Cocaine Abuse and Reproductive Function in Women

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INTRODUCTION

A number of abused drugs may compromise reproductive function and disrupt menstrual cycle regularity (Mello et al. 1992, pp. 575-621; Smith and Smith 1990; Teoh et al. 1994*a*, pp. 437-473; Mello and Mendelson 1997). Chronic abuse of alcohol and other drugs is associated with several neuroendocrine disorders that are expressed clinically as anovulation, luteal phase dysfunction, and amenorrhea. Single episodes of alcohol or other drug intoxication also may result in hormonal changes that impair menstrual cycle function. In addition to specific disorders of the menstrual cycle, the effects of such drugs on neuroendocrine hormones essential for normal reproductive function may compromise other aspects of women's health, including immune function, which in turn may enhance the risk for acquired immunodeficiency syndrome (AIDS).

This chapter summarizes some recent research on the effects of cocaine on neuroendocrine hormones that are essential for normal reproductive function. A more extensive review of cocaine's effects on anterior pituitary, gonadal, and adrenal hormones has been published elsewhere (Mello and Mendelson 1997). At present, relatively little is known about the mechanisms by which cocaine, alcohol, and other drugs of abuse disrupt the menstrual cycle. Although a number of drugs disrupt the menstrual cycle in similar ways, this does not mean that all drugs act through similar mechanisms. Regulation of the reproductive system is complex and depends on interactions among the hypothalamus, pituitary, ovaries, and adrenal glands. Each component of the reproductive system has both positive and negative feedback effects on each other component. An imbalance in any part of the hypothalamic-pituitary-ovarian and hypothalamic-pituitary-adrenal system can jeopardize these fragile feedback interrelationships. It seems unlikely that cocaine acts primarily at a single target site, but it is not yet known how

drugs of abuse affect the functional integration and regulation of the neuroendocrine system and how this, in turn, may be related to drug-induced disorders of reproductive function (see Mello and Mendelson 1997 for review).

CLINICAL DESCRIPTION OF MENSTRUAL CYCLE DISORDERS

A menstrual cycle occurs approximately every 28 days in women and higher primates throughout their reproductive lifespans. The hormonal changes that define the phases of the menstrual cycle are among the most fundamental of biological rhythms. The onset of menstruation defines the beginning of a cycle, the follicular phase, and heralds the development of the ovarian follicle that culminates in ovulation. Subsequently, the site of the ruptured ovarian follicle becomes the corpus luteum, and there is a concomitant increase in progesterone during the luteal phase. This postovulatory rise in progesterone is essential for the maintenance of the fertilized ovum if conception 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 cycle function include disorders of menstrual cycle duration as well as impairments in folliculogenesis, ovulation, and luteal phase adequacy. These disruptions 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 the failure to ovulate; and luteal phase dysfunction is defined either as a short luteal phase of 8 days or less from ovulation to menses or an inadequate luteal phase when progesterone levels are abnormally low but the interval from anovulation to menstruation is of normal length. Both anovulation and luteal phase dysfunction may occur in women who continue to menstruate. Cocaine and alcohol abuse also may result in disorders of prolactin regulation. These disorders may be expressed clinically as abnormally high prolactin levels, or hyperprolactinemia, which is sometimes associated with abnormal secretion of breast milk, a condition called galactorrhea. Cocaine and alcohol abuse both increase the risk for spontaneous abortion once pregnancy occurs.

Analysis of these disorders is complicated by the fact that each clinical entity may result from hormonal disruptions that occurred earlier

in the menstrual cycle. For example, although follicle-stimulating hormone (FSH) is only one determinant of normal folliculogenesis, adequate FSH levels are necessary for normal follicle development and maturation (Goodman and Hodgen 1983). Suppression of FSH may delay follicle maturation and subsequent ovulation or result in luteal phase dysfunction after timely ovulation. Abnormally high levels of either luteinizing hormone (LH) or estradiol during the follicular phase may contribute to FSH abnormalities and anovulation and/or luteal phase dysfunction (Dierschke et al. 1985, 1987; Zeleznik 1981). High levels of estrogens during the early luteal phase may shorten the cycle by 5 or 6 days, which is analogous to a luteal phase defect (Hutchison et al. 1987). Abnormally high or low prolactin levels also may be associated with luteal phase dysfunction (McNeely and Soules 1988). Hyperprolactinemia may also be a concomitant of amenorrhea. The continuing controversies and unresolved issues concerning the prevalence, differential diagnosis, and pathogenesis of luteal phase dysfunction have been critically examined by Stouffer (1990) and McNeely and Soules (1988). However, it appears that any drug-induced imbalance in anterior pituitary, gonadal, and adrenal hormones may lead to disruption of the normal menstrual cycle.

IMPLICATIONS OF POLYDRUG ABUSE

Polydrug abuse involving cocaine and other drugs appears to be increasingly common, so the contribution of a single drug to these reproductive disorders is often difficult to determine in clinical studies. Moreover, concurrent abuse of several drugs may increase the adverse consequences of single drug use (Kreek 1991, pp. 91-112). For these reasons the author and colleagues have examined the effects of acute and chronic exposure to cocaine in the female rhesus monkey. Neuroendocrine control of the menstrual cycle is similar in rhesus females and in women, so the rhesus monkey is a model of choice in reproductive biology. In studies of endocrine pharmacology, as well as basic reproductive biology, this model has led to new approaches to the study of clinical phenomena. For example, after the discovery of the importance of pulsatile gonadotropin release in neuroendocrine control of the menstrual cycle in rhesus monkeys (Knobil 1974, 1980), 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 (Crowley et al.

1985; Santoro et al. 1986). These abnormal LH pulsatile release patterns are associated with amenorrhea. Administration of synthetic hypothalamic luteinizing hormone-releasing hormone (LHRH) restored normal LH release patterns and fertility (Crowley et al. 1985; Filicori et al. 1994; Martin et al. 1993; Santoro et al. 1986). Although malnutrition and a number of medical disorders, as well as strenuous exercise, may contribute to amenorrhea, these findings suggest the possibility that cocaine and alcohol also may disrupt the pulsatile release of these essential hormones, resulting in amenorrhea; studies to evaluate this hypothesis are ongoing.

The primate model of cocaine and other drug self-administration is especially valuable for studying the effects of chronic drug use on neuroendocrine hormones. In laboratory studies, rhesus monkeys self-administer most drugs that are abused by humans, and the neuroendocrine effects of a single drug such as cocaine can be studied without the confounding influence of polydrug abuse, malnutrition, and concurrent medical disorders. Rhesus monkeys also can be used to study the effects of multiple drugs under controlled conditions (Mello et al. 1995*a*).

EFFECTS OF CHRONIC COCAINE SELF-ADMINISTRATION ON THE MENSTRUAL CYCLE

The effects of chronic cocaine self-administration on menstrual cycle duration and anterior pituitary and gonadal hormones have been examined for periods of 2 to 3 years in adult rhesus females (*Macaca mulatta*) (Mello et al. 1997). Drug-naive rhesus females were adapted to the laboratory for several months until stable ovulatory menstrual cycles occurred. Then the monkeys were implanted with intravenous catheters under aseptic conditions and trained to self-administer cocaine and food on a simple operant task. Monkeys were given access to cocaine in 4 sessions each day and were limited to 20 injections per session to minimize any possible adverse drug effects. Under these conditions, each monkey could control the frequency and amount of cocaine injected up to a limit of 8 mg/kg/day. Food self-administration sessions preceded each drug self-administration session so that cocaine intoxication would not compromise food intake. A nutritionally fortified banana pellet diet also was supplemented with fresh fruits and vegetables, multiple vitamins, and chow. Water was continuously available, and a 12-hour light-dark cycle was in effect. Monkeys remained healthy and active, and

food intake and body weight were normal under these limited cocaine access conditions.

Thus far, the effects of chronic cocaine self-administration on menstrual cycle duration have been examined in eight rhesus females and compared with six control females that were occasionally exposed to single doses of cocaine. Approximately 50 percent of all menstrual cycles were of abnormal duration in the cocaine self-administration group, whereas only 6 percent of cycles were abnormal in the control group. Abnormally short cycles, consistent with luteal phase defects, accounted for 17 percent of the abnormal menstrual cycles. The rest of the cycles of abnormal duration were longer than each monkey's precocaine baseline cycles by one or more standard deviation from the mean or met criteria for amenorrhea (60 days with no menses). There were 19 amenorrheic cycles when no menses occurred for 61 to 190 days. Approximately one-third of the menstrual cycles studied during cocaine self-administration were anovulatory as defined by midluteal phase progesterone levels below 4.5 ng/mL. These data suggest that chronic cocaine exposure disrupts menstrual cycle regularity in otherwise healthy monkeys studied under controlled conditions. The menstrual cycle disruptions observed are consistent with clinical reports on women who abuse cocaine and who are also polydrug abusers (Teoh et al. 1992) and with experimental evidence that 2 or more weeks of cocaine exposure disrupt estrous cyclicity in the rat (King et al. 1990, 1993).

ACUTE EFFECTS OF COCAINE ON NEUROENDOCRINE FUNCTION

Alcohol and other drugs may have different effects on neuroendocrine hormones if intoxication occurs occasionally or chronically through time (Mello et al. 1992, pp. 575-621; Mello and Mendelson 1997). Interpretation of the effects of *chronic* cocaine self-administration on the menstrual cycle is complemented by examination of the *acute* effects of single doses of cocaine on the neuroendocrine hormones that are essential for normal reproductive function. Neuroendocrine effects of single doses of cocaine eventually clarify the ways in which cocaine disrupts reproductive function.

Recent studies of the acute effects of alcohol as well as those of cocaine have challenged some common assumptions about how drugs

disrupt neuroendocrine regulation. Drug-related disorders of reproductive function have traditionally been attributed to a suppression of pituitary and gonadal hormones (Mello et al. 1992, pp. 575-621). The basic concept is that drugs disrupt regulation of the reproductive system by suppressing basal levels of essential hormones. Yet there is accumulating evidence that acute cocaine intoxication, as well as acute alcohol intoxication, may stimulate rather than suppress the release of LH from the anterior pituitary (Mello and Mendelson 1997). These data further complicate the understanding of how cocaine intoxication induces derangements of the menstrual cycle.

Cocaine's Effects on Luteinizing Hormone

In the normal menstrual cycle, a midcycle surge in LH stimulates ovulation, the release of the ovum from the ovary. One recent unexpected finding is that cocaine stimulates LH in female rhesus monkeys during both the follicular and the midluteal phases of the menstrual cycle (Mello et al. 1990*a*, 1993). Cocaine also stimulates LH in male humans and in male rhesus monkeys (Mello et al. 1993; Mendelson et al. 1992*a*). LH stimulation would not have been predicted from the basic pharmacological actions of cocaine. Cocaine inhibits dopamine reuptake and acts as an indirect dopamine agonist, and clinical studies have shown that administration of dopamine agonists suppresses rather than increases LH (see Yen 1986, pp. 178-263). Yet a significant increase in LH after acute cocaine administration has been a consistent and robust finding across species and in gonadally intact males and females. Moreover, in rhesus females, administration of cocaine concurrently with synthetic LHRH, the hypothalamic hormone that stimulates LH release, resulted in a significant enhancement of peak LH levels (Mello et al. 1990*b*).

One exception to this general finding is that cocaine has no effect on LH or FSH in ovariectomized rhesus monkeys (Mello et al. 1995*b*). The same doses of cocaine used in gonadally intact males and females, studied under the same conditions (Mello et al. 1990*a*, 1990*b*, 1993), did not change gonadotropin hormone levels in ovariectomized females even though plasma cocaine levels were equivalent (Mello et al. 1995*b*). Synthetic LHRH stimulated LH release in these ovariectomized females even though cocaine did not (Mello et al. 1995*b*). The reason for this difference between the acute effects of cocaine in intact and ovariectomized monkeys has not yet been determined, but one obvious

possibility is that ovariectomized monkeys have only trace amounts of estradiol, the ovarian hormone that is necessary for the LH periovulatory surge in a normal menstrual cycle. The role of estradiol in cocaine's stimulation of LH is undetermined, and the effects of cocaine on ovarian steroid hormones are unknown.

The implications of a cocaine-induced increase in LH for the biologic and reinforcing properties of cocaine are unclear, but it is interesting to speculate that if cocaine increases LH near midcycle, this increase in turn could trigger ovulation and result in an increased risk for pregnancy. Moreover, clinical studies suggest that sexual arousal is associated with increased LH levels (LaFerla et al. 1978), and the cocaine-induced increase in LH could be associated with the enhanced sexuality reported by some cocaine abusers (see Mello et al. 1990*a* for discussion).

Cocaine's Effects on Adrenocorticotropic Hormone

Cocaine also stimulates adrenocorticotropic hormone (ACTH) release from the anterior pituitary. Corticotropin-releasing hormone (CRH) cannot be measured directly in peripheral blood, but by implication, cocaine also stimulates CRH release because CRH stimulates ACTH release. These stimulatory effects of cocaine appear to be centrally mediated because administration of CRH antagonists prevents the cocaine-induced increase in ACTH (Rivier and Vale 1987).

Cocaine administration is followed by a rapid increase in ACTH in women (J.H. Mendelson, personal communication, November 1996), men, and rhesus males (Mendelson et al. 1992*b*, 1992*c*, pp. 131-155; Sarnyai et al. 1996; Teoh et al. 1994*b*). It is possible that these stimulatory effects of cocaine on ACTH and CRH may contribute to the menstrual cycle disorders observed in chronic cocaine abusers. It is well established that synthetic CRH administration has a direct suppressive effect on release of LH and FSH, and this in turn may result in anovulation and amenorrhea (Olster and Ferin 1987; Xiao and Ferin 1988). Yet cocaine stimulates both LH and ACTH after acute administration, and it is possible that chronic cocaine exposure may lead to disregulation of these feedback systems. The significance of rapid changes in ACTH for cocaine's reinforcing effects is unclear, but the time course parallels the time course of increases in plasma cocaine and

reports of positive changes in mood (Mendelson et al. 1992*b*, 1992*c*, pp. 131-155; Mello and Mendelson 1997).

In contrast to cocaine's stimulatory effects in men and women, cocaine had no effect on ACTH in ovariectomized monkeys even though synthetic CRH stimulated ACTH in the same animals (Sarnyai et al. 1995). The basis for the lack of cocaine stimulation of both ACTH and LH in ovariectomized females is unclear (Mello et al. 1995*b*; Sarnyai et al. 1995). However, as noted above, one possible explanation is the low levels of gonadal steroid hormones in ovariectomized monkeys compared with gonadally intact males and females. Studies are in progress to examine anterior pituitary responsivity to cocaine in ovariectomized females during ovarian steroid hormone replacement regimens.

Cocaine's Effects on Prolactin

Hyperprolactinemia is another endocrine abnormality sometimes associated with chronic cocaine abuse and with cocaine abstinence syndrome (Cocores et al. 1986; Dackis and Gold 1985; Mendelson et al. 1989). Analysis of the pulsatile release characteristics of prolactin in hyperprolactinemic male cocaine abusers revealed an increased peak amplitude but no change in pulse frequency (Mendelson et al. 1989). These data were interpreted to indicate that cocaine changed the dopaminergic inhibition of basal prolactin secretion.

The ways in which cocaine abuse may disrupt prolactin regulation are very complex (Mello and Mendelson 1997). Prolactin is a hormone that is under inhibitory dopaminergic control. Cocaine acts as an indirect dopamine agonist because it binds to the dopamine transporter and blocks the reuptake of dopamine. A single acute dose of cocaine decreases prolactin in rhesus males and females, presumably as a result of increasing dopamine levels (Mello et al. 1990*a*, 1993). This acute suppression of prolactin appears inconsistent with the hyperprolactinemia seen clinically. However, it is thought that chronic cocaine abuse may lead to a downregulation of dopamine receptors, sometimes referred to as "dopamine depletion," that is, decreased dopamine synthesis and secretion (Dackis and Gold 1985). Prolactin is secreted from the anterior pituitary by the lactotrophs. The dopamine-sensitive lactotrophs, which have primarily D_2 dopamine receptors,

secrete significantly more prolactin than thyrotropin-releasing-hormone-sensitive lactotrophs (Yen 1991, pp. 357-388). It is possible that chronic cocaine exposure may impair the sensitive regulatory feedback relationship between hypothalamic dopamine and prolactin to result in hyperprolactinemia seen clinically.

One way to study changes in prolactin regulation as a function of chronic cocaine exposure is to give infusions of exogenous dopamine and measure the degree to which prolactin is suppressed and the level to which prolactin increases after the dopamine infusion is stopped (Mello et al. 1994). Although exogenously administered dopamine does not cross the blood-brain barrier, it does act at the median eminence and the anterior pituitary (Yen 1979, pp. 387-416). This approach was used to determine whether there were progressive changes in the prolactin response to dopamine in rhesus females studied before cocaine exposure and after several months of cocaine self-administration (Mello et al. 1994).

The top panel of figure 1 shows the effects of dopamine infusions and interruptions on prolactin in four normal rhesus females studied before chronic cocaine exposure. These monkeys had low baseline prolactin levels (6.2 ng/mL) that significantly decreased to below 2 ng/mL during dopamine infusions. Prolactin returned to baseline levels after each dopamine infusion ended.

The bottom panel of figure 1 shows the effects of dopamine infusions in the same group of rhesus females after they had self-administered cocaine for an average of 74 days. These monkeys took an average of 4.78 mg/kg/day of cocaine during the 30 days before this study. Baseline levels of prolactin were significantly higher than before cocaine and now averaged 20 ng/mL. Dopamine infusions continued to suppress prolactin significantly, but after each dopamine infusion stopped, prolactin increased to about the same or higher levels than before cocaine exposure. There was a significant and progressive increase in prolactin levels after each dopamine infusion, and peak prolactin levels reached hyperprolactinemic levels of 60 ng/mL. Hyperprolactinemia is defined clinically by daytime prolactin levels above 25 ng/mL. These data suggest that dopamine probes can be used to unmask cocaine-related changes in prolactin regulation before the development of hyperprolactinemia (Mello et al. 1994).

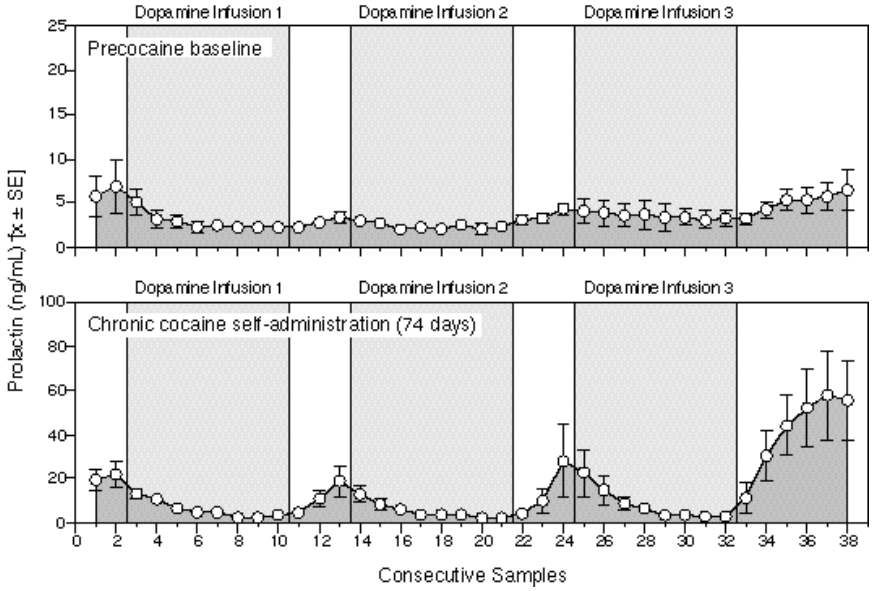

FIGURE 1. *Effects of dopamine infusions (10 µg/kg/min) and interruptions on prolactin (ng/mL) before and after chronic cocaine self-administration. A continuous infusion of dopamine (10 µg/kg/min) was started immediately after collection of samples 2, 13, and 24. Each dopamine infusion (shown as a shaded area) continued for 80 minutes and stopped abruptly after collection of samples 10, 21, and 32. Bolus samples for prolactin analysis were collected at 10-minute intervals except during the first two interruptions of the dopamine infusion when the first two samples were collected at 5-minute intervals. Prolactin levels (ng/mL) are shown on the left ordinate, and consecutive samples are shown on the abscissa. Each data point represents the mean ($\bar{x}$) (±SE) of four monkeys. The top panel shows the effects of dopamine infusions and interruptions on prolactin in drug-naive monkeys. The bottom panel shows the effects of dopamine infusions and interruptions on prolactin in the same monkeys after an average of 74 (±19) days of cocaine exposure. These monkeys had self-administered an average of 4.78 (±0.67) mg/kg/day of cocaine for the past 30 days.*

KEY: × = mean; SE = standard error

SOURCE: Mello et al. 1994. Copyright 1994 by the American Society for Pharmacology and Experimental Therapeutics (Bethesda, MD).

Evidence consistent with this notion comes from another monkey that had been exposed to cocaine for a total of 571 days at the time of an acute dopamine probe (figure 2). This monkey had taken the maximum amount of cocaine available, 8 mg/kg/day, for the past month. During a dopamine probe study, prolactin increased from a baseline of 28 ng/mL to a peak of 141 ng/mL after the first dopamine infusion stopped. This postdopamine increase in prolactin was more than five times higher than normoprolactinemic levels. Subsequently, this monkey lost her catheter and became markedly hyperprolactinemic during cocaine abstinence. The bottom panel of figure 2 shows dramatically hyperprolactinemic baseline prolactin levels of 326 ng/mL. A prolactin level above 300 ng/mL exceeds levels measured in human females during suckling (Yen 1991, pp. 357-388). Prolactin was suppressed to 154 ng/mL during dopamine infusion and then increased to 270 and 174 ng/mL after the dopamine infusion stopped (Mello et al. 1994).

The mechanisms underlying cocaine's effects on prolactin regulation and the clinical significance of cocaine-related hyperprolactinemia are poorly understood (Mello and Mendelson 1997). Hyperprolactinemia may contribute to menstrual cycle abnormalities and amenorrhea associated with chronic cocaine exposure. Moreover, from the broader perspective of women's health, prolactin abnormalities may compromise immune function (Reichlin 1993) and increase vulnerability to human immunodeficiency virus (HIV) infection. Clinical studies of chronic cocaine abusers have shown an increase in the size of the pituitary gland, or pituitary volume, which could reflect hyperplasia of the lactotrophs, the cells that release prolactin (Teoh et al. 1993). There is recent evidence that hyperprolactinemia may be associated with increased risk for relapse to cocaine abuse (Teoh et al. 1990; Weiss et al. 1994). These clinical findings suggest that hyperprolactinemia is a biological index of the severity of cocaine dependence that may predict relapse to cocaine abuse.

NEUROENDOCRINE HORMONES AND GENDER DIFFERENCES IN COCAINE'S EFFECTS

Cocaine, as well as other abused drugs, may disrupt the menstrual cycle by altering basal levels of critical neuroendocrine hormones. Moreover, recent evidence suggests possible hormonally mediated differences in cocaine's effects. Recall that cocaine stimulated LH

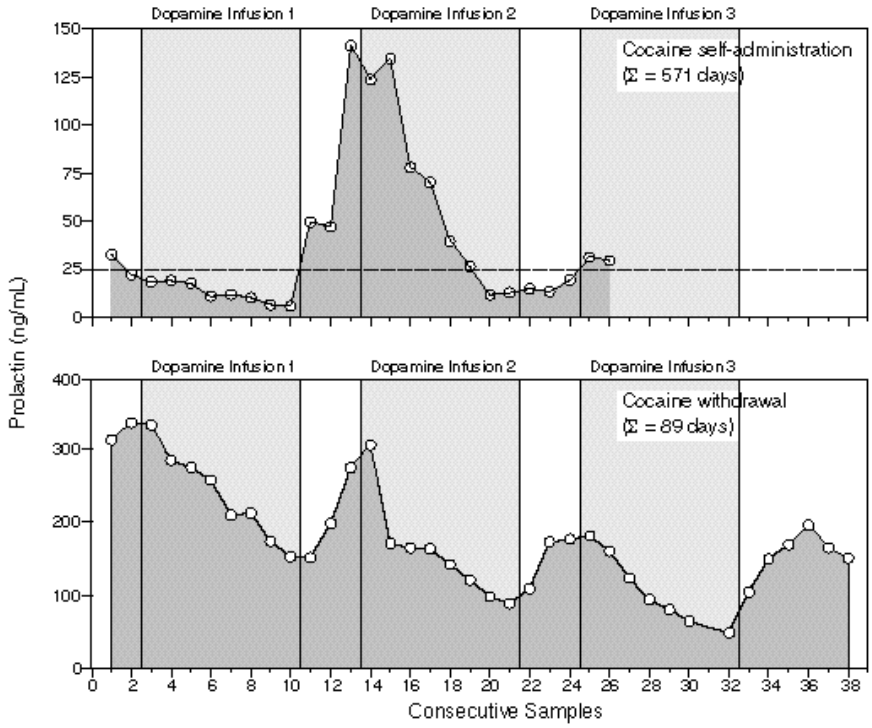

FIGURE 2. *Effects of dopamine infusions (10 µg/kg/min) and interruptions on prolactin (ng/mL) levels in one monkey during cocaine self-administration and after cocaine withdrawal. Dopamine infusion and sample collection procedures were the same as described for figure 1. The top panel shows the effects of dopamine infusions and interruptions on prolactin after a total of 571 days of cocaine exposure. At the time of the study, this monkey had self-administered cocaine for 215 consecutive days and had self-administered an average dose of 8 mg/kg/ day of cocaine for the past 30 days. The blood exfusion catheter clogged at sample 26, and the study was terminated. The bottom panel shows changes in prolactin in response to dopamine 89 days after abrupt withdrawal from a total of 989 days of cocaine self-administration.*

SOURCE: Mello et al. 1994. Copyright 1994 by the American Society for Pharmacology and Experimental Therapeutics (Bethesda, MD).

and ACTH release in normally cycling rhesus females and in human and rhesus males, but cocaine had no effect on these hormones in ovariectomized rhesus females (Mello and Mendelson 1997). Moreover, cocaine did not suppress prolactin in ovariectomized females as it did in intact males and females (Mello et al. 1995*b*). Because very low levels of ovarian steroid hormones are found in ovariectomized females, this suggests that estradiol may be important for the effects of cocaine on anterior pituitary hormones in normal females. It is reasonable to assume that female gonadal steroid hormones may confer health benefits as well as risks (Jaffe 1991, pp. 389-408), and the ways in which these hormones are modulated by cocaine, alcohol, and other abused drugs are an emerging area of inquiry.

In one instance, women were somewhat less vulnerable than men to an adverse consequence of cocaine (Levin et al. 1994). Cocaine abuse has been associated with a number of cerebrovascular disorders, including ischemic stroke and intracerebral and subarachnoid hemorrhage. The effects of cocaine on the brain can be measured with an imaging procedure called single photon emission computed tomography (SPECT). The author's group has reported that cerebral perfusion abnormalities in cocaine abusers are often indistinguishable from those in early AIDS dementia complex (Holman et al. 1992). SPECT analysis subsequently showed that cocaine abusers had more focal cerebral perfusion defects than normal controls (Levin et al. 1994). However, an unanticipated finding was that the nine female cocaine abusers had fewer cerebral perfusion defects in the frontal, temporal, and parietal lobes and in the basal ganglia than the nine men who were matched in terms of age. Moreover, these women reported having used more cocaine for a longer time than the men, an average of 15.3 years as opposed to 8.2 years (Levin et al. 1994).

Levin and coworkers (1994) concluded that these gender differences in cerebral perfusion defects could not be explained by differences in age, race, body mass index, alcohol use, cocaine use, or route of drug administration. Rather, it was postulated that estrogens and progestins may protect women from cocaine-associated cerebral vasospasm. This speculation is consistent with evidence that, before menopause, women have less atherosclerotic disease and less cerebrovascular disease than men. These clinical findings suggest that estrogen may protect women

from mild atherosclerosis. After menopause, estrogen replacement therapy reduces risk for premature cardiac disease and osteoporosis (Jaffe 1991, pp. 389-408).

It is increasingly recognized that changes in hormonal levels across the menstrual cycle may influence the pharmacokinetics and pharmacodynamics of treatment medications (Merkatz et al. 1993). Possible gender differences in drug efficacy or drug toxicity have led to changes in Food and Drug Administration policy and the development of clinical guidelines for inclusion of women in clinical trials (Merkatz et al. 1993). The extent to which gender differences in the biologic effects of drugs may reflect the differences in hormonal milieu between men and women is poorly understood. There is a recent report that peak plasma cocaine levels after intranasal administration were greater during the follicular phase than during the luteal phase of the menstrual cycle, but subjective reports of cocaine's effects were equivalent (Lukas et al. 1996). Men had higher peak plasma cocaine levels and appeared to have greater subjective responses to intranasal cocaine than women (Lukas et al. 1996).

COCAINE-NEUROENDOCRINE INTERACTIONS

One challenge for future research is to clarify the ways in which cocaine interacts with reproductive hormones to cause disorders of reproductive function. It is increasingly apparent that analysis of the effects of cocaine and other drugs on neuroendocrine function requires integrative physiological studies in women and in whole animal models because of the complex interrelationships among all the components of the hypothalamic-pituitary-gonadal and the hypothalamic-pituitary-adrenal axes. However, beyond these issues are many unanswered questions about how the hormonal milieu may modulate the vulnerability of the brain and the immune system to cocaine's toxic effects. Finally, the role of neuroendocrine hormones in cocaine reinforcement is unclear, but cocaine's rapid stimulation of LH and ACTH is consistent with the notion that these hormonal changes may contribute to the reinforcing properties of cocaine and other abused drugs (see Mendelson et al. 1992*c*, pp. 131-155) as well as to adverse drug effects on reproductive function.

In conclusion, either the acute stimulatory effect of cocaine intoxication on gonadotropins, estradiol, or ACTH or the suppressive effects of chronic intoxication may disrupt the functional integration of the endocrine system and lead to infertility disorders and menstrual cycle disruptions. In those instances where acute cocaine intoxication may facilitate premature ovulation and lead to enhanced fertility, disruption of maternal reproductive hormones may compromise pregnancy outcome (see Hutchings 1989). Whatever the relationship of alcohol- and other drug-related disruptions of maternal hormones to fetal growth and development, it is important to recognize that abused drugs have similar effects on the neuroendocrine system. Because the combined effects of several drugs may have more adverse medical consequences than the use of a single drug (Kreek 1991, pp. 91-112), polydrug abuse may increase risk for fetal developmental impairments. Unraveling the relative contributions of poor prenatal care, marginal medical status, and chronic drug abuse to fetal developmental abnormalities presents a formidable challenge (Hutchings 1989; Mayes et al. 1992). Drug avoidance is probably the best recommendation for a successful pregnancy and a healthy baby.

REFERENCES

Cocores, J.A.; Dackis, C.A.; and Gold, M.S. Sexual dysfunction secondary to cocaine abuse in two patients. *J Clin Psychiatry* 47:384-387, 1986.

Crowley, W.F., Jr.; Filicori, M.; Spratt, D.I.; and Santoro, N.F. The physiology of gonadotropin-releasing hormone (GnRH) secretion in men and women. *Rec Prog Horm Res* 41:473-526, 1985.

Dackis, C.A., and Gold, M.S. New concepts in cocaine addiction: The dopamine depletion hypothesis. *Neurosci Biobehav Rev* 9:469-477, 1985.

Dierschke, D.J.; Hutz, R.J.; and Wolf, R.C. Induced follicular atresia in rhesus monkeys: Strength-duration relationships of the estrogen stimulus. *Endocrinology* 117:1397-1403, 1985.

Dierschke, D.J.; Hutz, R.J.; and Wolf, R.C. Atretogenic action of estrogen in rhesus monkeys: Effects of repeated treatment. *Am J Primatol* 12:251-261, 1987.

Filicori, M.; Flamigni, C.; Dellai, P.; Cognigni, G.; Michelacci, L.; Arnone, R.; Sambataro, M.; and Falbo, A. Treatment of anovulation with pulsatile gonadotropin-releasing hormone: Prognostic factors and clinical results in 600 cycles. *J Clin Endocrinol Metab* 79:1215-1220, 1994.

Goodman, A.L., and Hodgen, G.D. The ovarian triad of the primate menstrual cycle. *Rec Prog Horm Res* 39:1-67, 1983.

Holman, B.L.; Garada, B.; Johnson, K.A.; Mendelson, J.H.; Hallgring, E.; Teoh, S.K.; Worth, J.; and Navia, B. A comparison of brain perfusion SPECT in cocaine abuse and AIDS dementia complex. *J Nucl Med* 33:1312-1315, 1992.

Hutchings, D.E. *Prenatal Abuse of Licit and Illicit Drugs.* New York: New York Academy of Sciences, 1989.

Hutchison, J.S.; Kubik, C.J.; Nelson, P.B.; and Zeleznik, A.J. Estrogen induces premature luteal regression in rhesus monkeys during spontaneous menstrual cycles, but not in cycles driven by exogenous gonadotropin-releasing hormone. *Endocrinology* 121:466-474, 1987.

Jaffe, R.B. The menopause and perimenopausal period. In: Yen, S.S.C., and Jaffe, R.B., eds. *Reproductive Endocrinology: Physiology, Pathophysiology, and Clinical Management.* 3d ed. Philadelphia: W.B. Saunders, 1991.

King, T.S.; Canez, M.S.; Gaskill, S.; Javors, M.A.; and Schenken, R.S. Chronic cocaine disruption of estrous cyclicity in the rat: Dose-dependent effects. *J Pharmacol Exp Ther* 264:29-34, 1993.

King, T.S.; Schenken, R.; Kang, I.; Javors, M.; and Riehl, R. Cocaine disrupts estrous cyclicity and alters the reproductive neuroendocrine axis in the rat. *Neuroendocrinology* 51:15-22, 1990.

Knobil, E. On the control of gonadotropin secretion in the rhesus monkey. *Rec Prog Horm Res* 30:1-46, 1974.

Knobil, E. The neuroendocrine control of the menstrual cycle. *Rec Prog Horm Res* 36:53-88, 1980.

Kreek, M.J. Multiple drug abuse patterns: Recent trends and associated medical consequences. In: Mello, N.K., ed. *Advances in Substance Abuse, Behavioral and Biological Research.* Vol. IV. London: Jessica Kingsley, 1991.

LaFerla, J.J.; Anderson, D.L.; and Schalch, D.S. Psychoendocrine response to sexual arousal in human males. *Psychosom Med* 40:166-172, 1978.

Levin, J.M.; Holman, B.L.; Mendelson, J.H.; Teoh, S.K.; Garada, B.; Johnson, K.A.; and Springer, S. Gender differences in cerebral perfusion in cocaine abuse: Technetium-99m-HMPAO SPECT study of drug-abusing women. *J Nucl Med* 35:1902-1909, 1994.

Lukas, S.E.; Sholar, M.B.; Lundahl, L.H.; Lamas, X.; Kouri, E.; Wines, J.D.; Kragie, L.; and Mendelson, J.H. Sex differences in plasma cocaine levels and subjective effects after acute cocaine administration in human volunteers. *Psychopharmacology* 125:346-354, 1996.

Martin, K.A.; Hall, J.E.; Adams, J.M.; and Crowley, W.F., Jr. Comparison of exogenous gonadotropins and pulsatile gonadotropin-releasing hormone for induction of ovulation in hypogonadotropic amenorrhea. *J Clin Endocrinol Metab* 77(1):125-129, 1993.

Mayes, L.C.; Granger, R.H.; Bornstein, M.H.; and Zuckerman, B. The problem of prenatal cocaine exposure: A rush to judgment. (Commentary.) *JAMA* 267(3):406-408, 1992.

McNeely, M.J., and Soules, M.R. Diagnosis of luteal phase deficiency: A critical review. *Fertil Steril* 50:1-15, 1988.

Mello, N.K., and Mendelson, J.H. Cocaine's effects on neuroendocrine systems: Clinical and preclinical studies. Special Issue on Current Issues in Psychostimulant Abuse Research. *Pharmacol Biochem Behav* 57:571-599, 1997.

Mello, N.K.; Mendelson, J.H.; Drieze, J.; and Kelly, M. Acute effects of cocaine on prolactin and gonadotropins in female rhesus monkey during the follicular phase of the menstrual cycle. *J Pharmacol Exp Ther* 254:815-823, 1990*a*.

Mello, N.K.; Mendelson, J.H.; Drieze, J.; and Kelly, M. Cocaine effects on luteinizing hormone-releasing hormone-stimulated anterior pituitary hormones in female rhesus monkey. *J Clin Endocrinol Metab* 71:1434-1441, 1990*b*.

Mello, N.K.; Mendelson, J.H.; Drieze, J.M.; Teoh, S.K.; Kelly, M.L.; and Sholar, J.W. Effects of dopamine on prolactin: Interactions with cocaine self-administration by female rhesus monkeys. *J Pharmacol Exp Ther* 270(3):1110-1120, 1994.

Mello, N.K.; Mendelson, J.H.; Kelly, M.; Diaz-Migoyo, N.; and Sholar, J.W. The effects of chronic cocaine self-administration on the menstrual cycle in rhesus monkeys. *J Pharmacol Exp Ther* 281:70-83, 1997.

Mello, N.K.; Mendelson, J.H.; and Teoh, S.K. Alcohol and neuroendocrine function in women of reproductive age. In: Mendelson, J.H., and Mello, N.K., eds. *Medical Diagnosis and Treatment of Alcoholism.* New York: McGraw-Hill, 1992.

Mello, N.K.; Negus, S.S.; Lukas, S.E.; Mendelson, J.H.; Sholar, J.W.; and Drieze, J. A primate model of polydrug abuse: Cocaine and heroin combinations. *J Pharmacol Exp Ther* 274:1325-1337, 1995*a*.

Mello, N.K.; Sarnyai, Z.; Mendelson, J.H.; Drieze, J.M.; and Kelly, M. Acute effects of cocaine on anterior pituitary hormones in male and female rhesus monkeys. *J Pharmacol Exp Ther* 266:804-811, 1993.

Mello, N.K.; Sarnyai, Z.; Mendelson, J.H.; Drieze, J.M.; and Kelly, M. The acute effects of cocaine on anterior pituitary hormones in ovariectomized rhesus monkeys. *J Pharmacol Exp Ther* 272:1059-1066, 1995*b*.

Mendelson, J.H.; Mello, N.K.; Teoh, S.K.; Ellingboe, J.; and Cochin, J. Cocaine effects on pulsatile secretion of anterior pituitary, gonadal, and adrenal hormones. *J Clin Endocrinol Metab* 69:1256-1260, 1989.

Mendelson, J.H.; Mello, N.K.; Teoh, S.K.; Lukas, S.E.; Phipps, W.; Ellingboe, J.; Palmieri, S.L.; and Schiff, I. Human studies on the biological basis of reinforcement. In: O'Brien, C.P., and Jaffe, J.H., eds. *Addictive States.* New York: Raven Press, 1992*c*.

Mendelson, J.H.; Teoh, S.K.; Mello, N.K.; and Ellingboe, J. Buprenorphine attenuates the effects of cocaine on adrenocorticotropin (ACTH) secretion and mood states in man. *Neuropsychopharmacology* 7:157-162, 1992*b*.

Mendelson, J.H.; Teoh, S.K.; Mello, N.K.; Ellingboe, J.; and Rhoades, E. Acute effects of cocaine on plasma adrenocorticotropic hormone, luteinizing hormone and prolactin levels in cocaine-dependent men. *J Pharmacol Exp Ther* 263(2):505-509, 1992*a*.

Merkatz, R.B.; Temple, R.; Sobel, S.; Feiden, K.; and Kessler, D.A. Women in clinical trials of new drugs. *N Engl J Med* 329:292-296, 1993.

Olster, D.H., and Ferin, N. Corticotropin-releasing hormone inhibits gonadotropin secretion in the ovariectomized rhesus monkey. *J Clin Endocrinol Metab* 65:262-267, 1987.

Reichlin, S. Neuroendocrine-endocrine-immune interactions. *N Engl J Med* 329:1246-1253, 1993.

Rivier, C., and Vale, W. Cocaine stimulates adrenocorticotropin (ACTH) secretion through a corticotropin-releasing factor (CRF)-mediated mechanism. *Brain Res* 422(2):403-406, 1987.

Santoro, N.; Filicori, M.; and Crowley, J. Hypogonadotropic disorders in men and women: Diagnosis and therapy with pulsatile gonadotropin-releasing hormone. *Endocr Rev* 7:11-23, 1986.

Sarnyai, Z.; Mello, N.K.; Mendelson, J.H.; Erös-Sarnyai, M.; and Mercer, G. Effects of cocaine on pulsatile activity of the hypothalamic-pituitary-adrenal axis in male rhesus monkeys: Neuroendocrine and behavioral correlates. *J Pharmacol Exp Ther* 277:225-234, 1996.

Sarnyai, Z.; Mello, N.K.; Mendelson, J.H.; Nguyen, P.; and Erös-Sarnyai, M. Effects of cocaine and corticotropin-releasing factor (CRF) on pulsatile ACTH and cortisol release in ovariectomized rhesus monkeys. *J Clin Endocrinol Metab* 80:2745-2751, 1995.

Smith, C.G., and Smith, M.T. Substance abuse and reproduction. *Semin Reprod Endocrinol* 8:55-64, 1990.

Stouffer, R.L. Corpus luteum function and dysfunction. *Clin Obstet Gynecol* 33:668-689, 1990.

Teoh, S.K.; Lex, B.W.; Mendelson, J.H.; Mello, N.K.; and Cochin, J. Hyperprolactinemia and macrocytosis in women with alcohol and polysubstance dependence. *J Stud Alcohol* 53:176-182, 1992.

Teoh, S.K.; Mello, N.K.; and Mendelson, J.H. Effects of drugs of abuse on reproductive function in women and pregnancy. In: Watson, R., ed. *Addictive Behaviors in Women.* Totowa, NJ: Humana Press, 1994*a*.

Teoh, S.K.; Mendelson, J.H.; Mello, N.K.; Weiss, R.; McElroy, S.; and McAfee, B. Hyperprolactinemia and risk for relapse of cocaine abuse. *Biol Psychiatry* 28:824-828, 1990.

Teoh, S.K.; Mendelson, J.H.; Woods, B.T.; Mello, N.K.; Hallgring, E.; Anfinsen, P.; Douglas, A.; and Mercer, G. Pituitary volume in men with concurrent heroin and cocaine dependence. *J Clin Endocrinol Metab* 76:1529-1532, 1993.

Teoh, S.K.; Sarnyai, Z.; Mendelson, J.H.; Mello, N.K.; Springer, S.A.; Sholar, J.W.; Wapler, M.; and Gelles, H. Cocaine effects on pulsatile secretion of ACTH in men. *J Pharmacol Exp Ther* 270:1134-1144, 1994*b*.

Weiss, R.D.; Hufford, C.; and Mendelson, J.H. Serum prolactin levels and treatment outcome in cocaine dependence. *Biol Psychiatry* 35:573-574, 1994.

Xiao, E., and Ferin, M. The inhibitory action of corticotropin-releasing hormone on gonadotropin secretion in the ovariectomized rhesus monkey is not mediated by adrenocorticotropic hormone. *Biol Reprod* 38:763-767, 1988.

Yen, S.S.C. Studies of the role of dopamine in the control of prolactin and gonadotropin secretion in humans. In: Fuxe, K.; Hokfelt, T.; and Luft, R., eds. *Central Regulation of the Endocrine System*. New York: Plenum Press, 1979.

Yen, S.S.C. Prolactin in human reproduction. In: Yen, S.S.C., and Jaffe, R.B., eds. *Reproductive Endocrinology: Physiology, Pathophysiology, and Clinical Management*. 2d ed. Philadelphia: W.B. Saunders, 1986.

Yen, S.S.C. Prolactin in human reproduction. In: Yen, S.S.C., and Jaffe, R.B., eds. *Reproductive Endocrinology*. 3d ed. Philadelphia: W.B. Saunders, 1991.

Zeleznik, A.J. Premature elevation of systemic estradiol reduces serum levels of FSH and lengthens the follicular phase of the menstrual cycle in rhesus monkeys. *Endocrinology* 109:352-355, 1981.

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