Available online at www.sciencedirect.com
SCIENCE DIRECT
Pharmacology, Biochemistry and Behavior 83 (2006) 56 – 66
PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR
www.elsevier.com/locate/pharmbiochembeh

Pharmacokinetics of repeated doses of intravenous cocaine across the menstrual cycle in rhesus monkeys

Suzette M. Evans *, Richard W. Foltin

Division on Substance Abuse, New York State Psychiatric Institute and Department of Psychiatry, College of Physicians and Surgeons of Columbia University, 1051 Riverside Drive, Unit 66, New York, NY 10032, U.S.A.

Received 13 September 2005; received in revised form 3 December 2005; accepted 7 December 2005
Available online 19 January 2006

Abstract

Numerous studies in rodents suggest that there are sex differences in response to cocaine that are related to fluctuations in the ovarian hormones of females. Given that female rhesus monkeys have menstrual cycles that are remarkably similar to those of humans, they provide an ideal laboratory animal model for assessing the effects of cocaine across the menstrual cycle. The present study assessed the effects of 4 injections of intravenous (i.v.) cocaine (0.00, 0.25 or 0.50 mg/kg), spaced 15 min apart, in 4 female rhesus monkeys. Each monkey was tested with each dose during 4 phases of the menstrual cycle: menses, midfollicular, periovulatory and midluteal. Estradiol and progesterone levels were measured each session before cocaine administration to verify phase of the menstrual cycle. Cocaine and cocaine metabolite levels were measured 5 min after each cocaine dose and 5, 15, 30, 45, 60 and 120 min after the last cocaine dose. Similarly, levels of luteinizing hormone (LH) and prolactin levels were measured before, 5, 15, 30, 45, 60 and 120 min after the last cocaine dose. Cocaine and metabolite levels increased as a function of dose, but there were minimal differences across the menstrual cycle following repeated injections of cocaine. With a few exceptions, LH levels decreased as a function of time within the session, with no differences as a function of cocaine dose. Cocaine produced transient increases in LH levels during the luteal phase, with maximal levels occurring after the second cocaine injection. Lastly, cocaine substantially decreased prolactin levels across all menstrual cycle phases. Taken together, these data indicate that any behavioral differences observed either across the menstrual cycle or between males and females, are probably not related to alterations in the pharmacokinetics of cocaine across the menstrual cycle.

Keywords: Cocaine; Pharmacokinetics; Cocaine metabolites; Rhesus monkey; Menstrual cycle; Luteinizing hormone; Prolactin

1. Introduction

Cocaine abuse continues to be a serious public heath problem and appears to be increasing in women. For instance, 10 years ago, women made up approximately 33% of the cocaine-abusing population (US DHHS, 1993), while in 2001, out of 1.2 million new users, 41% were women (SAMHSA, 2003). Moreover, numerous preclinical studies have shown that females are more sensitive than males to many of the behavioral effects of stimulants and the prevailing evidence is that gonadal hormones, particularly estrogen, contribute to these sex differences (see reviews by Lynch et al., 2002; Mello and Mendelson, 2002; Carroll et al., 2004; Festa and Quiñones-Jenab, 2004).

Given the increasing evidence that there are sex differences in response to cocaine, and that these differences might be related to fluctuations in gonadal hormone levels, studies have attempted to determine whether there are pharmacokinetic differences between males and females and whether hormonal fluctuations in females alter the pharmacokinetics of cocaine. Most studies in rodents have reported no differences in cocaine plasma levels between males and females (Van Haaren et al., 1997; Bowman et al., 1999; Festa et al., 2004; but see Van Luijtelaar et al., 1996). Further, while some studies have shown sex differences in cocaine metabolite levels, the results have been inconsistent (Bowman et al., 1999; Festa et al., 2004; Van Haaren et al., 1997; Chin et al., 2001) and the estrous cycle mostly ignored. One study in intact female rats found that benzoylecgonine (BZE) plasma levels, but not cocaine plasma levels, varied across the estrous cycle (Quiñones-Jenab et al., 1999). Another critical factor is that in the normal female rat, estradiol and progesterone fluctuate over a 4-day estrous cycle,

* Corresponding author. Tel.: +1 212 543 5895; fax: +1 212 543 6018.
E-mail address: se18@columbia.edu (S.M. Evans).

0091-3057/$ - see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.pbb.2005.12.007

whereas the human female hormones typically fluctuate over a 28-day menstrual cycle. Therefore, findings in rodents may not necessarily reflect what occurs in humans.

In contrast to rodents, the female rhesus monkey provides an ideal animal model for assessing the effects of cocaine across the menstrual cycle because they have a menstrual cycle almost identical in hormonal fluctuation and length to that of humans. Three studies assessed the pharmacokinetic effects of i.v. cocaine in male and female rhesus monkeys (Misra et al., 1977; Saady et al., 1994, 1995), but they did not directly compare males and females and did not control for menstrual cycle phase. Mello, Mendelson and colleagues have conducted a series of elegant studies investigating the effects of cocaine on gonadal and pituitary hormones in rhesus monkeys. While no differences in cocaine plasma levels were reported between males and females (Mello et al., 1993), cocaine plasma levels were only measured at a single time point and direct comparisons were not made between follicular (Mello et al., 1990) and luteal phase females (Mello et al., 1993). The only pharmacokinetic difference between males and midfollicular females following an acute dose of i.v. cocaine was that females had lower cocaine plasma levels 10 min after the injection, although there were no differences in peak cocaine plasma levels, time to peak or half-life (Mendelson et al., 1999a). In a subsequent study (Mello et al., 2000), midfollicular phase females were directly compared to midluteal phase females following an acute dose of cocaine and no differences in peak cocaine plasma levels or time to peak were observed. In a previous study conducted in our laboratory (Evans and Foltin, 2004) we reported no differences in cocaine plasma levels across the menstrual cycle in rhesus monkeys, but found that the cocaine metabolite levels [BZE and ecgonine methyl ester (EME)] showed the greatest increases in the luteal phase compared to the other phases, particularly following the highest dose of acute cocaine. To our knowledge only one study has administered repeated doses of i.v. cocaine to male and female monkeys (Mello et al., 2002) and failed to find any sex differences in peak cocaine plasma levels, time to peak cocaine plasma levels or half-life at either dose of cocaine tested. In that study, normally cycling females were tested in the midfollicular phase, but not all of the females tested were normally cycling.

Most studies in humans have not reported differences in cocaine plasma levels between men and women (Kosten et al., 1996; Sofuoglu et al., 1999; Mendelson et al., 1999b; Evans and Foltin, in press) or across the menstrual cycle (Sofuoglu et al., 1999; Mendelson et al., 1999b; Evans et al., 2002; Evans and Foltin, in press). In one study (Evans et al., 1999), women had higher cocaine plasma levels than men after smoking repeated doses of 50 mg cocaine, but this was most likely due to the fact that the women weighed less than the men. While another study (Lukas et al., 1996) found that men had higher cocaine plasma levels than women, and women had higher cocaine plasma levels during the follicular phase compared to the luteal phase following a single dose of intranasal cocaine, other studies in humans have not supported these findings. Only one study has reported on cocaine metabolite levels in humans (Evans and Foltin, in press), and the only pharmacokinetic difference was that women had significantly higher BZE plasma levels following repeated doses of 25 mg smoked cocaine than men. Based on the inconsistent data in rodents and the limited data available in both monkeys and humans, there appear to be minimal differences in the pharmacokinetics of cocaine either between males and females or as a function of fluctuating gonadal hormones in females. However, the studies that have been conducted thus far have several limitations, making it difficult to definitively conclude that there are no differences in cocaine pharmacokinetics across the menstrual cycle.

In a previous study (Evans and Foltin, 2004) we assessed the pharmacokinetic effects of single doses of cocaine across the menstrual cycle in rhesus monkeys and found few differences in the pharmacokinetic profile of cocaine across the menstrual cycle, although the cocaine metabolites did vary across the menstrual cycle, with both being increased in the luteal phase. The present study was designed to extend our previous research conducted in female monkeys by testing repeated administration of i.v. cocaine at four distinct phases of the menstrual cycle using a within-subject design. Further, cocaine and cocaine metabolite levels, specifically BZE and EME, were also measured. Most previous studies have reported that acute cocaine administration increases luteinizing hormone (LH) levels and decreases prolactin levels in humans and non-human primates (see review by Mello and Mendelson, 2002, but see Evans and Foltin, 2004). However, only a limited number of studies in monkeys and humans have assessed the effects of cocaine on LH levels across the menstrual cycle and none have assessed the effects of repeated cocaine administration on LH levels. Therefore, in the present study LH and prolactin levels were measured before and after repeated cocaine administration.

2. Method

2.1. Animals

Four adult female rhesus monkeys (*Macaca mulatta*), weighing between 6.0 and 8.3 kg, lived under the housing conditions described below for the 8 months of this experiment. Each monkey received a daily chow ration designed to maintain a stable body weight (4–10 High protein monkey diet #5047 chow, 15 g/chow, 3.37 Kcal/g; LabDiets®, PMI Feeds, Inc., St. Louis, MO), chewable vitamins and a piece of fruit daily. Body weights, determined weekly, remained stable throughout the study. Each monkey had access to two identically sized chambers (61.5 cm wide × 66.5 cm deep × 88 88 cm high; Hazleton Systems, Inc, Aberdeen, MD) connected by 40 × 40 cm openings. The sides of the chambers were slotted for a solid panel that prevented movement from one chamber to the next. These partitions were inserted when it was necessary to confine a monkey to one chamber (e.g., cage cleaning, TB testing). Water was freely available from spouts located on the back wall of both chambers. The room lights were illuminated from 0700 to 1900. The menstrual cycle of each monkey was monitored daily by recording the onset and

duration of menstrual bleeding. All aspects of animal maintenance and experimental procedures complied with the U.S. National Institutes of Health Guide for Care and Use of Laboratory Animals, and were approved by the New York State Psychiatric Institute Animal Care and Use Committee. The investigators and a veterinarian routinely monitored the health of the monkeys.

Because acute placement of female rhesus monkeys in primate chairs during the follicular phase increases cortisol and adrenocorticotropin hormone release and decreases pulsatile LH release (Norman et al., 1994), female monkeys were acclimated to daily chair restraint and received their daily fruit and vitamin ration while in a chair at the same time each day. Using two technicians, a pole and collar system was used to guide the monkeys out of the chamber and into the chair. Once monkeys were seated in the chair, their feet were placed into open-toed shoes mounted on the foot bars in order to secure the feet and legs for repeated blood sampling. All monkeys had been acclimated to this procedure before the study started. To reduce associating chair restraint with experimental sessions, throughout the study monkeys were chair restrained 2 additional days each week when they received treats, but did not receive cocaine or have blood drawn.

2.2. Cocaine administration and sample collection

The pharmacokinetic effects of repeated doses of cocaine were tested across four phases of the menstrual cycle. Each session lasted approximately 3 h and began at 9:30 AM. A 21-gauge butterfly cannula (Vacutainer® Brand blood collection set; Becton Dickinson, Franklin Lakes, NJ) was inserted into a saphenous vein in one leg and secured with tape for repeated blood collection. After obtaining a baseline blood sample for estradiol, progesterone, LH and prolactin plasma levels through a butterfly cannula in one leg, monkeys received four doses of cocaine (either 0.00, 0.25 or 0.50 mg/kg), spaced 15 min apart. All doses were administered in a 0.5 ml volume over 10 s through a butterfly cannula in the alternate leg (plasma for determination of cocaine levels cannot be taken from the same vein used to administer cocaine), followed by a 1.0 ml saline flush. Cocaine and metabolite levels were determined 5 min after each cocaine injection and 5, 15, 30, 45, 60 and 120 min after the last cocaine injection. LH and prolactin levels were determined before and 5, 15, 30, 45, 60 and 120 min after the last cocaine injection. Between each blood sample, saline was periodically flushed into the i.v. line to maintain patency and immediately before each sample, 0.5 ml of blood was withdrawn from the i.v. line and discarded. Over the course of an entire session, a total of 25 ml of blood was drawn.

Each female monkey was tested at 2 to 3 cycle phases each month to obtain a complete dose–response function at each cycle phase, i.e., 2 cocaine doses and placebo were tested at each of 4 menstrual cycle phases for a total of 12 test sessions per female monkey. The menstrual and follicular phases of the menstrual cycle were defined based on the onset of menstrual bleeding, with menstrual sessions on days 1–5 and follicular sessions on days 6–10 after the onset of menses. For the periovulatory and luteal sessions, sessions were scheduled based on the typical length of each individual monkey's menstrual cycle. Periovulatory sessions were scheduled approximately on days 12–15 days after the onset of menses, whereas luteal sessions were scheduled approximately on days 19–23 after the onset of menses. These days were later in monkeys who had menstrual cycles >28 days. While ovulation occurs shortly after a surge in LH and this is the primary indicator of when ovulation has occurred, determining LH levels on a daily basis was not possible. Moreover, the analytical laboratory could only assay LH levels in monkeys in batches every 3 months, thus it was not possible to use a verified LH surge to schedule periovulatory and luteal sessions. However, baseline estradiol and progesterone levels were used to define menstrual cycle phase and a menstrual cycle was classified as ovulatory if progesterone levels were $\geq$1.5 ng/ml during the periovulatory or luteal phases. In the event that sessions were aborted due to problematic data (e.g., difficulty maintaining venous access, problematic cocaine plasma levels, anovulatory menstrual cycle), these sessions were excluded from the data analyses and repeated during another menstrual cycle.

2.3. Cocaine

Cocaine hydrochloride (provided by The National Institute on Drug Abuse) was dissolved into sterile saline for injection U.S.P., in a concentration of 5 or 10 mg/ml, to allow similar injection volumes across the doses tested. Injections were administered into one of the saphenous veins of the leg in a 0.5 ml volume over 10 s, followed by 1.0 ml of sterile saline.

2.4. Plasma cocaine and metabolite analyses

Venous blood samples (approximately 1 ml) for cocaine were drawn from a butterfly cannula inserted into the saphenous leg vein and placed into tubes containing potassium oxalate and sodium fluoride. Samples were immediately mixed and were centrifuged within 30 min of collection, yielding approximately 0.5 ml of plasma, and stored frozen until the time of analysis. Cocaine, BZE and EME plasma levels were determined by the Nathan Kline Institute for Psychiatric Research (Orangeburg, NY). Cocaine, BZE and EME were analyzed by capillary gas chromatograph-mass spectrometry using deuterated internal standards, positive chemical ionization and simultaneous ion monitoring. The assay sensitivity was 1 ng/ml and intra- and inter-assay coefficients of variation were less than 6% for all compounds.

2.5. Plasma hormone analyses

Each experimental session, venous blood samples (2 ml at baseline, 1 ml at other time points) for estradiol and progesterone (only drawn at baseline before the cocaine injection), LH and prolactin were drawn from a butterfly cannula and placed into tubes containing SST® gel and clot

activator. Samples were centrifuged within 30 min of collection, yielding approximately 0.5 ml of plasma, and stored frozen until the time of analysis. Estradiol, progesterone, LH, and prolactin plasma levels were determined by Dr. Michel Ferin at the College of Physicians and Surgeons of Columbia University, Department of Obstetrics and Gynecology (New York, NY). Estradiol, progesterone and prolactin were measured by a commercial solid-phase, chemiluminescent enzyme immunoassay (*Immulite*, Diagnostic Products Co, DPC, Los Angeles, CA) validated for monkeys. Using this assay, progesterone levels $\geq$1.5 ng/ml during the periovulatory or luteal phase indicated that the monkey had a normal ovulatory cycle. The sensitivity of the estradiol assay was 20 pg/ml and the intra- and inter-assay coefficients of variation were 4.3 and 10.5, respectively. The sensitivity of the progesterone assay was 0.2 ng/ml and the intra- and inter-assay coefficients of variation were 6.6 and 7.9, respectively. The sensitivity of the prolactin assay was 0.5 ng/ml and the intra- and inter-assay coefficients of variation were 6.2 and 8.5, respectively. LH plasma levels were measured using a 5-day in-house radioimmunoassay (Xiao et al., 1994) in duplicate. Recombinant cynomolgus monkey LH was used as a standard and for iodination, and rabbit antiserum directed against recombinant cynomolgus monkey LH was used as the primary antibody. The sensitivity of the LH assay was 0.06 ng/ml and the intra- and inter-assay coefficients of variation were 7.9 and 13.1, respectively. Reagents were provided by the NIH.

2.6. Data analyses

Baseline (before drug administration) levels of estradiol, progesterone, LH and prolactin were analyzed separately using one-factor repeated-measures analyses of variance (ANOVA) with Phase (Menses, Follicular, Periovulatory, Luteal) as the factor. To assess the time course of cocaine, BZE and EME levels, these measures were analyzed separately using a three factor repeated-measures ANOVA with Phase as the first factor, Dose (0.25, 0.50 mg/kg) as the second factor and Time (9 time points per measure) as the third factor. For LH and prolactin, since there were menstrual cycle differences in baseline levels, these data were analyzed as percent change from baseline using a three factor repeated-measures ANOVA with Phase as the first factor, Dose (including 0 mg/kg cocaine) as the second factor and Time as the third factor. For the other pharmacokinetic measures described above, each one was analyzed separately using a two factor repeated-measures ANOVA with Phase as the first factor and Dose as the second factor. For all analyses, results were considered statistically significant if $p<0.05$, using Huynh–Feldt corrections where appropriate.

3. Results

3.1. Baseline hormone levels

The four female monkeys had normal ovulatory menstrual cycles ranging in length from 28 to 31 days (mean of 29.7 days). Table 1 shows the mean plasma levels of estradiol, progesterone, LH and prolactin (measured at baseline each session) at each phase of the menstrual cycle. Plasma levels of estradiol were significantly higher in the follicular phase compared to the other three phases (menstrual, $p<0.0001$; periovulatory, $p<0.0001$; luteal, $p<0.0001$). Plasma levels of progesterone showed a Phase effect [$F(3,3)=9.63$, $p<0.008$], with progesterone levels significantly higher in the periovulatory and luteal phases compared to the menstrual and follicular phases (periovulatory vs. menstrual, $p<0.004$; periovulatory vs. follicular, $p<0.003$; luteal vs. menstrual, $p<0.02$; luteal vs. follicular, $p<0.02$). Baseline plasma levels of LH also showed a Phase effect [$F(3,3)=10.05$, $p<0.03$], with LH levels significantly higher in the periovulatory phase compared to the other three phases (menstrual, $p<0.003$; follicular, $p<0.002$; luteal, $p<0.003$). Baseline plasma levels of prolactin in the luteal phase were significantly lower than the periovulatory phase ($p<0.05$) and tended to be lower than the menstrual phase ($p<0.06$).

3.2. Behavioral observations

Although no structured behavioral ratings were conducted each session, cocaine produced mydriasis, increased agitation, restlessness, and motor activity and decreased appetite as evidenced by the refusal of food treats (e.g., raisins, M&Ms®). These effects were not observed when saline was injected. After active doses of cocaine, particularly 0.50 mg/kg, the onset of behavioral effects was observed within 5 min and lasted up to 30 min after the last injection.

3.3. Cocaine and cocaine metabolite levels

Fig. 1 shows cocaine plasma levels as a function of cocaine dose, time within session, and menstrual cycle phase. Cocaine

Table 1
Baseline hormone plasma levels as a function of menstrual cycle phase

Phase	Estradiol (pg/ml)	Progesterone (ng/ml)	LH (ng/ml)	Prolactin (ng/ml)
Menses	62.67 (±17.81)	0.28 (±0.04)	1.03 (±0.21)	28.24 (±19.32)
Follicular	101.33 (±63.21)[a,c,d]	0.22 (±0.02)	0.93 (±0.09)	25.93 (±13.23)
Periovulatory	55.92 (±15.06)	2.20 (±1.24)[a,b]	1.92 (±0.48)[a,b,d]	28.73 (±11.69)
Luteal	59.58 (±16.83)	1.68 (±0.66)[a,b]	1.06 (±0.06)	15.52 (±7.70)[c]

Values represent the mean and ±1 SD.
For each hormone, comparisons were conducted across the 4 phases; [a] indicates a significant difference from menses; [b] indicates a significant difference from follicular; [c] indicates a significant difference from periovulatory; [d] indicates a significant difference from luteal.

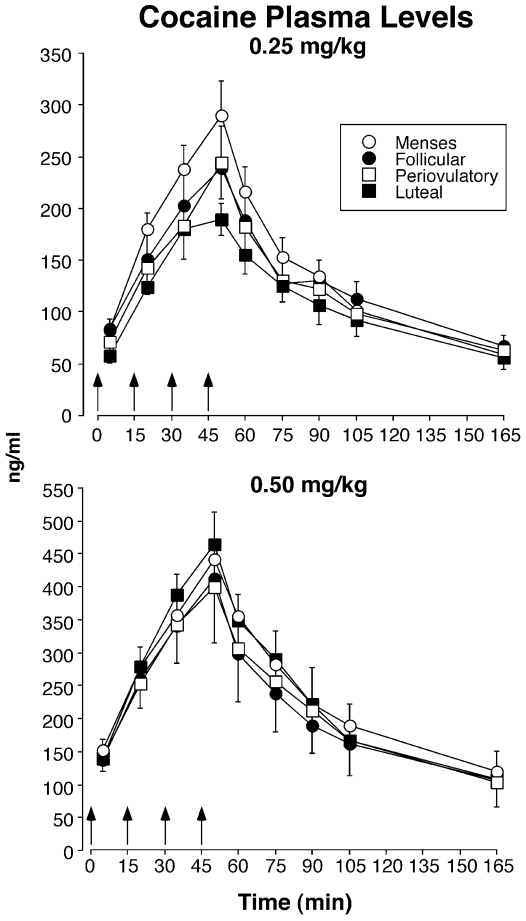

Fig. 1. Cocaine plasma levels following repeated i.v. injections of cocaine as a function of dose, time and menstrual cycle phase. Each panel represents a different cocaine dose and is plotted on a different scale to increase the ability to see differences based on menstrual cycle phase. Each data point represents the mean (±1 S.E.M) of 4 rhesus monkeys. Some error bars have been omitted for clarity and the absence of any bars indicates 1 S.E.M. fell within the area of the data symbol. The arrows indicate the time of each cocaine injection.

plasma levels increased as a function of Dose [$F(1,3)=35.47$, $p<0.01$], changed as a function of Time during the session [$F(8,24)=178.05$, $p<0.0001$], and showed a Dose × Time interaction [$F(8,72)=16.00$, $p<0.0001$]. Although cocaine plasma levels were higher during menses compared to the luteal phase after the fourth dose of 0.25 mg/kg cocaine, this effect was only observed at a single time point (50 min). Overall, there were no differences in cocaine plasma levels as a function of menstrual cycle phase. Since plasma cocaine levels were not measured earlier than 5 min after each injection, by default, all peak cocaine levels were observed 5 min after the final injection. For 0.25 mg/kg cocaine, mean cocaine levels were 74.25 ng/ml 5 min after the first injection and increased to 240.75 ng/ml 5 min after the fourth injection. Correspondingly, for 0.50 mg/kg cocaine, mean cocaine levels were 142.00 ng/ml 5 min after the first injection and increased to 428.50 ng/ml 5 min after the fourth injection.

Fig. 2 shows BZE plasma levels as a function of cocaine dose, time within session, and menstrual cycle phase. BZE plasma levels increased as a function of Dose [$F(1,3)=31.52$, $p<0.02$], changed as a function of Time [$F(8,24)=41.46$, $p<0.03$] and there was a Dose × Time interaction [$F(8,72)=14.77$, $p<0.0001$]. However, there were no differences in BZE plasma levels as a function of menstrual cycle phase. BZE levels increased throughout the session, with maximal levels of 63.25 and 102.75 ng/ml at 165 min following repeated doses of 0.25 and 0.50 mg/kg cocaine, respectively.

Fig. 3 shows EME plasma levels as a function of cocaine dose, time within session, and menstrual cycle phase. EME plasma levels increased as a function of Dose [$F(1,3)=77.90$, $p<0.004$], changed as a function of Time [$F(8,24)=95.09$, $p<0.0001$] and showed a Dose × Time interaction [$F(8,72)=10.61$, $p<0.0002$]. However, there were no differences in EME plasma levels as a function of menstrual cycle phase. Similar to BZE levels, EME levels increased throughout the session, with maximal levels of 28.00 and 49.50 ng/ml at 165 min following repeated doses of 0.25 and 0.50 mg/kg cocaine, respectively.

3.4. LH and prolactin plasma levels

Fig. 4 shows LH plasma levels, as percent change from baseline, as a function of cocaine dose, time within session, and menstrual cycle phase. LH plasma levels changed as a function of Time [$F(8,24)=7.500$, $p<0.04$] and showed a

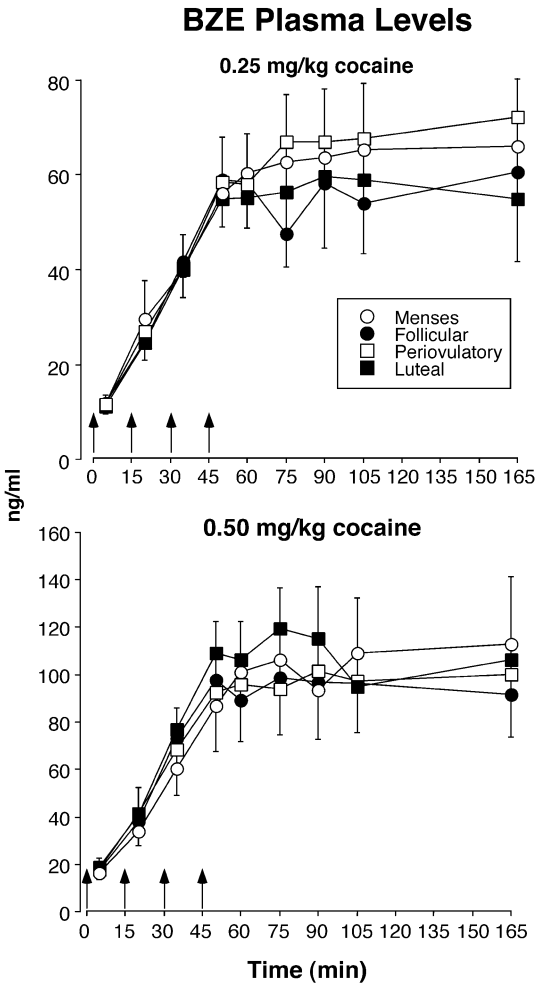

Fig. 2. Benzoylecgonine (BZE) plasma levels following repeated i.v. injections of cocaine as a function of dose, time and menstrual cycle phase. See Fig. 1 for details.

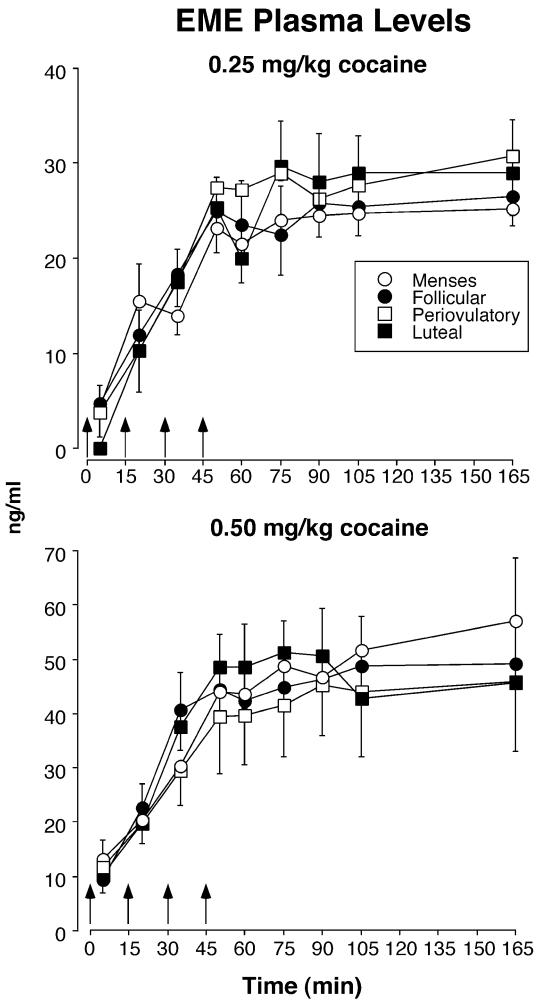

Fig. 3. Ecgonine methyl ester (EME) plasma levels following repeated i.v. injections of cocaine as a function of dose, time and menstrual cycle phase. See Fig. 1 for details.

Phase × Time interaction [$F(24,72)=3.77$, $p<0.01$]. When placebo cocaine (0.00 mg/kg cocaine) was administered, LH plasma levels remained stable or decreased, with the greatest decreases in LH plasma levels occurring during the periovulatory phase. Overall, there was no main effect of cocaine dose on LH levels. However, cocaine did produce transient increases (approximately 30% increase relative to baseline) in LH during the luteal phase after the second injection of either 0.25 or 0.50 mg/kg cocaine, which was followed by a decrease to below baseline levels. Similar to placebo cocaine, LH levels remained stable across the session or decreased, with the greatest decreases observed during the periovulatory phase, following repeated doses of cocaine.

Fig. 5 shows prolactin plasma levels as a function of cocaine dose, time within session, and menstrual cycle phase. Prolactin plasma levels decreased as a function of Dose [$F(2,6)=117.17$, $p<0.001$], decreased as a function of Time during the session [$F(8,24)=76.81$, $p<0.0001$], and showed a Dose × Time interaction [$F(16,72)=14.19$, $p<0.0001$]. Overall, there were no differences in prolactin plasma levels as a function of menstrual cycle phase. However, the top panel of Fig. 5 shows that when placebo cocaine (0.00 mg/kg cocaine) was administered, prolactin plasma levels decreased as a function of time during the session across all menstrual cycle phases, with the greatest decreases observed during the periovulatory phase. Maximal reductions in prolactin levels, collapsed across the menstrual cycle phases, were approximately 50% of baseline at the end of the session (28% reduction in the follicular phase to

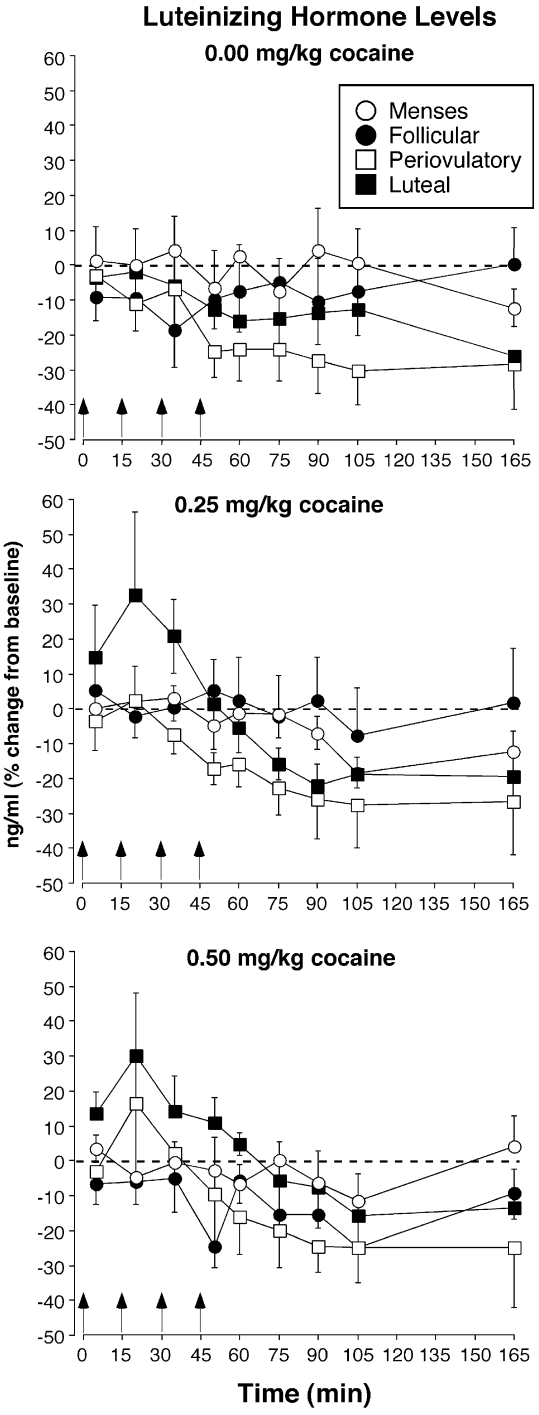

Fig. 4. Luteinizing hormone (LH) plasma levels, expressed as percent change from baseline, following repeated i.v. injections of cocaine as a function of dose, time and menstrual cycle phase. Each data point represents the mean (±1 S.E.M) of 4 rhesus monkeys. Some error bars have been omitted for clarity and the absence of any bars indicates 1 S.E.M. fell within the area of the data symbol. The arrows indicate the time of each cocaine injection.

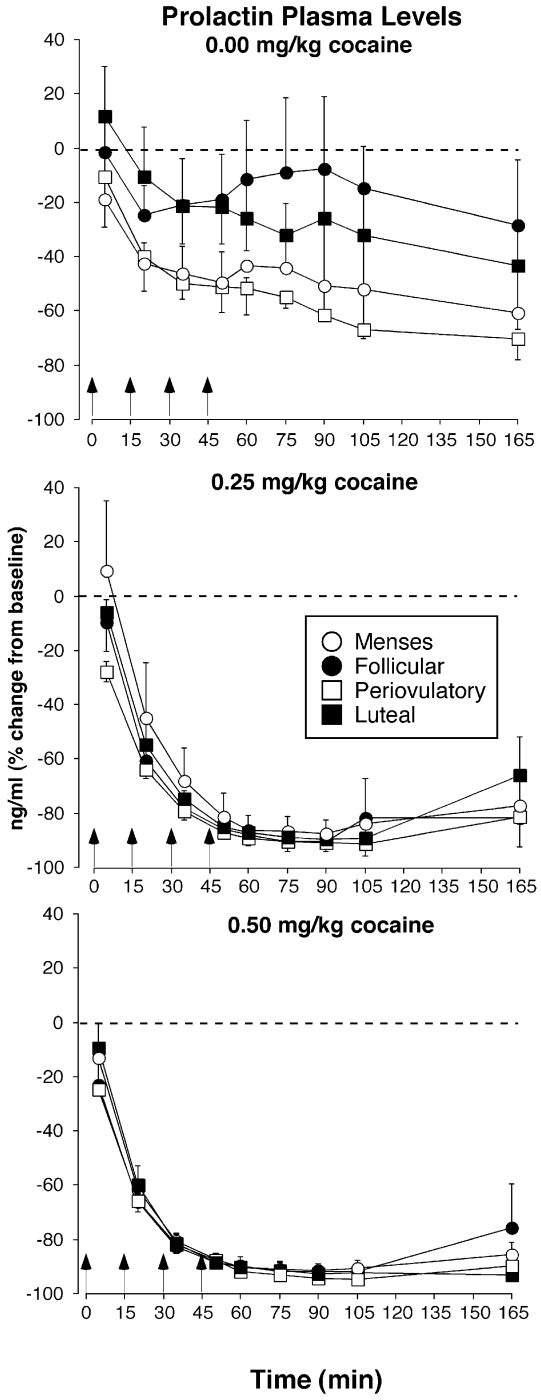

Fig. 5. Prolactin plasma levels, expressed as percent change from baseline, following repeated i.v. injections of cocaine as a function of dose, time and menstrual cycle phase. See Fig. 4 for details.

70% reduction in the periovulatory phase). Cocaine administration produced rapid and dramatic decreases in prolactin levels. After the first injection of cocaine, prolactin levels decreased by approximately 8% to 17% of baseline levels following 0.25 and 0.50 mg/kg cocaine, respectively. However, after the second injection, prolactin levels decreased by 55% and 63% relative to baseline following 0.25 and 0.50 mg/kg cocaine, respectively. After all 4 cocaine injections, prolactin levels were reduced by approximately 90% relative to baseline for both cocaine doses and prolactin levels were still attenuated at the end of the session.

4. Discussion

4.1. Pharmacokinetics of cocaine and cocaine metabolites

To our knowledge, this is the first study to comprehensively assess the pharmacokinetics of repeated cocaine doses across the menstrual cycle in rhesus monkeys. Overall, there was no evidence that the pharmacokinetics of cocaine or cocaine metabolites (BZE and EME), varied consistently across the menstrual cycle. Cocaine plasma levels increased following each injection and as a function of cocaine dose. When collapsed across the 4 menstrual cycle phases, cocaine plasma levels 5 min after the first injection of 0.25 and 0.50 mg/kg were 74 and 142 ng/ml, respectively. These levels are comparable to what we observed in a previous study using the same doses and time point (Evans and Foltin, 2004). Previous studies in rhesus monkeys have typically observed peak cocaine plasma levels within 2–9 min after acute dosing (Evans and Foltin, 2004; Mello et al., 2000, 2002; Mendelson et al., 1999a; Zhou et al., 2001). Similarly, in humans, the time to achieve peak cocaine plasma levels after i.v. cocaine administration has ranged from 4 to 8 min (e.g., Cone, 1995; Evans et al., 1996; Foltin and Fischman, 1991; Javaid et al., 1978; Mendelson et al., 1999b).

In the present study, cocaine plasma levels increased with each successive injection; cocaine plasma levels 5 min after the fourth cocaine injection of 0.25 and 0.50 mg/kg were 241 and 429 ng/ml, respectively. Similarly, both BZE and EME plasma levels increased as a function of cocaine dose. In fact, even though blood samples were collected up to 120 min after the last cocaine injection, cocaine metabolite levels had either peaked or were still rising. In a previous study conducted in 2 pregnant monkeys (Zhou et al., 2001), BZE levels peaked approximately 1.7 h after an acute dose of 1.00 mg/kg i.v. cocaine. Studies in human males have also shown that BZE levels continue to rise for up to 75 min after the last cocaine dose (Isenschmid et al., 1992) and can remain elevated for up to 6 h after a single i.v. dose of cocaine (Cone, 1995).

No differences in cocaine or metabolite plasma levels were noted across the menstrual cycle in this study. These findings contrast to some extent with our previous study (Evans and Foltin, 2004). In that study, female rhesus monkeys had slightly lower cocaine plasma levels in the periovulatory phase following an acute dose of 0.25 mg/kg i.v. cocaine, whereas the greatest increases in BZE and EME plasma levels were in the luteal phase compared to the other phases, particularly following an acute dose of 1.00 mg/kg cocaine. The present study was conducted in the same laboratory as our previous study using virtually identical procedures (e.g., animals, technicians, assays for cocaine and hormone levels). The inability to show changes across the menstrual cycle in cocaine metabolite levels in the present study is most likely due to administering repeated doses of cocaine, rather than acute

doses, and not collecting samples for several hours after the last dose.

Several studies in rodents have assessed changes in cocaine pharmacokinetics following either acute or repeated cocaine administration. Most studies have reported no differences in cocaine plasma levels between males and females (Van Haaren et al., 1997; Bowman et al., 1999; Festa et al., 2004). Although differences in cocaine metabolites have been reported, the results have been inconsistent. For instance, some studies have shown higher BZE levels in males (Bowman et al., 1999; Festa et al., 2004), others have shown higher BZE levels in females (Chin et al., 2001) and others have shown no differences in BZE levels between males and females (Van Haaren et al., 1997; Chin et al., 2002). While the cocaine metabolite EME isn't measured as often as BZE, two studies (Bowman et al., 1999; Festa et al., 2004) found that female rats had higher levels than male rats. Unfortunately, most studies have not measured both cocaine and cocaine metabolite levels. In addition, the cocaine-dosing regimen has varied across studies, and differences in cocaine pharmacokinetics depend on whether cocaine is administered acutely or chronically (Chin et al., 2001; Van Haaren et al., 1997; Quiñones-Jenab et al., 2000). Further, few studies have controlled for the estrous cycle. One study in female rats (Quiñones-Jenab et al., 1999) reported no differences in cocaine levels, but lower BZE levels during estrus and proestrus than during metestrus/diestrus following three injections of cocaine spaced one hour apart. In a subsequent study (Quiñones-Jenab et al., 2000), ovariectomized female rats treated with estrogen and progesterone had lower BZE plasma levels than females treated with either estrogen alone or progesterone alone following repeated cocaine administration. Unfortunately, the route of cocaine administration and the dosing regimen used in these rodent studies, coupled with the differences between the monkey menstrual cycle and the rat estrous cycle, make direct comparisons difficult.

Several studies have assessed the pharmacokinetics of cocaine in rhesus monkeys. For instance, in a study by Mello et al. (2002), male and female monkeys were administered 4 injections of i.v. cocaine (0.4 or 0.8 mg/kg), spaced 30 min apart. While that study found no sex differences in cocaine plasma levels, the role of the menstrual cycle on cocaine pharmacokinetics could not be determined because cycling females were only tested during the follicular phase, and non-cycling females were included. Consistent with the present study, Mello et al. (2000) also failed to show differences in cocaine pharmacokinetics as a function of menstrual cycle phase in rhesus monkeys. Further, no differences in cocaine pharmacokinetics have been observed in ovariectomized monkeys chronically treated with ovarian steroid hormone replacement compared to untreated ovariectomized monkeys (Mello et al., 2004a).

Similarly in humans, most studies have reported little evidence of differences in cocaine plasma levels between men and women (Sofuoglu et al., 1999; Mendelson et al., 1999b; Evans and Foltin, in press; but see Lukas et al., 1996 and Evans et al., 1999) or as a function of menstrual cycle phase following either acute doses of i.v. cocaine (Mendelson et al., 1999b), or repeated doses of smoked cocaine (Sofuoglu et al., 1999; Evans et al., 2002; Evans and Foltin, in press). To our knowledge, only one study in humans assessed cocaine metabolite levels as a function of menstrual cycle phase in normally cycling women (Evans and Foltin, in press) and there was no evidence that either BZE or EME plasma levels varied between the follicular and luteal phases. Those data were based on a single blood sample taken 4 min after administration of the sixth dose of smoked cocaine, so it is unclear if differences would have been detected if samples had been obtained further out into the session. That study did show that BZE plasma levels were significantly higher in females than in males following repeated doses of smoked cocaine, but this was only observed after 25 mg cocaine. One other study administered a single dose of intranasal cocaine to females taking triphasic oral contraceptives and there was no evidence that cocaine or cocaine metabolite levels varied at different "phases" of the cycle (Kouri et al., 2002). Based on the data available in both monkeys and humans, there appear to be minimal differences in the pharmacokinetics of cocaine across the menstrual cycle or between males and females.

4.2. Effects of cocaine on LH

In the present study, cocaine did not produce consistent increases in LH levels. In fact, transient increases in LH plasma levels were observed only when cocaine was administered during the luteal phase, with no differences between the two cocaine doses. Otherwise, LH plasma levels either remained stable or decreased during the session. Further, the greatest reductions over time in LH plasma levels were during the periovulatory phase. These findings vary slightly from our previous study (Evans and Foltin, 2004). In that study an acute dose of 1.00 mg/kg i.v. cocaine produced increases in LH plasma levels during both the menstrual and follicular phases, but decreases during the periovulatory and luteal phases. Similar to the present study, that study also showed that the greatest decreases in LH plasma levels relative to baseline occurred during the periovulatory phase. The discrepancy between our previous study and the current study is most likely due to acute versus repeated cocaine administration.

While previous studies in laboratory animals and humans have typically shown that LH plasma levels increase following cocaine administration (see Mello and Mendelson, 2002 for a comprehensive review), the cocaine-induced increases in LH plasma levels can vary depending upon the dose or the menstrual cycle phase. For instance, Mello et al. (1990) showed that acute doses of i.v. cocaine (0.4 and 0.8 mg/kg) increased LH plasma levels in female monkeys who were only tested during the early follicular phase. In a subsequent study (Mello et al., 1993), only the higher dose of cocaine (0.8 mg/kg) increased LH levels in male monkeys and in female monkeys tested during the midluteal phase and these increases in LH plasma levels remained above baseline for 40–50 min. In the present study, LH levels increased only after the first two injections of cocaine during the luteal phase, then actually

began to decline following the last two cocaine injections. One possible, but unlikely, explanation for the lack of consistent increases in LH levels observed in the present study is that blood samples were drawn in monkeys while restrained in a chair. While chair restraint alone has been shown to decrease LH levels, particularly during the follicular phase (Norman et al., 1994), the studies conducted by Mello et al. (1990) and Mello et al. (1993) showing cocaine-induced increases in LH have also used a chair-restraint system, but in anesthetized monkeys. Another possible explanation is that since LH is released in a pulsatile fashion (Hotchkiss and Knobil, 1994), the integrated plasma collection procedure used in previous studies (Mello et al., 1990, 1993) may better capture the pulsatile release compared to bolus samples collected in the present study. Lastly, another factor that may have contributed to observing only transient increases in LH levels is that the LH assay procedure used in the present study differed from other laboratories.

In rodents, dose-related changes in LH have also been observed following acute doses of cocaine, with low doses increasing LH and high doses decreasing LH (Dada and Horacek, 1991; King et al., 2001; Steger et al., 1981). In humans, acute doses of cocaine have been shown to increase LH levels in cocaine-dependent men (Mendelson et al., 1992), cocaine-naïve men (Heesch et al., 1996) and in women (Mendeslon et al., 2001). However, this effect appears to be more pronounced in men, with men showing increased levels of LH following acute doses of i.v. cocaine (0.2 and 0.4 mg/kg), whereas in women, only the higher dose of cocaine increased LH levels regardless of whether they were tested in the follicular phase or the luteal phase (Mendelson et al., 2001).

There is increasing evidence that the presence of gonadal hormones, as well as the actual levels, appears to be crucial to observe cocaine-induced increases in LH levels. Several studies have shown that cocaine fails to alter LH levels in ovariectomized monkeys (Mello et al., 1995, 2004a; Sarnyai et al., 1995). In fact, in ovariectomized monkeys, acute cocaine administration only increased LH levels when females were chronically treated with progesterone alone, but not when progesterone was combined with estradiol or when estradiol was given alone. Only when large acute doses of cocaine (2–4 mg/kg, i.v.) are administered to ovariectomized monkeys (Canez et al., 1992), are decreases in LH levels observed. Interestingly, a recent study in rhesus monkeys (Mello et al., 2004b) suggests that cocaine-induced increases in LH plasma levels can vary depending on estradiol levels in the follicular phase; cocaine only increased LH levels in females who had low estradiol levels (<100 pg/ml), but when estradiol levels were high, LH levels did not change after cocaine administration. In the present study, only one of the four monkeys had estradiol levels consistently >100 pg/ml during the follicular phase, making it impossible to examine the data in a similar manner. Taken together, these studies suggest that the effects of cocaine on the stimulation of LH appear to be dependent on a variety of factors, including cocaine dose and gonadal steroid hormone status.

4.3. Effects of cocaine on prolactin

Lastly, in the present study cocaine produced rapid and substantial decreases in prolactin plasma levels, with no differences as a function of menstrual cycle phase or between the two doses of cocaine. These findings are consistent with the existing literature documenting that acute cocaine administration decreases prolactin levels (see Mello and Mendelson, 2002 for review). This dramatic decrease in prolactin levels is most likely due to the inhibitory effects of dopamine on both the synthesis and secretion of prolactin (e.g., Yen, 1979; Ben-Jonathan, 1985). Indirect dopamine agonists, such as cocaine, may reduce prolactin levels by increasing dopamine levels (e.g., Yen and Jaffe, 1999; Heesch et al., 1996).

Acute cocaine administration has been shown to decrease prolactin in most rodent studies despite differences in cocaine dose and route of administration (Baumann and Rothman, 1993; Levy et al., 1992; Steger et al., 1981, but see Pilotte et al., 1990). More extensive research has assessed the effects of cocaine administration on prolactin in rhesus monkeys. For instance, in one study, acute doses of either 0.4 or 0.8 mg/kg i.v. cocaine suppressed prolactin levels in female monkeys tested in the follicular phase within about 10 min, with the lowest levels relative to baseline (18–34%) being observed within 60–70 min (Mello et al., 1990). However, by the end of the session, prolactin levels were beginning to return to baseline and in some animals, exceeded baseline levels. Similarly, in a subsequent study (Mello et al., 1993), both doses of cocaine decreased prolactin levels in male monkeys, whereas only the high dose of cocaine decreased prolactin levels in females tested during the midluteal phase. In the present study, four successive injections of either 0.25 or 0.50 mg/kg i.v. cocaine decreased prolactin levels 80–90% relative to baseline levels and these levels were still substantially suppressed at the end of the session (120 min after the last injection), irrespective of menstrual cycle phase. An interesting finding from the present study was that prolactin levels were also decreased following repeated injections of saline (0 mg/kg cocaine), although not to the same extent as following cocaine. Unfortunately, the elegant studies by Mello et al. (1990, 1993) did not include a saline condition for comparison, although several early studies have observed few fluctuations in prolactin levels across the menstrual cycle in drug-naïve monkeys (Quadri and Spies, 1976; Milmore, 1978). However, as with LH, the effects of acute cocaine administration on prolactin levels appear to depend on gonadal hormone status; cocaine does not alter prolactin levels in ovariectomized female monkeys, but attenuates prolactin levels in females given hormone replacement with estradiol alone, progesterone alone or estradiol in combination with progesterone (Mello et al., 2004a).

Relatively few laboratory studies in humans have examined the effects of acute cocaine administration on prolactin levels, and the results have varied across studies. When intranasal cocaine (2 mg/kg) was administered to cocaine-naïve men (Heesch et al., 1996), prolactin levels decreased. In cocaine-

dependent men (Mendelson et al., 1992), administration of either 30 mg i.v. cocaine or placebo produced only small decreases in prolactin. This may have been in part due to the relatively low baseline levels of prolactin. Similarly, in another study 40 mg i.v. cocaine did not alter prolactin levels in male cocaine users (Baumann et al., 1995). While these studies differed with respect to the route of administration, the major difference is related to the previous drug history of the participants. The study by Heesch et al. (1996) was conducted in normal males, while the other two studies were conducted in males with chronic histories of cocaine and other drug abuse. In contrast to acute cocaine administration, there is evidence from both the preclinical and clinical literature that chronic cocaine exposure disrupts prolactin regulation and in some cases may result in hyperprolactinemia (see review by Mello and Mendelson, 2002).

4.4. Limitations

This study had several limitations. One limitation was the small number of animals tested. This is somewhat unavoidable due to the expensive and difficulty obtaining normally cycling female rhesus monkeys. Another limitation was that estradiol and progesterone were not measured after cocaine administration and cocaine samples were not collected more frequently to assess trough levels before each cocaine injection, or beyond 120 min after the last cocaine injection. Given that monkeys were tested 2–3 times each month, the amount of blood that could be safely drawn at that frequency was restricted. The inability to take blood samples more often and for a longer period of time limits the conclusions that can be made, particularly regarding the cocaine metabolite levels. This study also did not include a comparison group of male monkeys, but based on previous studies described above conducted in monkeys and humans, there is little evidence that there are substantial sex differences regarding the pharmacokinetics of cocaine.

4.5. Implications

There is a growing body of pre-clinical and clinical literature indicating that the behavioral response to stimulants such as cocaine, vary as a function of gonadal hormone status and sex. The results of the present study, in combination with previous studies, indicate that any behavioral differences observed either across the menstrual cycle or between males and females, are probably not related to alterations in the pharmacokinetics of cocaine. However, the existing literature, including the present study, shows that cocaine administration does alter hormones, such as LH and prolactin, which are crucial to normal reproductive function. Research on the effects of chronic cocaine exposure using a non-human primate model are important to examine how alterations in neuroendocrine regulation affect the behavioral response to cocaine and reproductive function. Given that cocaine remains a major public health problem and appears to be increasing among women (SAMHSA, 2004), understanding the interaction between cocaine, hormones and behavior will facilitate the development of effective treatment strategies for cocaine abusers that may need to be different for women.

Acknowledgements

This research was supported by DA-12675 from The National Institute on Drug Abuse, and approved by the New York State Psychiatric Institute Animal Care and Use Committee. The assistance of April Modrzakowski, Julian Perez, Angel Ramirez, and Dr. Mohamed Osman is gratefully acknowledged.

References

Baumann MH, Rothman RB. Effects of acute and chronic cocaine on the activity of tuberoinfundibular dopamine neurons in the rat. Brain Res 1993; 608:175–9.

Baumann MH, Gendron TM, Becketts KM, Henningfield JE, Gorelick DA, Rothman RB. Effects of intravenous cocaine on plasma cortisol and prolactin in human cocaine abusers. Biol Psychiatry 1995;38:751–5.

Ben-Jonathan N. Dopamine: a prolactin-inhibiting hormone. Endocr Rev 1985; 6:564–89.

Bowman BP, Vaughn SR, Walker QD, Davis SL, Little PJ, Scheffler NM, et al. Effects of sex and gonadectomy on cocaine metabolism in the rat. J Pharmacol Exp Ther 1999;290:1316–23.

Canez MS, Samuels MH, Luther MF, King TS, Schenken RS. Cocaine impairs gonadotropin secretion in oophorectomized monkeys. Am J Obstet Gynecol 1992;167:1785–93.

Carroll ME, Lynch WJ, Roth ME, Morgan AD, Cosgrove KP. Sex and estrogen influence drug abuse. Trends Pharmacol Sci 2004;25:273–9.

Chin J, Sternin O, Wu H-B, Fletcher H, Perrotti L, Jenab S, et al. Sex differences in cocaine-induced behavioral sensitization. Cell Mol Biol 2001;47:1089–95.

Chin J, Sternin O, Wu H-B, Burrell S, Lu D, Jenab S, et al. Endogenous gonadal hormones modulate behavioral and neurochemical responses to acute and chronic cocaine administration. Brain Res 2002;945:123–30.

Cone EJ. Pharmacokinetics and pharmacodynamics of cocaine. J Anal Chem 1995;19:459–78.

Dada MO, Horacek MJ. Acute effects of intravenous administration of cocaine on circulating luteinizing hormone, follicle-stimulating hormone and prolactin concentrations in rats. Res Commun Subst Abuse 1991;12: 197–208.

Evans SM, Foltin RW. Pharmacokinetics of intravenous cocaine across the menstrual cycle in rhesus monkeys. Neuropsychopharmacology 2004; 29:1889–900.

Evans SM, Foltin RW. Exogenous progesterone attenuates the subjective effects of smoked cocaine in women, but not in men. Neuropsychopharmacology; in press.

Evans SM, Cone EJ, Henningfield JE. Arterial and venous cocaine plasma concentrations in humans: relationship to route of administration, cardiovascular, effects and subjective effects. J Pharmacol Exp Ther 1996;279: 1345–56.

Evans SM, Haney M, Fischman MW, Foltin RW. Limited sex differences in response to binge smoked cocaine use in humans. Neuropsychopharmacology 1999;21:445–54.

Evans SM, Haney M, Foltin RW. The effects of smoked cocaine during the follicular and luteal phases of the menstrual cycle in women. Psychopharmacology 2002;159:397–406.

Festa ED, Quiñones-Jenab V. Gonadal hormones provide the biological basis for sex differences in behavioral responses to cocaine. Horm Behav 2004; 46:509–19.

Festa ED, Russo SJ, Gazi FM, Niyomchai T, Kemen LM, Lin SN, et al. Sex differences in cocaine-induced behavioral responses, pharmacokinetics, and monoamine levels. Neuropharmacology 2004;46:672–87.

Foltin RW, Fischman MW. Smoked and intravenous cocaine in humans: acute tolerance, cardiovascular and subjective effects. J Pharmacol Exp Ther 1991;257:247–61.

Heesch CM, Negus BH, Bost JE, Keffer JH, Snyder RW II, Eichhorn EJ. Effects of cocaine on anterior pituitary and gonadal hormones. J Pharmacol Exp Ther 1996;278:1195–2000.

Hotchkiss J, Knobil E. The menstrual cycle and its neuroendocrine control. In: Knobil E, Neill JD, editors. The physiology of reproduction. New York: Raven Press; 1994. p. 711–49.

Isenschmid DS, Fischman MW, Foltin RW, Caplan YH. Concentration of cocaine and metabolites in plasma of humans following intravenous administration and smoking of cocaine. J Anal Toxicol 1992;16:311–4.

Javaid JL, Fischman M, Schuster CR, Dekirmenjian H, Davis JM. Cocaine plasma concentration: relation to physiological and subjective effects in humans. Science 1978;202:227–8.

King TS, McNichol M, Canez MS, Javors MA, Schenken RS. Effect of acute administration of cocaine on pituitary gonadotropin secretion in female rats. Reproduction 2001;122:723–9.

Kosten TR, Kosten TA, McDougle CJ, Hameedi FA, McCance EF, Rosen MI, et al. Gender differences in response to intranasal cocaine administration to humans. Biol Psychiatry 1996;39:147–8.

Kouri EM, Lundahl LH, Borden KN, McNeil JF, Lukas SE. Effects of oral contraceptives on acute cocaine response in female volunteers. Pharmacol Biochem Behav 2002;74:173–80.

Levy AD, Li Q, Alvarez Sanz MC, Rittenhouse PA, Kerr JE, Van de Kar LD. Neuroendocrine responses to cocaine do not exhibit sensitization following repeated cocaine exposure. Life Sci 1992;51:887–97.

Lukas SE, Sholar M, Lundahl LH, Lamas X, Kouri E, Wines JD, et al. Sex differences in plasma cocaine levels and subjective effects after acute cocaine administration in human volunteers. Psychopharmacology 1996; 125:346–54.

Lynch WJ, Roth MN, Carroll ME. Biological basis of sex differences in drug abuse: preclinical and clinical studies. Psychopharmacology 2002;164:121–37.

Mello NK, Mendelson JH. Cocaine, hormones, and behavior: clinical and preclinical studies. Horm Brain Behav 2002;5:665–745.

Mello NK, Mendelson JH, Drieze J, 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 1990;254:815–23.

Mello NK, Sarnyai Z, Mendelson JH, Drieze JM, Kelly M. Acute effects of cocaine on anterior pituitary hormones in male and female rhesus monkeys. J Pharmacol Exp Ther 1993;266:804–11.

Mello NK, Sarnyai Z, Mendelson JH, Diaz-Migoyo N, Kelly M. The acute effects of cocaine on anterior pituitary hormones in ovariectomized rhesus monkeys. J Pharmacol Exp Ther 1995;272:1059–66.

Mello NK, Mendelson JH, Kelly M, Bowen C. The effects of cocaine on basal and human chorionic gonadotropin-stimulated ovarian steroid hormones in female rhesus monkeys. J Pharmacol Exp Ther 2000;294:1137–45.

Mello NK, Bowen CA, Mendelson JH. Comparison of plasma cocaine levels during a "binge" pattern of cocaine administration in male and female rhesus monkeys. Psychopharmacology 2002;164:19–26.

Mello NK, Mendelson JH, Negus SS, Kelly M. Ovarian steroid hormone modulation of the acute effects of cocaine on luteinizing hormone and prolactin levels in ovariectomized rhesus monkeys. J Pharmacol Exp Ther 2004a;308:156–67.

Mello NK, Mendelson JH, Negus SS, Kelly M, Knudson I, Roth ME. The effects of cocaine on gonadal steroid hormones and LH in male and female rhesus monkeys. Neuropsychopharmacology 2004b;29:2024–34.

Mendelson JH, Teoh SK, Mello NK, Ellingboe J, Rhoades E. Acute effects of cocaine on plasma adrenocorticotropic hormone, luteinizing hormone and prolactin levels in cocaine-dependent men. J Pharmacol Exp Ther 1992; 263:505–9.

Mendelson JH, Mello NK, Negus SS. Effects of luteinizing hormone—releasing hormone on plasma cocaine levels in rhesus monkeys. J Pharmacol Exp Ther 1999a;289:791–9.

Mendelson JH, Mello NK, Sholar MB, Siegel AJ, Kaufman MJ, Levin JM, et al. Cocaine pharmacokinetics in men and in women during the follicular and luteal phases of the menstrual cycle. Neuropsychopharmacology 1999b;21:294–303.

Mendelson JH, Sholar MB, Siegel AJ, Mello NK. Cocaine's effects on luteinizing hormone in women during the follicular and luteal phases of the menstrual cycle and in men. J Pharmacol Exp Ther 2001;296:972–9.

Milmore JE. Influence of ovarian hormones on prolactin release in the rhesus monkey. Biol Reprod 1978;19:593–6.

Misra AL, Giri VV, Patel MN, Alluri VR, Mule SJ. Disposition and metabolism of [−3H] cocaine in acutely and chronically treated monkeys. Drug Alcohol Depend 1977;2:261–72.

Norman RL, McGlone J, Smith CJ. Restraint inhibits luteinizing hormone secretion in the follicular phase of the menstrual cycle in rhesus macaques. Biol Reprod 1994;50:16–26.

Pilotte NS, Sharpe LG, Dax EM. Multiple, but not acute, infusions of cocaine alter the release of prolactin in male rats. Brain Res 1990;512:107–12.

Quadri SK, Spies HG. Cyclic and diurnal patterns of serum prolactin in the rhesus monkey. Biol Reprod 1976;14:495–501.

Quiñones-Jenab V, Ho A, Schlussman SD, Franck J, Kreek MJ. Estrous cycle differences in cocaine-induced stereotypic and locomotor behaviors in Fischer rats. Behav Brain Res 1999;101:15–20.

Quiñones-Jenab V, Perrotti LI, Mc Monagle J, Ho A, Kreek MJ. Ovarian hormone replacement affects cocaine-induced behaviors in ovariectomized female rats. Pharmacol Biochem Behav 2000;67:417–22.

Saady JJ, Bowman ER, Aceto MD. Cocaine-induced rausch: overt behaviour and plasma concentrations in rhesus monkeys. Eur J Drug Metab Pharmacokinet 1994;19:41–6.

Saady JJ, Bowman ER, Aceto MD. Cocaine, ecgonine methyl ester, and benzoylecgonine plasma profiles in rhesus monkeys. J Anal Toxicol 1995; 19:571–5.

Sarnyai Z, Mello NK, Mendelson JH, Ngyuen PH, Eros-Sarnyai M. Effects of cocaine and corticotropin-releasing factor (CRF) on pulsatile ACTH and cortisol release in ovariectomized rhesus monkeys. J Clin Endocrinol Metab 1995;80:2745–51.

Sofuoglu M, Dudish-Poulsen S, Nelson D, Pentel PR, Hatsukami DK. Sex and menstrual cycle differences in the subjective effects from smoked cocaine in humans. Exp Clin Psychopharmacol 1999;7:274–83.

Steger RW, Silverman AY, Johns A, Asch RH. Interactions of cocaine and delta-9-tetrahydrocannabinol with the hypothalamic–hypophysial axis of the female rat. Fertil Steril 1981;35:567–72.

Substance abuse and mental health service administration. Results from the 2002 National Survey on Drug Use and Health: National Findings (Office of Applied Studies, NHSDA Series H-22, DHHD Publication on. SMA 03-3836). Rockville MD; 2003.

Substance abuse and mental health services administration. Office of applied studies. Treatment episode data set (TEDS). Highlights-2002. National Admissions to Substance Abuse Treatment Services, DASIS Series: S-22, DHHS Publication No. (SMA) 04-3946, Rockville, MD; 2004.

US Department of Health and Human Services Preliminary Estimates from the 1993 National Household Survey on Drug Abuse. Washington, DC: Substance Abuse and Mental Health Services Administration; 1993.

Van Haaren F, Garcea M, Anderson K, Tebbett I. Cocaine and benzoylecgonine in serum microsamples of intact and gonadectomized male and female Wistar rats. Pharmacol Biochem Behav 1997;58:421–4.

Van Luijtelaar EL, Dirksen R, Vree TB, van Harren F. Effects of acute and chronic cocaine administration on EEG and behaviour in intact and castrated male and intact and ovariectomized female rats. Brain Res Bull 1996;40:43–50.

Xiao E, Xia L, Shanen D, Khabele D, Ferin M. Stimulatory effects of interleukin-induced activation of the hypothalamo–pituitary–adrenal axis on gonadotropin secretion in ovariectomized monkeys replaced with estradiol. Endocrinology 1994;135:2093–8.

Yen SSC. Studies of the role of dopamine in the control of prolactin and gonadotropin secretion in humans. In: Fuxe K, Hokfelt T, Luft R, editors. Central regulation of the endocrine system. New York: Plenum Press; 1979. p. 387–416.

Yen SSC, Jaffe RB. Prolactin in human reproduction. In: Yen SSC, Jaffe RB, Barbieri RL, editors. Reproductive endocrinology, 4th ed. Philadelphia: Saunders; 1999. p. 257–83.

Zhou M, Song Z-M, Lidow MS. Pharmacokinetics of cocaine in maternal and fetal rhesus monkeys at mid-gestation. J Pharmacol Exp Ther 2001;297:556–62.