in infertile women, administration of synthetic LHRH restored normal LH release patterns (31,47,91, 92,113,175). These findings suggest that cocaine, as well as other abused drugs, may disrupt the pulsatile release of gonadotropin hormones to result in amenorrhea, and studies to evaluate this hypothesis in women and in female rhesus monkeys are ongoing in our laboratory. Chronic cocaine abuse did not appear to alter the pulsatile release patterns of LH in men (139).

In the remainder of this section, preclinical studies of the effects of chronic cocaine exposure on reproductive function are described. There have been relatively few studies designed to examine cocaine's effects on the menstrual cycle or the estrous cycle or on indices of ovarian function in animal models. However, there is general agreement that chronic cocaine exposure disrupts the menstrual cycle in rhesus monkeys and the estrous cycle in rodents. Cocaine had minimal effects on ovarian function in rabbits and on sexual behavior in rats and mice, which is consistent with the fact that human cocaine abusers do reproduce. The teratogenic effects attributed to cocaine and other drug abuse continue to be a major public health concern (40,73,118,157). The complex literature on cocaine's teratogenic effects is beyond the scope of this review, but it is interesting to note that prenatal cocaine exposure alters the responsivity of ACTH and corticosterone (18,19) and impairs sexual differentiation in rats (160).

Preclinical Studies of the Effects of Chronic Cocaine Administration on Reproductive Function

Chronic cocaine effects on the menstrual cycle in rhesus monkeys. The primate model of cocaine and other drug self-administration is especially valuable for studying the effects of chronic drug use on neuroendocrine hormones. Rhesus monkeys self-administer most drugs that are abused by humans, and the patterns of drug self-administration are often similar (16,63,121,131). Thus, the neuroendocrine effects of a single drug, such as cocaine, can be studied in rhesus monkeys without the confounding influence of polydrug abuse, malnutrition, and concurrent medical disorders. One important advantage of drug self-administration procedures relative to investigator-determined drug administration is that each monkey controls the frequency and amount of cocaine injected. Previous studies have shown that response-independent cocaine administration resulted in higher rates of lethality than self-administration of the same amounts of cocaine in rats (42).

We examined the effects of chronic cocaine self-administration for two or more years on menstrual cycle duration and anterior pituitary and gonadal hormone levels in adult rhesus females (*Macaca mulatta*) (128). Eight monkeys maintained on cocaine and food self-administration were compared with six control females that were occasionally exposed to an acute dose of cocaine (0.4 or 0.8 mg/kg IV) once every 2 or 3 months for 2–3 years. Drug-naive rhesus females were adapted to the laboratory for several months until stable ovulatory menstrual cycles occurred. Then monkeys in the cocaine group were implanted with intravenous catheters under aseptic conditions and trained to self-administer food pellets and intravenous cocaine on a simple operant task. Monkeys were given access to cocaine (0.1 mg/kg/injection) in four sessions each day and were limited to 20 injections per session to minimize any possible adverse drug effects. Under these conditions, monkeys could self-administer up to 8 mg/kg of cocaine per day. Food self-administration sessions preceded drug self-administration sessions so that cocaine intoxication would not compromise food intake. A nutritionally fortified banana pellet diet was supplemented with fresh fruits and vegetables, multiple vitamins, and chow. Water was continuously available, and a 12 Light:12 Dark cycle was in effect. Monkeys remained healthy and active, and food intake and body weight were normal under these conditions of limited access to cocaine self-administration.

Thus far, the effects of chronic cocaine self-administration on menstrual cycle duration have been examined for over 200 menstrual cycles, and the control group has been studied for over 150 menstrual cycles. The frequency of occurrence of cycles that were one standard deviation shorter or longer than each monkey's average baseline cycles was tabulated. In the control group, 94% of the menstrual cycles were of normal duration, whereas in the cocaine group, approximately one-half of all menstrual cycles were of abnormal duration. Abnormally short menstrual cycles accounted for half of these aberrant menstrual cycles. Abnormally short menstrual cycles are consistent with luteal phase defects, and most cycles analyzed to date have been anovulatory, as inferred from low progesterone levels during the luteal phase. The remainder of the cycles of abnormal duration were longer than each monkey's precocaine baseline cycles by one or more standard deviations from the mean. Seven cycles were amenorrheic and no menses occurred for 63–174 days. These data suggest that chronic cocaine exposure disrupts menstrual cycle regularity in otherwise healthy monkeys studied under controlled laboratory conditions. The menstrual cycle disruptions observed are consistent with clinical reports in cocaine abusers who are also polydrug abusers (205). These studies are continuing, and analysis of the endocrine characteristics of the menstrual cycles is ongoing.

Chronic cocaine effects on the estrous cycle. The estrous cycle in rodents occurs every 4–5 days throughout the year (50). The sequential stages of proestrus (1 day), estrus (1 day), and diestrus (2 days) correspond functionally to the follicular, periovulatory, and luteal phases of the menstrual cycle in higher primates. During proestrus, there is rapid maturation of ovarian follicles followed by ovulation and then formation and regression of the corpus luteum. Estrous cyclicity can be defined as the number of changes of the normal pattern of proestrus followed by estrus the next day. Estrous cycle irregularities associated with cocaine were first observed in a study designed to determine if the estrous cycle affected rates of cocaine self-administration (171). After training and observation of behavior during one complete estrous cycle, rats were exposed to a progressive ratio schedule in which the response requirement per cocaine injection was gradually increased from 1 to a maximum of 999 responses until rats stopped responding for a period of 1 h (the progressive ratio breakpoint). It was found that the progressive ratio breakpoints were significantly higher during estrus than during the other phases of the estrous cycle. However, when cocaine was available on a low response requirement (a fixed ratio of 1) cocaine self-administration did not vary with stages of the estrous cycle (171). In addition, females attained significantly

higher progressive ratio breakpoints (264 responses/injection) than did the males (48 responses/injection), whereas at low response requirements males tended to self-administer slightly more cocaine than females. Although estrous cyclicity was not the primary dependent variable in this study, 6 of the 11 females developed irregular estrous cycles, which were first detected after 18 days of cocaine self-administration. These data were interpreted to suggest that the high levels of estradiol associated with estrus might enhance cocaine's reinforcing effects (171).

In a study of chronic cocaine effects on estrous cyclicity, groups of rats received daily subcutaneous injections of 10 mg/kg cocaine for 3 weeks or for 6 weeks, and the control group received subcutaneous injections of saline for 6 weeks (88). Estrous cyclicity was assessed with vaginal smear cytology. The saline-treated rats had normal 4-day estrous cycles, whereas the cocaine-treated rats developed cycle irregularities within 7 days of treatment. Approximately 63% of the rats had irregular estrous cycles characterized by repetitive days of estrus, absence of proestrus, and prolonged periods of diestrus. Cocaine treatment appeared to reduce ovulation because significantly fewer oocytes were retrieved after sacrifice on the day of estrus. Subsequent studies showed that the degree of disruption of estrous cyclicity was cocaine-dose dependent (89). Groups of rats were injected with saline or 1, 5, 10, or 20 mg/kg/day of cocaine subcutaneously. Following cocaine treatment, rats were evaluated for capacity to return to cycle normalcy. Because weight loss can also result in disruption of the estrous cycle, a control group was put on restricted food to limit weight gain to levels comparable to rats receiving the highest dose of cocaine. Estrous cyclicity was significantly disrupted at doses of 10 and 20 mg/kg cocaine in comparison to saline and low-dose (1–5 mg/kg) cocaine treatment. Estrus and diestrus reoccurred repeatedly, and there was a frequent absence of proestrus. A cocaine dose of 8.9 mg/kg/day was required to reduce the number of proestrus/estrus events by 50%, i.e., changes in the normal pattern of proestrus followed the next day by estrus. Ovulation, as inferred from oocyte retrieval after sacrifice, was also significantly reduced in the groups that received 10 and 20 mg/kg/day of cocaine. Hormone measurements at each phase of the estrous cycle were obtained after sacrifice by decapitation. In contrast to cocaine's acute stimulatory effects on LH in rhesus monkeys (124,125,132) and human males (65,140), LH levels measured at proestrus and diestrus were significantly lower after chronic high-dose cocaine treatment than after low-dose or placebo treatment. However, FSH levels were not significantly different across treatment conditions. After cessation of chronic cocaine treatment, over half of the rats given 10 mg/kg/day of cocaine returned to normal estrous cycles, whereas few of the rats treated with 20 mg/kg/day regained normal estrous cycles over a 5–6-week period of observation (89).

Mice appear to be somewhat more resilient to the adverse effects of cocaine than rats. Female house mice were exposed to cocaine and followed over two generations (26). They were given saline or 40 mg/kg/day of cocaine in two divided doses for 13 days beginning on the day after weaning (day 22) until mating. This cocaine treatment regimen delayed the first estrus, slowed growth and development, and reduced the number of pups born per litter in comparison to control mice. However, cocaine treatment did not affect the age of first pregnancy, the number of mice that became pregnant, or the duration of pregnancy. Subsequently, lactating females were treated with cocaine (40 mg/kg/day, b.i.d.), and on the day after weaning, the cocaine-exposed pups were treated with cocaine (20 or 40 mg/kg/day) for 11 days until mating. Cocaine exposure during nursing did not differentiate the groups. Treatment of the juvenile mice with the lower dose of cocaine did not significantly impair mating or successful pregnancy, whereas the higher dose of cocaine delayed puberty but did not impair subsequent reproductive effectiveness. It was concluded that the adverse effects of cocaine on pubertal development were transient (26).

Chronic cocaine effects on reproductive function in male rats. The effects of chronic treatment with cocaine on several measures of sexual behavior were examined in male rats. Males were treated with saline or cocaine (15 or 30 mg/kg/day SC) for 72–90 days. After 75 days of treatment, males were given access to a receptive female at 20 h after the last cocaine injection. Cocaine treatment had no effect on sexual behavior as measured by latency to first intromission and ejaculation, number of intromissions until ejaculation, and postejaculatory intervals. Testicular weight, testicular structure, and sperm morphology also did not differ between cocaine-treated males and controls. These findings are inconsistent with reports of ultrastructural changes in rat testicular structure after several hours of cocaine exposure (172). Paternal cocaine treatment also did not effect litter size, birth weight, sex distribution, or body weight at weaning. The major difference between cocaine-treated and control males was in measures of hyperactivity, and the offspring of cocaine-treated males were also more active than the offspring of controls (3).

Effects of chronic cocaine exposure on ovarian function in rabbits. One distinctive feature of the rabbit ovarian cycle is that ovulation occurs in response to copulation (158). Although there are seasonal variations in estrous behavior, rabbits are reflex ovulators, and ovulation usually occurs within 9–10 h after mating. Thus, the rabbit model has some advantages for studying the effects of cocaine on ovarian function. Interestingly, the ovulatory capacity of the rabbit appears to be quite resilient and was not impaired by low to moderate doses of cocaine (6,86,87).

When rabbits were given six injections of cocaine (4 mg/kg/injection) at 1-h intervals on the day after mating, ovulatory efficiency was enhanced in comparison to saline control treatment (101 ovulations from 122 large follicles after cocaine and 68 ovulations from 98 large follicles after saline) (6). The higher rates of ovulation observed are consistent with cocaine's stimulation of LH. In mated rabbits, the same cocaine treatment regimen did not affect implantation measured on day 8 of pregnancy (6). In other studies, female rabbits were given cocaine (0, 10, 20, 40, or 80 mg/kg SC) for 5 days, and hCG (75 IU IV) was administered on the last day of cocaine exposure to induce follicle maturation (86). A unilateral ovariectomy was performed, and the number of follicles larger than 1 mm in diameter were counted. There were no differences in the number of ovarian follicles or the oocytes retrieved as a function of cocaine dose (86). These data indicate that short-term cocaine exposure does not interfere with the final stages of ovum maturation (86). In vitro fertilization of the oocytes collected from cocaine-exposed and control rabbits was performed to determine if fertilization varied as a function of cocaine dose (86). There were no differences in the number of oocytes fertilized, the fertilization rate, or the cleavage rate among fertilized oocytes. There was a cocaine dose-dependent (10–40 mg/kg) change in ovarian steroid hormone levels. Progesterone levels decreased in venous blood and in follicular fluid samples, and this decrease was accompanied by elevated estradiol levels. Low progesterone levels are consistent with compromised corpus luteum development and with spontaneous abortion. However, the effects of co-

caine were evaluated at only one time after exposure, so general conclusions from this study are limited. The absence of detectable pathology was surprising in view of the fact that convulsions and irritability were observed at cocaine doses of 40 mg/kg and above. The 80-mg/kg dose of cocaine was highly toxic, and two of the five rabbits died (86).

The effects of 5 days of cocaine treatment (40 mg/kg SC) on mating-induced ovulation and hCG-induced ovulation (75 IU IV) were compared with vehicle control treatment (87). Twenty-four hours after ovulation induction, one fallopian tube was removed and flushed to recover the ova, and the number of fresh corpora lutea on the ovary was counted during laparotomy. For inducing ovulation, hCG was more effective than mating. Ovulation occurred in all the cocaine + hCG- and vehicle + hCG-treated rabbits. Equivalent corpora lutea developed in hCG-treated rabbits after cocaine and vehicle control treatment. In contrast, none of the cocaine-treated rabbits ovulated after mating, whereas 6 of the 10 mated controls ovulated. Because cocaine + hCG-treated rabbits had as many oocytes as controls, whereas mated cocaine-treated rabbits did not ovulate or release LH, this was interpreted to indicate that cocaine suppresses ovulation in the rabbit by reducing hypothalamic pituitary release of LH rather than by inhibiting ovarian responsivity to hCG stimulation (87).

Single daily injections of cocaine (4 mg/kg) or vehicle were administered to pregnant rabbits, and the effects on fetal and placental weight and delivery were examined (6). The weight gain in cocaine-treated rabbits was lower than in controls, but there were no differences in fetal and placental weights on days 15 and 22 of pregnancy. There were also no differences in the number or weight of corpora lutea per ovary in the cocaine-treated animals, and peripheral and ovarian vein progesterone levels were equivalent (6). Taken together, these studies indicate that cocaine does not consistently suppress mating-induced ovulation and does not disrupt hCG-induced ovulation or pregnancy in the rabbit model of ovarian function.

CONCLUSIONS

Cocaine interacts with many neuromodulatory systems in brain and has both direct and indirect effects on anterior pituitary, gonadal, and adrenal hormones. The comodulatory interactions between these hormones have been emphasized throughout this review. An obvious limitation of studies of cocaine's effects on single hormones, at a single time point, is that the effects measured cannot reflect the full spectrum of interactions within the neuroendocrine system. However, studies conducted thus far have begun to elucidate some of the complex effects of cocaine on regulation of hormone release.

Acute cocaine administration stimulates the release of ACTH, LH, and FSH from the anterior pituitary and suppresses the release of prolactin in several species under a variety of experimental conditions. These acute effects of cocaine on specific hormones are consistent with its actions as a monoamine reuptake inhibitor. For example, cocaine is an indirect dopamine agonist, and prolactin is under inhibitory dopaminergic control. ACTH release is controlled by CRH, which in turn is regulated by serotonin, dopamine, and norepinephrine. Gonadotropin stimulation was not predictable from the pharmacology of cocaine because exogenous dopamine administration suppresses LH in clinical studies, and the basis for cocaine's stimulation of LH is poorly understood. Considerably less is known about the acute effects of cocaine on gonadal steroid hormones. However, the importance of estradiol and progesterone in modulating cocaine's stimulatory effects can be inferred from observations that in ovariectomized rhesus monkeys, cocaine does not stimulate LH or ACTH release. The possible contribution of gonadal steroid hormones, rather than pituitary dysfunction, to these effects is suggested by the fact that synthetic LHRH and CRF each stimulate significant increases in LH and ACTH in ovariectomized monkeys.

It has been difficult to detect effects of chronic cocaine exposure on single hormones. With few exceptions, basal levels of specific hormones after chronic cocaine treatment do not differ from control conditions. Furthermore, administration of a challenge dose of cocaine, or other stimulating agent, seldom reveals a significant change in the target hormone response after chronic cocaine exposure, although there are some exceptions to this general finding. One interpretation of these observations is that the effects of cocaine are transient and limited to the duration of action of each dose of cocaine. Alternatively, it is possible that repeated hormonal stimulation or suppression by cocaine eventually may disrupt the regulatory feedback system. Some evidence in support of this hypothesis comes from studies of the effects of chronic cocaine exposure on prolactin. Repeated episodes of prolactin suppression by cocaine may evolve into hyperprolactinemia following chronic cocaine use.

There has been relatively little experimental attention to the consequences of chronic cocaine exposure on reproductive function. Measures of menstrual cycle adequacy are one index of the integrative actions of anterior pituitary and gonadal hormones over time. The complex changes in hormone release patterns that define the menstrual cycle have been well characterized, and detailed studies may reveal subtle, yet functionally significant, changes during chronic cocaine exposure. Clinical evidence of cocaine's disruptive effects on reproductive function is often complicated by the fact that many human cocaine abusers are polydrug abusers. Because abuse of opiates and alcohol also may be associated with menstrual cycle disorders such as amenorrhea, anovulation, and luteal phase dysfunction, it is difficult to attribute these disorders to cocaine alone. Animal models offer many advantages for the study of cocaine's effects on reproductive function, and neuroendocrine control of the menstrual cycle in rhesus monkeys and in women is very similar. Only a few studies have examined cocaine's effects on the menstrual or estrous cycle, but chronic cocaine exposure consistently results in abnormal cycles in rats and monkeys. In rhesus monkeys, the menstrual cycle abnormalities observed are similar to clinical reports of amenorrhea, anovulation, and luteal phase dysfunction. Estrous cycle abnormalities persist after high-dose cocaine treatment, and the long-term effects of cocaine on the menstrual cycle in rhesus monkeys are currently under investigation.

Evaluation of chronic drug effects on reproductive function in animal models also offers an opportunity for the convergence of experimental approaches from endocrinology and behavioral science. Most studies considered in this review have examined the effects of relatively high doses of cocaine, often at the convulsant threshold. Yet most animals will self-administer cocaine (as well as many other drugs abused by man), so it is possible to evaluate the effects of chronic cocaine exposure under conditions where animals remain healthy and control their level of drug intake. There is compelling evidence that the toxic effects of cocaine in animal models are determined by whether or not animals control their cocaine intake and by the actual cocaine dose, and these issues should be considered in the design of future studies.

It has been evident throughout this review that much remains to be learned about the consequences of cocaine expo-

sure on regulation of anterior pituitary, gonadal, and adrenal hormones. This area offers many exciting opportunities to explore the interactions between cocaine and the neuroendocrine system. Recent advances in endocrinology, endocrine pharmacology, neurobiology, and behavioral science should facilitate progress in understanding the ways in which cocaine affects the regulation of neuroendocrine hormones. Data obtained from multidisciplinary integrative studies in animal models should have heuristic value for neurobiology as well as clinical relevance for understanding the functional consequences of cocaine abuse.

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