Effects of Cocaine on Luteinizing Hormone in Women during the Follicular and Luteal Phases of the Menstrual Cycle and in Men

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ABSTRACT
Cocaine stimulates luteinizing hormone (LH) release in rhesus monkeys and in men, but its effects on LH in women are unknown. Cocaine (0.2 and 0.4 mg/kg i.v.) was administered to groups of follicular and luteal phase women (N = 22) and to men (N = 12) to examine the influence of gender and menstrual cycle phase on cocaine and LH interactions. All subjects met American Psychiatric Association Diagnostic and Statistical Manual IV criteria for cocaine abuse, and menstrual cycle phase was verified by estradiol and progesterone measures. Baseline LH levels were equivalent between groups. Peak cocaine levels did not differ significantly between men and women and averaged between 87 ± 21 and 124 ± 18 ng/ml after 0.2 mg/kg cocaine and between 227 ± 22 and 287 ± 21 ng/ml after 0.4 mg/kg cocaine. The lower dose of cocaine (0.2 mg/kg) significantly increased LH levels in men (P < 0.001) but not in women at either phase of the menstrual cycle. The higher dose of cocaine (0.4 mg/kg) stimulated significant increases in LH in men (P < 0.001) and in women at both phases of the menstrual cycle (P < 0.004–0.001). Although cocaine’s effects on LH in women were dose-dependent, there were no significant differences as a function of menstrual cycle phase. LH remained significantly elevated longer in men (32 min) than in women (8 and 12 min). This gender difference in cocaine’s potency in stimulating LH was unexpected.

Cocaine abuse and dependence are among the most prevalent drug abuse problems in the United States (National Institute on Drug Abuse, 1999). Chronic cocaine abuse is associated with a number of medical problems, including cardiovascular, cerebral vascular, and infectious disorders, and disruption of reproductive function (Mello, 1998). However, it has been difficult to attribute the reproductive dysfunctions observed clinically to cocaine alone (Mello and Mendelson, 1997). One approach to this question is to systematically examine the effects of acute cocaine administration on basal levels of hormones that are essential for the normal menstrual cycle. Preclinical studies have consistently shown that cocaine stimulates significant increases in luteinizing hormone (LH) levels. In rhesus monkeys, an acute dose of cocaine (0.4 and 0.8 mg/kg i.v.) significantly increased LH in normally cycling early follicular and mid-luteal phase females and in males (Mello et al., 1990a, 1993). LH increased significantly within 10 to 20 min after i.v. cocaine administration and remained above baseline levels for 40 to 50 min. Moreover, cocaine enhanced luteinizing hormone-releasing-hormone (LHRH)-stimulated increases in LH in follicular phase rhesus females (Mello et al., 1990b). Deconvolutional analysis showed that the half-life of LH was not significantly altered after cocaine administration and the LH increase appears to reflect a burst of hypothalamic LHRH release (Mello and Mendelson, 1997). These findings were surprising because cocaine acts centrally as an indirect dopamine agonist by blocking dopamine uptake by the dopamine trans-

ABBREVIATIONS: LH, luteinizing hormone; LHRH, luteinizing hormone-releasing hormone; ACTH, adrenocorticotropin hormone; hCG, human chorionic gonadotropin; RIA, radioimmunoassay.
porter (Kuhar et al., 1991; Woolverton and Johnson, 1992). Moreover, exogenous dopamine agonist administration suppresses LH in both men and women (Yen, 1979). In contrast, dopamine administration, at a dose that significantly suppressed prolactin secretion, did not alter LH levels in follicular phase female rhesus monkeys (Mello et al., 1997b). Similarly, in ovariectomized rhesus monkeys, infusion of dopamine did not decrease basal or LHRH-stimulated LH (Spies et al., 1980; Pavaasuthipaisit et al., 1981). These discrepant findings may represent a species difference in the effects of exogenous dopamine on LH.

Intravenous cocaine administration stimulated LH in cocaine- and opioid-dependent men (Mendelson et al., 1992) and intranasal cocaine stimulated LH in cocaine-naive men (Heesch et al., 1996). The effects of cocaine on LH in women are unknown, and the potential significance of LH stimulation for the menstrual cycle dysfunction associated with chronic cocaine exposure is unclear. A binge pattern of cocaine use, with doses taken as often as every 15 min, has been reported by cocaine abusers (Gawin and Kleber, 1985; Ward et al., 1997). If repeated episodes of cocaine abuse were associated with increased levels of LH in women during the follicular phase, this could contribute to the menstrual cycle abnormalities observed. Specifically, alterations in LH pulsatile release patterns and/or abnormal LH levels could disrupt gonadotropin and ovarian steroid feedback systems. This in turn could delay or impede normal follicle maturation and result in anovulatory menstrual cycles, luteal phase dysfunction, and amenorrhea (Hotchkiss and Knobil, 1994). Higher rates of pulsatile LH release were observed in rhesus females during chronic cocaine self-administration (Mello et al., 2000a), a finding consistent with cocaine's acute stimulation of LH release.

One goal of the present study was to examine the acute effects of cocaine on LH in women who were occasional cocaine abusers and to determine whether these effects were cocaine-dose related. Women were studied during the follicular and the luteal phases of the menstrual cycle to evaluate the possible contribution of the hormonal milieu to cocaine's effects. Preclinical studies suggest that ovarian steroid hormones are essential for cocaine to stimulate anterior pituitary hormones (Mello et al., 1995; Sarnyai et al., 1995). Cocaine had no effect on LH or ACTH in ovariectomized monkeys, even though synthetic LHRH and corticotropin-releasing factor stimulated release of LH and ACTH, respectively (Mello et al., 1995; Sarnyai et al., 1995).

A second goal was to compare the effects of cocaine on LH in men and women studied under identical conditions. Gender differences in cocaine’s cerebrovascular effects in humans (Levin et al., 1994; Kaufman et al., 2001) and cardiovascular and behavioral effects in rodents have been reported (for review, see Mello and Mendelson, 1997). However, we are unaware of any previous clinical reports of the possible contribution of gender to cocaine’s effects on LH.

### Materials and Methods

#### Subjects

Twenty-two adult females and 12 males provided informed consent for participation in this study. The study was approved by the Institutional Review Board of the McLean Hospital. Only men and women who fulfilled American Psychiatric Association Diagnostic and Statistical Manual (DSM-IV) criteria for a diagnosis of cocaine abuse (305.6) were selected. Volunteers with any lifetime DSM-IV Axis 1 disorder other than cocaine abuse and nicotine dependence were excluded. Women who were using oral contraceptive medication were excluded. Pregnancy tests (hCG C6 subunit blood tests) were completed on the morning before cocaine administration to ensure that no women had become pregnant since prestudy screening. All men and women selected for study were in good physical health and had normal medical and laboratory screening examinations. All subjects were drug-free on the study day as assessed by a qualitative urine drug screen described below (Triage Biodiagnost, San Diego, CA).

Women were studied at two phases of the menstrual cycle. The follicular phase was defined as 5 to 9 days following the onset of menses. The luteal phase of the menstrual cycle was defined as 18 to 22 days after the onset of menses. Menstrual cycle phase was estimated from each woman’s self-reports. Progesterone and estradiol levels were obtained on the day of the study to verify menstrual cycle phase. Two doses of intravenous cocaine (0.2 and 0.4 mg/kg) were studied at each phase of the menstrual cycle. The characteristics of men and women at each menstrual cycle phase in each of the two cocaine dose groups are summarized in Table 1. These subjects did not differ significantly with respect to age and body mass index. As indicated in Table 1, each dose of cocaine was studied in a group of six men. The 0.2-mg/kg dose of cocaine was studied in five women during the follicular phase of the menstrual cycle, and in five women during the luteal phase of the menstrual cycle. The 0.4-mg/kg dose of cocaine was studied in six women during the follicular phase of the menstrual cycle, and in six women during the luteal phase of the menstrual cycle.

#### Screening Procedures

**Pregnancy Tests.** Serum pregnancy tests were completed on the morning before cocaine or placebo administration to ensure that no women had become pregnant since the prescreening. The Stanbio QuPID Plus Test (Stanbio Laboratory, Inc., San Antonio, TX) is a qualitative immunoassay for the detection of human chorionic go-

#### Table 1

<table>
<thead>
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<th>Subject characteristics</th>
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<tr>
<td>Number of Subjects</td>
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<tr>
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</tr>
<tr>
<td>Follicular phase women</td>
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<tr>
<td></td>
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<tr>
<td>Luteal phase women</td>
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<td></td>
</tr>
<tr>
<td>Men</td>
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BMI, body mass index.
nadotropin (hCG) in serum. The test uses a combination of monoclonal and polyclonal antibody reagents to selectively detect elevated levels of hCG. The Stanbio QuPID Plus Test for Pregnancy detects hCG concentrations of 20 mIU/ml and greater in serum.

Urine Drug Screens. It is important for subject safety, as well as to avoid confounding of the dependent variables, to ensure that subjects have not used any drugs before administration of intravenous cocaine. On the morning of each study day, urines were collected and analyzed with a Triage screen. The Triage Panel for Drugs of Abuse (Triage Biosite Diagnostics) is a rapid multiple immunosay system for the qualitative detection of the major metabolites of these drugs of abuse in urine at the following cut-off concentrations (recommended screening cut-off concentrations by the Substance Abuse and Mental Health Services Administration): phenylcyclidine, 25 ng/ml; benzodiazepines, 300 ng/ml; cocaine, 300 ng/ml; amphet-

5.3%, respectively. All plasma samples for hormone and cocaine analysis were collected after intravenous administration and reach peak levels within 4 to 5 min. These doses of cocaine have proved to be safe and induce significant changes in mood states and physiological responses in our previous clinical studies (Kauffman et al., 1998; Mendelson et al., 1998; Sholar et al., 1998).

Cocaine Administration Procedures. These studies were carried out on a clinical research ward. Cocaine was administered intravenously over an interval of 1 min. Subjects were studied in a semisupine position, and heart rate, blood pressure, and EKGs were continuously monitored with a Hewlett-Packard EKG monitor (model 78 352A) for 10 min before intravenous cocaine administration and for 2 h following intravenous injection. A physician certified in cardio pulmonary resuscitation was present during each study, and a cardiac defibrillator and appropriate emergency treatment medications were located in the study room.

Sample Collection Procedures. Baseline samples for analysis of LH, estradiol, and progesterone in women and testosterone and LH in men were collected 4 min before i.v. cocaine injection. Samples for LH and plasma cocaine analysis were collected at 2, 4, 8, 12, 16, 20, 30, 40, 60, 80, and 120 min following completion of the cocaine injection. This sampling frequency was based on previous observations that cocaine levels in plasma increase rapidly within 2 min after intravenous administration and reach peak levels within 4 to 5 min (Evans et al., 1996; Mendelson et al., 1999b; Sholar et al., 1998). All plasma samples for hormone and cocaine analysis were collected from an intravenous catheter in the arm opposite the arm in which cocaine was injected intravenously. Blood samples for hormone analysis were collected in heparinized tubes. Blood samples for cocaine analysis were transferred to heparinized Vacutainer tubes containing sodium fluoride and acetic acid (to prevent the hydrolysis of cocaine). All samples were iced immediately, centrifuged, and plasma was removed and frozen at −70°C for cocaine analysis.

Cocaine Hydrochloride Preparation. Cocaine hydrochloride was acquired from the National Institute on Drug Abuse in powder form and was dissolved in sterile water for intravenous injection by the McLean Hospital pharmacy. Sterility was ensured by passing the solution through a 0.22-μm Millipore filter and subjecting it to a Limulus Amebocyte Lysate test for detection of gram negative bacterial endotoxins. The test kit is manufactured by Whittaker Bioproducts (Walkersville, MD).

LH Assay. Serum LH was determined in duplicate by a direct, double antibody RIA method, using kits purchased from Incstar Corporation (Stillwater, MN). The assay sensitivity was 9.2 ng/ml and the intra- and interassay coefficients of variation were 2.9 and 5.3%, respectively.

Estrogen Assay. Serum estradiol was determined in duplicate by a direct, double antibody RIA method, using kits purchased from Diagnostic Product Corporation (Los Angeles, CA). The assay sensitivity was 1.1 pg/ml and the intra- and interassay coefficients of variation were 2.0 and 7.8%, respectively.

Progesterone Assay. Serum progesterone was determined in duplicate by Coat-A-Count RIA method, using kits purchased from Diagnostic Products Corporation. The assay sensitivity was 0.06 ng/ml and the intra- and interassay coefficients of variation were 4.0 and 5.1%, respectively.

Testosterone Assay. Serum total testosterone was determined in duplicate by Coat-A-Count RIA method, using kits purchased from Diagnostic Products Corporation. The assay sensitivity was 2.3 ng/dl and the intra- and interassay coefficients of variation were 3.0 and 5.9%, respectively.

Data Analysis. Progesterone and estradiol levels during the follicular and luteal phases of the menstrual cycle were analyzed with a two-way ANOVA for menstrual cycle phase and cocaine dose. Plasma cocaine and LH values for subjects were analyzed using a 3 (group) × 12 (time) repeated measures ANOVA. If significant main effects were detected, one-way ANOVAs were performed to identify the times at which groups differed significantly. The statistical significance of temporal covariance between LH and plasma cocaine levels was determined by regression analyses.

Estimates of the primary kinetic parameters (i.e., peak plasma concentrations (Cmax) and time to peak plasma concentration (Tmax) of LH were obtained directly from a nonlinear regression-estimation software program based on the Manual of Pharmacologic Calculations with Computer Programs using PHARM/PCS, version 4.2 (MicroComputer Specialist MCS, Philadelphia, PA). LH concentrations were fitted to a single dose, one-compartment model with bolus input, first order output, and elimination. Plasma concentrations were weighted by the reciprocal of the predicted concentrations. These pharmacokinetic parameters were analyzed with an ANOVA to determine whether there were any differences between males and females. ANOVAs also were used to compare pharmacokinetic parameters at each dose between males and follicular phase females.

Results

Ovarian Steroid Hormone Levels during the Follicular and Luteal Phases of the Menstrual Cycle. Analysis of ovarian steroid hormone levels confirmed that women were in the mid-follicular phase or the mid-luteal phase of the menstrual cycle on the study day. Average baseline estradiol and progesterone levels during each phase of the menstrual cycle for each cocaine dose group are summarized in Table 2. Average estradiol and progesterone levels during the luteal phase were significantly higher than during the follicular phase (P < 0.0001) in both the 0.2 and the 0.4 mg/kg cocaine dose groups. Estradiol and progesterone levels were equivalent in the two cocaine dose groups during the follicular phase and during the luteal phase of the menstrual cycle.

Baseline Testosterone Levels in Men. Baseline testosterone levels did not differ significantly before cocaine administration. In the 0.2 mg/kg cocaine dose group, baseline testosterone levels averaged $537 \pm 89$ ng/dl. In the 0.4 mg/kg cocaine dose group, baseline testosterone levels averaged $424 \pm 35$ ng/dl.


Baseline LH Levels in Men and Women. In women studied during the follicular phase, precocaine baseline LH levels averaged 57 ± 9 ng/ml in the 0.2 mg/kg cocaine dose group and 69 ± 3 ng/ml in the 0.4 mg/kg cocaine dose group. In women studied during the luteal phase, precocaine baseline LH levels averaged 50 ± 11 ng/ml in the 0.2 mg/kg cocaine dose group and 67 ± 14 ng/ml in the 0.4 mg/kg cocaine dose group. In men, precocaine baseline LH levels averaged 55 ± 6 and 49 ± 5 ng/ml in the low- and high-dose cocaine groups. There were no statistically significant differences in baseline LH levels in follicular phase women or in luteal phase women before cocaine administration. Male LH levels were also equivalent to LH levels in women before low- and high-dose cocaine administration.

Cocaine Plasma Levels in Women. Plasma cocaine levels in women after intravenous administration of 0.2 and 0.4 mg/kg cocaine are shown in Fig. 1. Peak plasma cocaine levels were cocaine dose-dependent in women studied during the follicular and during the luteal phase of the menstrual cycle. Peak plasma cocaine levels after 0.4 mg/kg i.v. cocaine were significantly higher than after 0.2 mg/kg i.v. in women at both phases of the menstrual cycle (P < 0.003). Cocaine reached peak plasma levels within 4 min after i.v. administration of 0.2 mg/kg i.v. and averaged 124 ± 18 ng/ml during the follicular phase and 87 ± 21 during the luteal phase. Although peak plasma cocaine levels were lower during the luteal phase, these differences did not achieve statistical significance (P = 0.18). Peak plasma cocaine levels after 0.4 mg/kg cocaine averaged 287 ± 21 and 264 ± 37 ng/ml during the follicular and the luteal phase of the menstrual cycle, respectively, and these levels were not significantly different.

Effects of Cocaine on Luteinizing Hormone Levels in Women. Figure 2 shows that cocaine's effects on LH were dose-dependent in women during both phases of the menstrual cycle. LH levels did not change significantly from baseline after administration of 0.2 mg/kg cocaine in women studied at the follicular phase or at the luteal phase. After administration of 0.4 mg/kg cocaine, LH began to increase within 4 min and reached peak levels of 85 ± 10 and 84 ± 15 ng/ml within 16 min during the follicular and luteal phases, respectively. LH remained significantly above baseline for 4 min (16–20 min postcocaine) in follicular phase women and for 8 min (12–20 min postcocaine) in luteal phase women. LH increased significantly above baseline within 16 min in follicular phase women when plasma cocaine levels averaged 221 ± 19 ng/ml. In women studied during the luteal phase, LH increased significantly within 12 min after 0.4 mg/kg cocaine administration when plasma cocaine levels averaged 239 ± 35 ng/ml.

Cocaine Plasma Levels and Effects on Luteinizing Hormone Levels in Men. Plasma cocaine levels in men after intravenous administration of 0.2 and 0.4 mg/kg cocaine are shown in Fig. 3. top. Cocaine plasma levels were maximal within 8 min after cocaine administration and remained elevated for 60 to 80 min. In men, the average peak cocaine levels reached after administration of 0.4 mg/kg cocaine (227 ± 22 ng/ml) were significantly higher than after administration of 0.2 mg/kg cocaine (95 ± 15 ng/ml) (P < 0.002).

<table>
<thead>
<tr>
<th>Number of Subjects</th>
<th>Cocaine Dose</th>
<th>Follicular Phase (Cycle Days 5–9)</th>
<th>Luteal Phase (Cycle Days 18–22)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Estradiol (pg/ml)</td>
<td>Progesterone (ng/ml)</td>
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<tr>
<td></td>
<td></td>
<td>pg/ml ± S.E.</td>
<td>ng/ml ± S.E.</td>
</tr>
<tr>
<td>5</td>
<td>0.2 mg/kg/i.v.</td>
<td>29.6 ± 8.5</td>
<td>0.51 ± 0.08</td>
</tr>
<tr>
<td>6</td>
<td>0.4 mg/kg/i.v.</td>
<td>39.4 ± 9.4</td>
<td>0.62 ± 0.12</td>
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**TABLE 2**

Ovarian steroid hormone levels in women during the follicular and luteal phases of the menstrual cycle.
Both doses of cocaine significantly increased LH levels in men ($P < 0.01$) (Fig. 3, bottom). After administration of 0.2 mg/kg cocaine, LH levels increased significantly within 8 min and reached peak levels of $77 \pm 9$ ng/ml within 20 min when plasma cocaine levels averaged $86 \pm 16$ ng/ml. LH remained significantly higher than baseline for 32 min (between 8 and 40 min). After administration of 0.4 mg/kg cocaine, LH increased significantly within 8 min and reached peak levels of $72 \pm 3$ ng/ml within 20 min when plasma cocaine levels averaged $169 \pm 17$ ng/ml. LH remained significantly higher than baseline for 32 min (between 8 and 40 min). Thus, higher cocaine levels did not result in significantly greater increases in LH in men.

**Gender Comparisons of the Effects of Cocaine on LH.** Figure 4 shows peak plasma cocaine levels and peak LH levels for men and follicular and luteal phase women after administration of 0.2 and 0.4 mg/kg cocaine. Although cocaine stimulated significant increases in LH in both men and women, cocaine was more potent in altering LH in men than in women. A low dose of cocaine (0.2 mg/kg i.v.) did not increase LH in women at either phase of the menstrual cycle but significantly increased LH in men. Peak cocaine levels after administration of 0.2 mg/kg cocaine were higher in women than in men, but these differences were not statistically significant.

This gender difference was also evident in a regression analysis of the correlation between LH and plasma cocaine levels. In men, increases in LH levels were significantly correlated with plasma cocaine levels after administration of 0.2 mg/kg cocaine ($P = 0.007$; $r = 0.79$; $r^2 = 0.63$) and after
administration of 0.4 mg/kg cocaine \((P = 0.005; r = 0.70; r^2 = 0.49)\). In women, there were no significant correlations between LH levels and plasma cocaine levels after administration of 0.2 mg/kg cocaine in either the follicular phase group \((P = 0.1095; r = 0.44; r^2 = 0.20)\) or the luteal phase group \((P = 0.3902; r = 0.25; r^2 = 0.06)\). In contrast, after administration of 0.4 mg/kg cocaine, LH and plasma cocaine levels were significantly correlated in both the follicular phase women \((P = 0.01; r = 0.64; r^2 = 0.41)\) and in the luteal phase women \((P = 0.0004; r = 0.81; r^2 = 0.66)\).

The pharmacological profile of LH after 0.4 mg/kg i.v. cocaine was not significantly different in men and follicular and luteal phase women. The \(T_{\text{max}}\) (min) of LH was 18 \(\pm\) 0.9 min in men and 16 \(\pm\) 1.5 min and 16 \(\pm\) 1.0 min in follicular and luteal phase women, respectively. The \(C_{\text{max}}\) (ng/ml) was 73 \(\pm\) 2.7 ng/ml for men and 88 \(\pm\) 9.8 and 85 \(\pm\) 14.6 ng/ml for follicular and luteal phase women, respectively.

**Discussion**

**Stimulation of LH by Cocaine.** LH increased significantly after administration of 0.4 mg/kg i.v. cocaine in both men and women. This is the first study of the effects of cocaine on LH in women and in male cocaine abusers who were not dependent on cocaine or other drugs. These findings extend the generality of previous reports that cocaine stimulates LH release in male and female rhesus monkeys (Mello et al., 1990a,b, 1993). Cocaine (30 mg i.v. or 4.28 mg/70 kg) also increased LH levels in cocaine- and opioid-dependent men (Mendelson et al., 1992) and intranasal cocaine (2 mg/kg) increased LH levels in cocaine-naive men (Heesch et al., 1996). In our previous studies of cocaine- and opioid-dependent men, significant increases in LH were detected within 5 min and reached peak levels within 15 min (Mendelson et al., 1992). A similar time course of LH increases was observed in male cocaine abusers in the present study. Significant increases in LH were measured within 8 min after both doses of i.v. cocaine, and peak levels of LH occurred after 20 min.

The time course of changes in LH in women after 0.4 mg/kg cocaine was comparable to that observed in female rhesus monkeys after 0.8 mg/kg i.v. cocaine administration, although differences in sample collection procedures complicate comparisons (Mello et al., 1990a,b, 1993). In rhesus females, integrated samples were collected at 10-min intervals and significant LH increases were detected within 10 to 20 min. In women, bolus samples were collected at 4-min intervals for 20 min, and significant LH increases were detected within 12 to 16 min. LH remained significantly above baseline levels for 40 to 50 min in mid-follicular and mid-luteal phase rhesus females (Mello et al., 1990a, 1993) whereas in women, the duration of significant changes in LH was relatively brief (4 or 8 min). In follicular phase rhesus monkeys, administration of synthetic LHRH (100 \(\mu\)g i.v.) significantly increased LH within 10 min after placebo-cocaine, 0.4 and 0.8 mg/kg i.v. cocaine, and LH remained significantly above baseline for the duration of the sampling period (100 min) (Mello et al., 1990b).

**Gender-Related Differences in the Effects of Cocaine.** Two gender differences were observed in the effects of cocaine on LH. Cocaine was more potent in stimulating LH in men than in women, and LH remained significantly elevated longer after cocaine administration in men than in women. It was surprising to find that a low dose of cocaine stimulated LH in men, but did not stimulate LH in women at either phase of the menstrual cycle. This gender difference did not appear to be accounted for by differences in baseline LH levels or peak plasma cocaine levels. Baseline LH levels were equivalent in all subjects, and there were no significant gender differences in plasma cocaine levels after 0.2 mg/kg cocaine. Moreover, peak plasma cocaine levels were slightly higher in follicular phase females than in males. Men and women were matched for body mass index, age, and reported history of cocaine use. We have previously reported that there were no significant gender differences in the pharmacokinetic profiles of intravenous cocaine users (Mendelson et al., 1999b) so it is unlikely that dispositional factors accounted for the greater potency of low doses of cocaine in men. Similarities in reported cocaine use patterns between men and women argue against the possibility that women were more tolerant to cocaine’s effects. Cocaine stimulated significantly higher levels of another anterior pituitary hormone, ACTH, in occasional cocaine users than in cocaine-dependent men, and this appeared to reflect cocaine tolerance (Mendelson et al., 1998). However, the women in the present study were not cocaine-dependent.

The observed differences in duration of significant LH
stimulation in men (32 min) and women (8 or 12 min) after 0.4 mg/kg cocaine were also unexpected. One factor that may have contributed to these findings is a gender difference in cocaine’s interactions with estradiol and testosterone. The possible importance of gonadal steroid hormones in modulating cocaine’s effects on LH has been suggested by the finding that cocaine did not increase LH levels in ovariec-tomized females (Mello et al., 1995). This lack of effect could not be attributed to impaired pituitary function because synthetic LHRH stimulated a significant increase in LH in these ovariec-tomized females (Mello et al., 1995). In the present study, estradiol and testosterone levels were not measured following cocaine administration, so the possible contribution of these gonadal steroid hormones to the observed gender differences cannot be determined from these data.

Intranasal cocaine did not alter testosterone in men (Heesch et al., 1996), and the effects of cocaine on estradiol in women are unknown. However, we have recently discovered that cocaine (0.8 mg/kg i.v.) stimulates estradiol in mid-follicular rhesus females (Mello et al., 2000b). If cocaine also stimulates estradiol in women, estradiol could have decreased the duration of the LH response to cocaine through its negative feedback effects (Hotchkiss and Knobil, 1994; Yen, 1999). The effects of cocaine on testosterone in human males have not been determined, but in rhesus monkeys testosterone increased 80 min after cocaine administration (Mello et al., 1993). Because this testosterone increase was detected 50 min after the cocaine-induced LH peak, this was interpreted as reflecting LH stimulation of testosterone (Mello et al., 1993). In normal men, episodic increases in LH release are usually followed by increases in testosterone within 10 to 20 min (Veldhuis et al., 1987). No comparable gender differences in the effects of cocaine on LH were observed in rhesus monkey males and females. A low dose of cocaine (0.4 mg/kg) did not increase LH significantly, whereas a higher dose (0.8 mg/kg) was followed by significant LH increases in males and in mid-follicular and mid-luteal females (Mello et al., 1990a, 1993).

LH release can also be stimulated by administration of synthetic LHRH and by opioid antagonists such as naloxone and naltrexone. Opioid antagonists are thought to stimulate LH by antagonism of endogenous opioid inhibition of hypothalamic LHRRH, whereas synthetic LHRH mimics hypothalamic LHRH and stimulates pituitary gonadotropes to release LH (Yen, 1999). In rhesus monkeys, the LH response to these provocative tests also reveals some gender differences. For example, male rhesus monkeys were more sensitive to stimulation by synthetic LHRH than rhesus females (Mendelson et al., 1999a). In that study, LHRH (15 or 30 μg/kg i.v.) stimulated a rapid and significant increase in LH in males that was enhanced by cocaine (0.8 mg/kg i.v.). The LH increase was sustained for a total of 30 min after LHRH alone and an additional 160 min after the addition of cocaine. In follicular phase females, LH did not increase significantly until 40 min after LHRH administration and remained significantly above baseline for only 10 min. This gender difference in the LH response to LHRH was similar to that observed in the present study. Similarly, the opioid antagonist naltrexone (0.25, 0.50, and 1.0 mg/kg i.v.) significantly increased LH within 20 to 40 min and testosterone within 60 min in rhesus males but did not stimulate LH release in early (days 1–3) or late (days 10–12) follicular phase rhesus females (Mello et al., 1989). These findings were consistent with an extensive clinical literature showing that opioid antagonists are most effective in stimulating gonadotropin release during the luteal phase of the menstrual cycle (Yen, 1999). Thus, a pharmacological challenge acting at the level of the pituitary (LHRH) or the hypothalamus (naltrexone) was ineffective in stimulating LH release during the follicular phase, whereas cocaine stimulated LH release at both phases of the menstrual cycle in rhesus females (Mello et al., 1990a, 1993) and in women in the present study. These data suggest that cocaine may stimulate LH through a different mechanism than synthetic LHRH or naltrexone.

**Implications of Cocaine’s Stimulation of LH.** The adverse effects of repeated stimulation of LH by cocaine on reproductive function can be inferred from the disruptions of the menstrual cycle associated with chronic cocaine self-administration (Mello et al., 1997a; Mello, 1998). However, the mechanisms that account for cocaine’s stimulation of LH are unknown. Cocaine’s stimulation of LH in rhesus monkeys appears to reflect a burst of hypothalamic LHRH and not a change in LH disposition according to a deconvolution analysis (Mello and Mendelson, 1997). As noted earlier, cocaine’s actions as an indirect dopamine agonist may not be directly relevant to its effects on LH. Exogenous dopamine administration did not increase or decrease LH in rhesus monkeys (Spies et al., 1980; Pava-suthipaisit et al., 1981; Mello et al., 1997a) but decreased LH in humans (Yen, 1979), and the role of endogenous dopamine in LH regulation remains controversial (Yen, 1999). LH release is controlled by many neuro-modulatory systems in brain (Hotchkiss and Knobil, 1994; Yen, 1999) and the relative contribution of cocaine’s effects on estradiol, dopamine, norepinephrine, and endogenous opioid systems remains to be determined (Mello and Mendelson, 1997).

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**References**


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