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ORIGINAL INVESTIGATION

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The effects of smoked cocaine during the follicular and luteal phases of the menstrual cycle in women

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Abstract *Rationale:* Few studies have systematically determined whether the response to cocaine in human females is related to hormonal fluctuations at different phases of the menstrual cycle. *Objectives:* To investigate the responses to repeated doses of smoked cocaine in women during two phases of the menstrual cycle using a within-subject design. *Methods:* Eleven non-treatment seeking female cocaine smokers were administered smoked cocaine during the follicular and mid-luteal phases of the menstrual cycle. The order of menstrual cycle phase was counterbalanced across women and the order of cocaine doses was randomized. During each phase, there were four cocaine administration sessions. During each session, participants could smoke up to six doses of cocaine (either 0, 6, 12, or 25 mg cocaine base, depending on the session) at 14-min intervals. *Results:* The number of cocaine doses administered did not vary between the follicular and luteal phases. After cocaine administration, heart rate and several ratings – such as "good drug effect", "high", "stimulated", and "drug quality ratings" – were increased more during the follicular phase than the luteal phase, although, for some measures, these effects varied based on the cocaine dose. Further, dysphoric mood during the luteal phase was improved after cocaine administration. *Conclusions*: These results indicate that the cardiovascular and subjective effects of repeated doses of smoked cocaine are complex and vary as a function of menstrual cycle phase and cocaine dose.

Keywords Cocaine · Females · Menstrual cycle · Hormone concentration · Subjective effect · Cardiovascular effect

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Introduction

Numerous preclinical studies have documented sex differences between male and female rodents in response to stimulants, with female rodents being more sensitive than male rodents to several behavioral effects of stimulant administration (Becker et al. 1982; Roberts et al. 1989; van Haaren and Meyer 1991; Haney et al. 1994; Lynch and Carroll 1999, 2000; Sell et al. 2000). Moreover, these differences between males and females appear to be related to fluctuations in the ovarian hormones of females. In the normal female rat, estradiol and progesterone fluctuate over a 4-day estrous cycle, with both hormones peaking during proestrus, whereas, during estrus, levels of estradiol are relatively stable and progesterone levels are minimal (Butcher et al. 1974; Smith et al. 1975). Several studies have demonstrated that the greatest increase in behavioral activity in females occurs when stimulants are administered during estrus than during other phases of the estrous cycle (Becker et al. 1982; Becker and Cha 1989; Diaz-Veliz et al. 1994; Quiñones-Jenab et al. 1999; Sell et al. 2000). Similarly, during estrus, female rats (1) have higher progressive ratio breakpoints for cocaine self-administration (Roberts et al. 1989; Hecht et al. 1999), (2) show greater disruptions in the regulation of cocaine self-administration (Lynch et al. 2000), and (3) select the highest cocaine dose (Lynch et al. 2000). Ovariectomy has been shown to reduce the behavioral effects of stimulants (Becker et al. 1982; Camp et al. 1986; Roberts et al. 1987; Haney et al. 1994; Sircar and Kim 1999), whereas exogenously administered estradiol has been shown to restore or enhance the behavioral effects of stimulants in ovariectomized female rodents (Castner et al. 1993; Grimm and See 1997; Sircar and Kim 1999; Sell et al. 2000). Taken together, these preclinical findings indicate that there are sex differences in the behavioral response to stimulants, and these differences may be related to ovarian hormone levels, specifically estrogen.

Although several controlled studies have evaluated the direct effects of cocaine administration in humans

(Kosten et al. 1996; Lukas et al. 1996; Haney et al. 1998; Evans et al. 1999; Mendelson et al. 1999; Sofuoglu et al. 1999), most have reported minimal sex differences in response to cocaine. More recently, several studies have specifically addressed the role of menstrual cycle phase in the response to stimulants such as amphetamine and cocaine. The human female has a 28-day menstrual cycle; the mid-follicular phase is characterized by increasing levels of estradiol, whereas progesterone levels are negligible. The luteal phase is characterized by rising progesterone levels that peak during the mid-luteal phase (7–12 days after ovulation), and estradiol levels are also elevated during this time. Justice and de Wit (1999) reported that several subjective effects ("like drug", "want more drug", "high", and "euphoria") were greater during the follicular phase than the mid-luteal phase following a single dose of amphetamine (15 mg). These findings are consistent with preclinical studies suggesting that estrogen may enhance the behavioral response to a stimulant drug, whereas high levels of progesterone may mask these effects during the luteal phase. However, a subsequent study from the same laboratory (Justice and de Wit 2000a) comparing the effects of 15 mg oral amphetamine during the early and late follicular phases failed to replicate the previous findings. Lukas et al. (1996) found that women had higher cocaine plasma levels during the follicular phase than the luteal phase following a single dose of 0.9 mg/kg intranasal cocaine. In a study by Mendelson et al. (1999), the only menstrual cycle difference following a single dose of either 0.2 mg/kg or 0.4 mg/kg i.v. cocaine was that cocaine plasma levels after 0.4 mg/kg cocaine peaked faster in follicular phase women compared to luteal phase women. Similarly, Sofuoglu et al. (1999) compared the effects of a single dose of smoked cocaine (0.4 mg/kg) in women and reported no differences in cardiovascular response or cocaine plasma concentrations between luteal and follicular phase women. However, maximal ratings of "feel high" were significantly greater in follicular phase women than luteal phase women. Unfortunately, the latter two studies tested separate groups of women in each phase making it difficult to adequately address changes in the effects of cocaine across the menstrual cycle. Despite the inconsistencies across the few studies conducted in humans, the underlying commonality is that the response to a stimulant is enhanced during the follicular phase of the menstrual cycle and this effect is consistent with existing preclinical data.

The purpose of the present study was to extend and improve upon previous research in humans by determining the response to repeated doses of smoked cocaine during the follicular and mid-luteal phases of the menstrual cycle in female cocaine abusers. The strengths of the present study were that (1) a dose–response function for smoked cocaine (0, 6, 12, and 25 mg crack cocaine) was determined during the follicular and mid-luteal phases of the menstrual cycle; (2) repeated doses of smoked cocaine (up to six within a session) were administered, rather than a single acute dose; and (3) a within-subject design was used such that all females were tested under all conditions.

Materials and methods

Participants

Eleven female research volunteers (ten African-American and one Caucasian), 32–43 years of age (mean 38 years), with current histories of smoking cocaine were solicited through newspaper advertisement in New York, N.Y. Participants reported currently spending US $120–1350 (mean US $397) per week on cocaine and using cocaine an average of 3–4 days each week. All participants smoked tobacco cigarettes (mean 11 cigarettes per day). Participants had completed a mean of 12 years of education (10–14 years) and had a mean body mass index (BMI) of 26 (19–36). All were medically and psychiatrically healthy based on a physical examination, electrocardiogram, chest X-ray, complete blood chemistries (including pseudocholinesterase levels), urinalyses, and a Structured Clinical Interview to assess DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th edn.) axis-I disorders (SCID I; First et al. 1994). None was receiving psychiatric treatment or seeking treatment for their drug use and none of the participants was using hormonal contraceptives or any other prescription medication. Also, women were not pregnant (based on blood pregnancy tests) or nursing, and had not had an abortion or been pregnant within the previous 6 months. Lastly, none of the participants suffered from premenstrual dysphoric disorder based on (1) the 95-item retrospective self-report Premenstrual Assessment Form (Halbreich et al. 1982), which was completed at initial screening, and (2) the 21-item Daily Ratings Form (Endicott et al. 1986) used to prospectively track mood changes across the menstrual cycle which participants completed each evening before going to bed throughout the study (for details, see Evans et al. 1998).

Each participant signed a consent form, approved by the Institutional Review Boards of The College of Physicians and Surgeons of Columbia University and The New York State Psychiatric Institute. The consent form described the study, outlined possible risks, and indicated that cocaine would be administered, possibly on a daily basis. Participants were paid for their participation in multiple weekly payments not to exceed a value of US $300 each week.

Design and experimental procedures

After signing the study consent form, participants began filling out Daily Rating Forms each evening. Each participant was prospectively tracked for several weeks before the first inpatient admission and throughout the study to determine menstrual cycle length and time of ovulation. They were paid to report to the laboratory twice a week to return completed forms and pick up new forms. They were also instructed to notify the research nurse when menstruation started. During the mid-follicular phase (the specific day that participants began the ovulation testing depended on their typical menstrual cycle length), participants were paid to come to the laboratory every weekday to provide a urine sample so the research nurse could estimate the time of ovulation using OvuQuick (Quidel Corp., San Diego, Calif.; Martini et al. 1994). They were tested daily until a positive result was obtained. If ovulation testing occurred over a weekend, participants were instructed on how to use the test cassettes and they brought in their urine samples from the weekend so the research nurse could confirm the test results. The test is simple to use and is 96–99% accurate at detecting luteinizing hormone (LH) in urine. The day of ovulation was used to schedule the mid-luteal admission.

Participants were admitted to the NIH-funded Irving Center for Clinical Research in the Presbyterian Hospital on two occasions for a period of 4 days (3 nights) each time. While residing at the Clinical Research Center, all participants had access to television,

radio, and video-taped movies but were not permitted to leave the unit unless accompanied by a staff member. Participants who smoked tobacco cigarettes were allowed to smoke throughout their inpatient stay. However, smoking was not allowed during experimental sessions, which lasted approximately 2.5 h each.

One inpatient admission was scheduled during the follicular phase so that cocaine administration sessions occurred between 6 days and 10 days after the onset of menstruation when progesterone levels were minimal and estradiol levels rising. The other inpatient admission was scheduled during the mid-luteal phase, 7–12 days after the urinary ovulation test kit had indicated that ovulation occurred, so that cocaine administration sessions were conducted when progesterone concentrations were maximal. The order of admissions was counterbalanced between participants so that six were tested first during the follicular phase and five were tested first during the luteal phase. The day following each inpatient admission, women participated in laboratory sessions twice per day for 2 days and they were discharged on the fourth inpatient day.

Experimental sessions

During each menstrual cycle phase, cocaine administration sessions occurred at 0900 hours and again at 1300 hours on two consecutive days, for a total of four sessions. During each session, participants could smoke up to six doses of cocaine (either 0, 6, 12, or 25 mg cocaine base, depending on the session) at 14-min intervals. The dose order within each phase was randomized, and the dose order for the two phases was not identical for a given individual.

During experimental sessions, each participant was seated in a comfortable lounge chair in front of a computer monitor on which subjective-effects questions were displayed. A computer mouse was used for completion of the subjective-effects questionnaires. An 18-gauge catheter (Quik-Cath, Travenol Laboratories, Deerfield, Ill.) was inserted into a subcutaneous vein in one arm for blood collection. An electrocardiogram was continuously monitored via chest electrodes (MAC PC, Marquette Electronics, Milwaukee, Wis.), while heart rate and blood pressure were recorded every 2 min (Sentry II – Model 6100 automated vital signs monitor, NBS Medical, Costa Mesa, Calif.) beginning 20 min prior to drug administration. A Macintosh computer located in an adjacent room was used for automated data collection.

Each cocaine administration session began with 20 min of baseline vital signs and participants completing the baseline subjective-effects questionnaires at −10 min. Participants were instructed that the purpose of the study was to assess their response to repeated doses of cocaine at different phases of their menstrual cycle. This was not a self-administration session, but participants were told they had the option of refusing a dose. During each session, participants were administered the cocaine dose available that session at 14-min intervals for a total of six doses per session, with the first dose given at time 0. Pyrolysis of the cocaine base was accomplished by the nurse holding the flame from a pipe lighter on the cocaine. Participants were instructed to take one large inhalation and to hold the inhalation as long as they normally would outside of the laboratory. During the administration of cocaine, participants were blindfolded so they could not see the size of the cocaine dose. When 0 mg cocaine (placebo) was administered, an empty stem was lit for participants and they inhaled warm air.

During the session, the subjective-effects questionnaire was repeated 4 min after the administration of each cocaine dose (even if a dose was refused), as well as 15 min after the last cocaine dose. Cocaine was not given on any trial that any cardiovascular measure was above our criteria for safe drug administration (heart rate >130 beats/min, diastolic pressure >100 mmHg, systolic pressure >165 mmHg). During all sessions, participants were continuously monitored via a one-way mirror by research nurses located in the adjacent room, and participants could communicate with nurses via an intercom system.

During each session, blood was drawn for determination of cocaine plasma levels at baseline (before drug administration), 4 min after the first dose, and 4 min after the sixth dose. Blood was drawn for determination of progesterone and estradiol levels before administration of the first cocaine dose each experimental day (baseline) to verify menstrual cycle phase.

Subjective-effects questionnaires

A computerized questionnaire was completed repeatedly during each session: 10 min before the first cocaine dose, 4 min after each cocaine dose, and 15 min after the last cocaine dose. The questionnaire consisted of a series of 100-mm visual analog scales (VASs) labeled “not at all” (0 mm) at one end and “extremely” (100 mm) at the other. Eighteen of these VASs were labeled “stimulated”, “high”, “anxious”, “sedated”, “depressed”, “hungry”, “friendly”, “miserable”, “on edge”, “alert”, “tired”, “talkative”, “self-confident”, “social”, “irritable”, “confused”, “good drug effect”, and “bad drug effect”. Four VASs were used to operationalize drug craving and were labeled “I want...” “...cocaine”, “...heroin”, “...ethanol”, and “...nicotine”. Three VASs were related specifically to the cocaine dose the participant had just received and were labeled “the choice was of high quality”, “the choice was potent”, and “I liked the choice”. A final question asked the participants “how much would you pay for the dose you just received?”, with a range of US $0–25.

Drug

Cocaine base, derived from cocaine hydrochloride (provided by The National Institute on Drug Abuse) as described by Foltin et al. (1990), was prepared by the Presbyterian Hospital Research Pharmacy.

Hormone assays

Each experimental day (2 days during the follicular phase and 2 days during the mid-luteal phase), before cocaine administration, venous blood samples (approximately 6 ml) for estradiol and progesterone measurements were drawn from an indwelling catheter into tubes containing SST gel and clot activator. Samples were centrifuged within 30 min of collection, yielding approximately 3 ml plasma, and stored frozen until the time of analysis.

Estradiol and progesterone concentrations were determined by Dr. Michel Ferin at the College of Physicians and Surgeons of Columbia University, Department of Obstetrics and Gynecology (New York, N.Y.). Estradiol and progesterone were measured using a solid-phase ^{125}I radioimmunoassay (RIA; Coat-A-Count, Diagnostic Products Corp., Los Angeles, Calif.). Intra- and interassay coefficients of variation were less than 3% for estradiol. Progesterone measurement required prior extraction with petroleum ether (Aldrich Chemical Co., Milwaukee, Wis.). Intra- and interassay coefficients of variation were 4.8% and 9.1%, respectively, for progesterone.

Cocaine analysis

Venous blood samples (approximately 6 ml) for cocaine measurements were drawn from an indwelling catheter into tubes containing potassium oxalate and sodium fluoride. Samples were immediately mixed and placed on ice until they could be centrifuged. They were centrifuged within 30 min of collection, yielding approximately 3 ml plasma, and stored frozen until the time of analysis. Blood samples for cocaine were obtained at baseline (before the first cocaine dose), 4 min after the first dose, and 4 min after the sixth dose.

Cocaine blood concentrations were determined by Mr. Thomas Cooper at the Nathan Kline Institute for Psychiatric Research

(Orangeburg, N.Y.). Cocaine was analyzed using capillary gas chromatograph–mass spectrometry with deuterated internal standards, positive chemical ionization, and simultaneous ion monitoring. Intra- and interassay coefficients of variation were less than 6%.

Data analysis

Mean heart rate, systolic pressure, and diastolic pressure, averaged across 8 min, were collected beginning 10 min before the first cocaine dose, 2 min after each cocaine dose, and 15 min after the last cocaine dose, for a total of eight measurements within a session. Similarly, each VAS was collected eight times within a session. Each cardiovascular measure and each VAS item was analyzed separately. In addition, the VAS was subjected to a cluster analysis that resulted in five clusters: "bad drug effects" consisted of seven items related to negative drug effects ("bad drug effect", "anxious"); "mood states" consisted of five items ("self-confident", "friendly"); "on edge/miserable" consisted of two items ("on edge", "miserable"); "positive drug effects" consisted of three items ("high", "good drug effect", "stimulated"); and "drug quality ratings" consisted of three items related to the cocaine dose the participant had just received ("drug quality", "drug potency", "drug liking").

To determine whether there were any baseline cardiovascular or subjective differences as a function of menstrual cycle phase, two-factor repeated-measures analyses of variance with phase (follicular vs luteal) as the first factor and dose (0, 6, 12, and 25 mg) as the second factor were conducted using the baseline data collected each session before cocaine administration. Because there were several main baseline phase effects, to determine whether repeated doses of cocaine produced differential effects as a function of menstrual cycle phase (without the confound of underlying menstrual cycle phase differences), the repeated-dose effects of cocaine within a session were examined using three-factor repeated-measures analyses of variance with phase (follicular vs luteal) as the first factor, dose (0, 6, 12, and 25 mg) as the second factor, and time as the third factor (seven times for both cardiovascular and subjective-effects measures) with data expressed as a change from baseline. For each measure, planned contrasts were conducted with each cocaine dose separately (combined across the seven time points) to compare the effects of cocaine between the two phases. Lastly, cocaine plasma concentrations were analyzed separately using a three-factor repeated-measures analysis of variance with phase, dose, and time (baseline, 4 min after the first dose, and 4 min after the sixth dose) as the three factors.

For all analyses, results were considered statistically significant if $P<0.05$, using Huynh-Feldt corrections where appropriate.

Table 1 Summary of significant differences between the follicular (*F*) and luteal (*L*) phases at each cocaine dose condition

Measure	Placebo	6 mg	12 mg	25 mg
Cardiovascular				
Systolic pressure (↑)[a]	–	L > F[b]	–	–
Diastolic pressure (↑)	–	L > F	L > F	L > F
Heart rate (↑)	L > F	–	F > L	F > L
Subjective effects				
"Bad drug effects" cluster	–	L > F	L > F	F > L
Anxious (↑)	–	L > F	–	F > L
Bad drug effect	–	–	L > F	–
Confused	F > L	L > F	–	–
Depressed	L > F	L > F	L > F	F > L
Irritable	L > F	–	F > L	F > L
Sedated (↑)	–	–	–	F > L
Tired (↓)	–	L > F	L > F	F > L
"Mood states" cluster	L > F	F > L	F > L	F > L
Alert	L > F	–	F > L	F > L
Friendly	–	–	–	F > L
Self-confident	L > F	F > L	F > L	F > L
Social	–	–	F > L	–
Talkative	–	–	–	F > L
"On edge/miserable" cluster (↓)	L > F	F > L	F > L	F > L
Miserable	L > F	F > L	F > L	F > L
On edge	–	F > L	–	F > L
"Positive drug effects" cluster (↑)	–	–	F > L	F > L
Good drug effect (↑)	L > F	–	F > L	F > L
High (↑)	–	–	F > L	F > L
Stimulated (↑)	–	F > L	F > L	F > L
"Drug quality ratings" cluster (↑)	–	F > L	F > L	L > F
Drug liking (↑)	L > F	F > L	F > L	L > F
Drug potency (↑)	–	F > L	F > L	L > F
Drug quality (↑)	–	–	F > L	L > F
Pay (US $) (↑)	–	–	F > L	L > F
Want cocaine (↑)	L > F	L > F	F > L	L > F
Want nicotine	–	L > F	L > F	F > L
Want alcohol	L > F	–	L > F	F > L
Hungry	–	–	L > F	L > F

[a] (↑)or (↓) indicates a significant main effect of cocaine dose ($P<0.05$) and the direction of the effect

[b] L > F or F > L indicates the direction when there were significant differences between the two menstrual cycle phases based on planned comparisons of the seven follicular phase time points and the seven luteal phase time points for that dose condition at $P<0.05$. Analyses were based on change from baseline scores. (-) indicates an insignificant effect

Results

All women had normal ovulatory menstrual cycles ranging in duration from 21 days to 35 days. Both mean estradiol and progesterone levels were higher during the luteal phase than during the follicular phase (estradiol $P=0.06$; progesterone $P<0.0001$). During the follicular phase, mean (±SEM) estradiol levels were 85±18.4 pg/ml (minimum 23.5 pg/ml; maximum 156.5 pg/ml) and progesterone levels were 0.53±0.07 ng/ml (minimum 0.2 ng/ml; maximum 0.8 ng/ml), whereas during the luteal phase mean estradiol levels were 143.6±24.6 pg/ml (minimum 77.5 pg/ml; maximum 343.0 pg/ml) and progesterone levels were 10.0±1.3 ng/ml (minimum 8.5 ng/ml; maximum 16.4 ng/ml).

Based on the Daily Ratings Form, none of the participants experienced substantial premenstrual mood changes during the study. More importantly, on the days that cocaine sessions were conducted, mean Daily Ratings Form scores (range 1–6) were similar between the luteal phase (1.40±0.15) and the follicular phase (1.18±0.06).

Phase differences

Three measures showed a main baseline (i.e., before cocaine administration) difference as a function of menstrual cycle phase. Resting heart rate was significantly higher during the luteal phase than the follicular phase

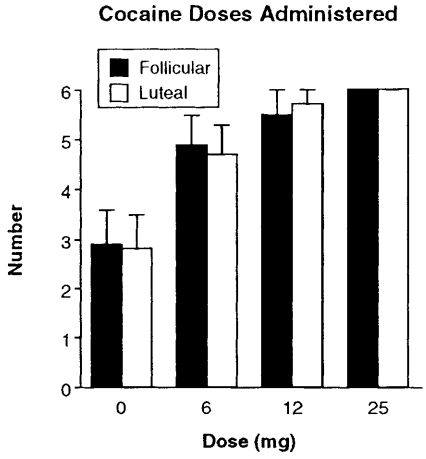


Fig. 1 Mean number of cocaine doses administered as a function of menstrual cycle phase and cocaine dose. The maximum possible number of cocaine doses within a session was six. *Data points* show means of 11 individuals; *bars* represent the mean+SEM

(81.3 bpm vs 75.4 bpm, respectively; $P<0.02$). Ratings of "I want cocaine" were also significantly higher during the luteal phase than the follicular phase (49.6 vs 41.8, respectively; $P<0.05$). Similarly, ratings of the "on edge/miserable" cluster were significantly higher during the luteal phase than the follicular phase (67.9 vs 60.8, respectively; $P<0.04$).

Consistent with the baseline differences noted above, Table 1 shows that, when placebo was administered, 12 measures were higher during the luteal phase than the follicular phase. Specifically, when placebo was administered, women reported more dysphoria (e.g., ratings of "depressed", "irritable", "miserable") and greater cravings for cocaine and alcohol during the luteal phase than the follicular phase.

Cocaine administration

During each session, a maximum of six cocaine doses could be administered. Figure 1 shows that when placebo was administered, only half of the doses were administered, with the other dose opportunities having being refused. When active cocaine doses were available, an average of 5–6 of the 6 available doses were administered, and, at the highest dose (25 mg), all six doses were administered. There were no significant differences in the number of cocaine doses administered as a function of menstrual cycle phase.

Cocaine plasma levels

Table 2 shows cocaine plasma levels as a function of cocaine dose, time within session, and menstrual cycle phase. Cocaine plasma levels increased as a function of the dose administered each session ($P<0.0001$). Correspondingly, within a session, cocaine plasma levels increased from baseline, the first dose of cocaine, and the last dose of cocaine ($P<0.0001$). However, at these limited number of time points sampled, there were no differences in cocaine plasma levels between the follicular phase and the luteal phase.

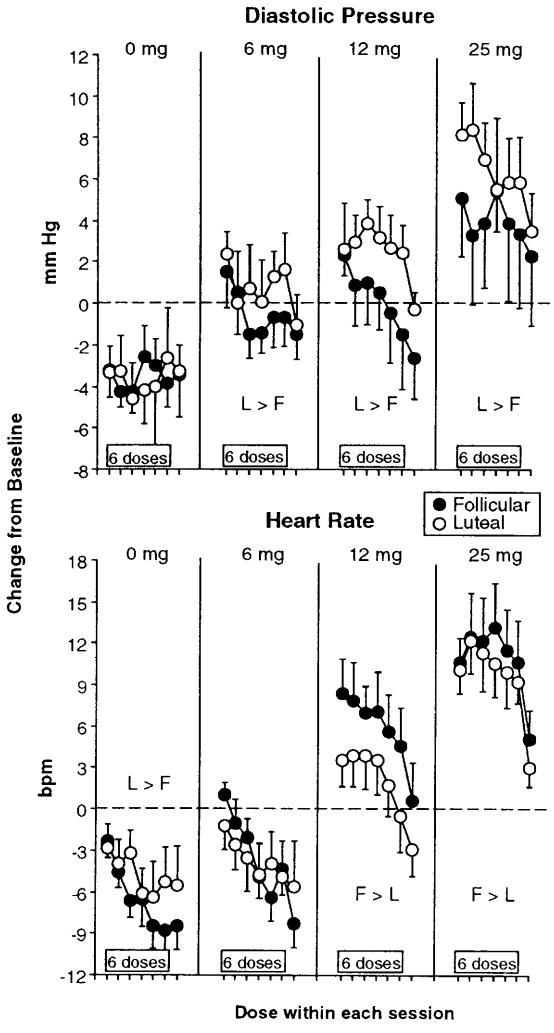
Table 2 Comparison of cocaine plasma levels as a function of cocaine dose and menstrual cycle phase. Values represent the mean and ±1 SEM. Baseline is 5–10 min before the first cocaine dose; 4 min is 4 min after the first cocaine dose; and 74 min is 4 min after the last cocaine dose of each session

Cocaine dose and time	Cocaine concentrations (ng/ml)	
	Follicular phase	Luteal phase
Placebo		
Baseline	10.2±6.1	3.3±1.9
4 min	7.2±4.7	1.7±1.2
74 min	5.8±3.5	0.5±0.6
6 mg Cocaine		
Baseline	6.4±3.6	12.3±5.5
4 min	39.2±4.4	27.3±5.8
74 min	99.0±11.3	81.7±14.6
12 mg Cocaine		
Baseline	4.5±2.5	9.9±6.4
4 min	87.1±19.0	76.9±12.9
74 min	229.8±21.3	230.3±30.3
25 mg Cocaine		
Baseline	7.2±3.3	11.6±9.6
4 min	133.9±12.7	128.0±29.2
74 min	388.4±37.8	396.6±42.3

Effects of cocaine within a session

Cocaine produced dose-related increases in all of the cardiovascular measures and most of the subjective-effects measures (indicated by arrows in Table 1). Table 1 also shows that, for most measures, there were differences between the luteal phase and the follicular phase, and that the direction of these differences were often related to cocaine dose. For instance, although many measures were higher during the luteal phase than the follicular phase following placebo, the effects shifted as the dose of cocaine increased, such that several measures were higher during the follicular phase than the luteal phase after repeated doses of 6, 12, and 25 mg cocaine.

Cocaine increased systolic pressure ($P<0.005$), diastolic pressure ($P<0.009$), and heart rate ($P<0.0001$) in a dose-related manner. Figure 2 shows that for diastolic pressure, these increases were consistently higher during the luteal phase than the follicular phase for all three cocaine doses (6 mg $P<0.005$; 12 mg $P<0.0001$; 25 mg $P<0.0001$). Cocaine increased heart rate more in the follicular phase than the luteal phase following repeated doses of 12 mg cocaine ($P<0.0001$) and 25 mg cocaine ($P<0.05$). For systolic pressure, phase differences were only observed following repeated doses of 6 mg cocaine (Table 1).



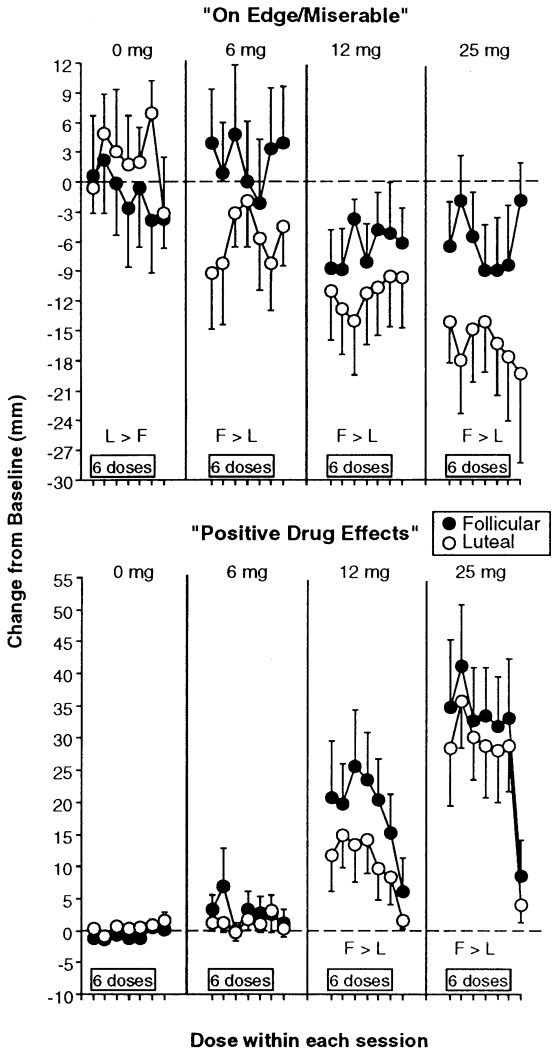


Fig. 2 Time-course functions of diastolic pressure and heart rate (expressed as change from baseline) as a function of menstrual cycle phase and cocaine dose. The *first six time points* for each dose condition represent data collected following each of the six cocaine doses in a session, and the *last time point* represents data collected 15 min after the last cocaine dose. *Data points* show means of 11 individuals; *vertical bars* show ±SEM. Some *error bars* have been omitted for clarity and some fell within the area of the data symbol. *L* (luteal) > *F* (follicular) or *F* > *L* indicates the direction when there were significant differences between the two menstrual cycle phases based on planned comparisons of the seven follicular phase time points and the seven luteal phase time points for that dose condition

Fig. 3 Time-course functions of the subjective-effects clusters "on edge/miserable" and "positive drug effects" (expressed as change from baseline) as a function of menstrual cycle phase and cocaine dose. See Fig. 2 for details

As shown in Fig. 3, when placebo was administered, ratings of the "on edge/miserable" cluster were higher during the luteal phase than the follicular phase. However, cocaine administration produced dose-related decreases in ratings of the "on edge/miserable" cluster ($P<0.05$) and, more importantly, these decreases were greater during the luteal phase than the follicular phase following all three cocaine doses (6 mg $P<0.0001$; 12 mg $P<0.005$; 25 mg $P<0.0001$), indicating an improvement in mood following cocaine during the luteal phase. Figure 3 also shows that ratings of the "positive drug effects" cluster increased as a function of cocaine dose ($P<0.0004$), with greater increases observed during the follicular phase than the luteal phase following repeated doses of the two highest doses of cocaine (12 mg $P<0.0001$; 25 mg $P<0.01$).

Ratings of the "mood states" cluster (data not shown) showed a main phase effect ($P<0.02$), with higher ratings observed during the follicular phase than the luteal phase following all three cocaine doses (6 mg $P<0.05$; 12 mg $P<0.01$; 25 mg $P<0.0001$). Decreases in ratings of the "mood states" cluster were observed primarily during the luteal phase following 25 mg cocaine (mean decrease of 12.5 mm). Further, ratings of the "bad drug effects" cluster were significantly higher during the follicular phase (mean of 9 mm) than the luteal phase (mean of 3 mm) following repeated doses 25 mg cocaine ($P<0.0001$) due to decreases during the luteal phase (data not shown).

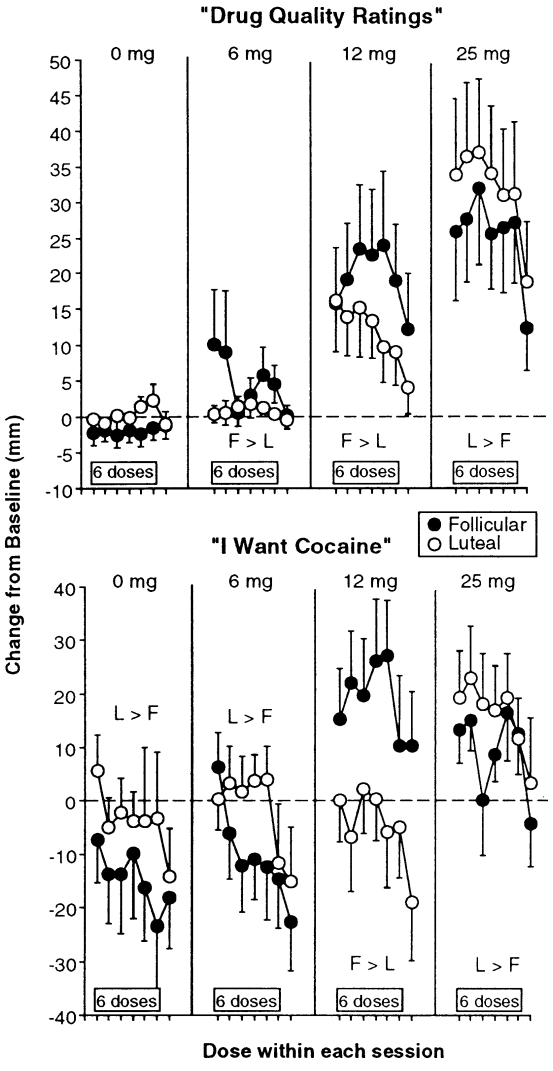


Fig. 4 Time-course functions of the subjective-effects clusters "drug quality ratings" and "I want cocaine" (expressed as change from baseline) as a function of menstrual cycle phase and cocaine dose. See Fig. 2 for details

The top panel of Fig. 4 shows that the "drug quality ratings" cluster also increased as a function of cocaine dose ($P<0.0009$); these ratings were increased to a greater extent during the follicular phase than the luteal phase following repeated doses of 6 mg ($P<0.03$) and 12 mg cocaine ($P<0.001$), then shifted to being greater during the luteal phase than the follicular phase following repeated doses of 25 mg cocaine ($P<0.005$). The amount of money women were willing to pay for the dose paralleled the findings from the "drug quality ratings" cluster in that there was a shift from the 12 mg cocaine dose to the 25 mg cocaine dose (data not shown; Table 1). As shown in the bottom panel of Fig. 4, desire for cocaine (expressed as "I want cocaine") was significantly increased during the luteal phase compared with the follicular phase following repeated doses of placebo ($P<0.003$), 6 mg cocaine ($P<0.05$), and 25 mg cocaine ($P<0.03$). In contrast, following repeated doses of 12 mg cocaine ($P<0.0001$), desire for cocaine was significantly greater during the follicular phase than the luteal phase.

Discussion

The present study determined a dose–response function of the effects of repeated smoked cocaine doses in the same women during the follicular and luteal phases of the menstrual cycle. The number of cocaine doses administered was similar between the two menstrual cycle phases and, based on the limited number of blood samples collected, there were no differences in cocaine plasma levels between the follicular and luteal phases. Smoked cocaine significantly increased blood pressure, heart rate, and a number of subjective-effects measures in a dose-related manner. Moreover, women responded differently to both the cardiovascular and subjective effects of cocaine as a function of menstrual cycle phase, and these differences depended on cocaine dose and the specific measure. Several ratings such as "good drug effect", "high", and "stimulated" ("positive drug effects" cluster) were increased more during the follicular phase than the luteal phase following cocaine administration. A similar profile of increased ratings during the follicular phase was observed for the "drug quality ratings" cluster (e.g., "drug liking", "drug potency", "drug quality") following repeated doses of 6 mg and 12 mg smoked cocaine, but not following repeated doses of 25 mg smoked cocaine.

The enhanced subjective response to cocaine during the follicular phase in the present study extends and confirms the few studies that have been conducted in humans. For instance, ratings of "high" were increased more during the follicular phase than the luteal phase in one study that tested a single dose of smoked cocaine (Sofuoglu et al. 1999). Similarly, oral amphetamine increased several positive subjective effects (e.g., "high", "euphoria") to a greater extent during the follicular phase in another study (Justice and de Wit 1999). However, in the study by Lukas et al. (1996), the subjective response to intranasal cocaine did not differ as a function of menstrual cycle phase, even though a range of subjective questions sensitive to alterations in mood were measured (e.g., the Profile of Mood States questionnaire). Also, ratings of "high" did not vary as a function of menstrual cycle phase following acute i.v. cocaine administration (Mendelson et al. 1999).

The only menstrual cycle phase difference in cardiovascular activity noted at baseline was that resting heart rate was significantly higher during the luteal phase than the follicular phase. This finding is consistent with other studies that have measured cardiovascular functioning during the menstrual cycle in normal women (Manhem and Jern 1994; Moran et al. 2000) and in the study by Lukas et al. (1996) before intranasal cocaine was administered. However, when cocaine was administered in the present study, heart rate increased to a greater extent during the follicular phase than the luteal phase, whereas di-

astolic blood pressure increased to a greater extent during the luteal phase than the follicular phase. These cardiovascular responses to cocaine are somewhat inconsistent with previous studies. Mean heart rate (expressed as change from baseline) was slightly higher during the follicular phase than the luteal phase following intranasal cocaine (Lukas et al. 1996) and no differences in blood pressure were noted. Two other studies also observed no differences in heart rate or blood pressure between the two menstrual cycle phases following cocaine administration (Mendelson et al. 1999; Sofuoglu et al. 1999). At this time, it is difficult to reconcile any inconsistencies in the few studies that have assessed the effects of cocaine in humans across the menstrual cycle due to differences across studies with respect to the route of cocaine, the range of doses, and the number of doses administered.

Interestingly, several ratings related to dysphoria were increased during the luteal phase compared with the follicular phase in the absence of cocaine (when placebo was administered). For instance, women reported being more "on edge/miserable", "depressed", and "irritable" and had greater cravings for cocaine during the luteal phase than the follicular phase. Thus, although none of these women met criteria for premenstrual dysphoric disorder based on the prospective Daily Rating Forms, they experienced mild dysphoric mood symptoms during the luteal phase in the absence of any cocaine administration. In the few studies that have examined the effects of stimulants across the menstrual cycle in humans, minimal mood alterations specifically related to menstrual cycle phase have been noted. For example, the only baseline menstrual cycle phase difference noted by Sofuoglu et al. (1999) was opposite to the present findings; in that study, the women who were tested during the follicular phase had higher baseline ratings of desire for cocaine than those tested during the luteal phase. In another study, the only subjective difference between the two phases of the menstrual cycle was that women reported feeling less content during the luteal phase (Lukas et al. 1996). Similarly, women reported higher ratings of "down" during the luteal phase than the follicular phase (Justice and de Wit 1999). Further, there was some limited evidence in the present study that cocaine administration improved the negative mood state during the luteal phase. Specifically, ratings of the "on edge/miserable" cluster were higher during the luteal phase in the absence of cocaine, whereas cocaine administration decreased these ratings during the luteal phase. These findings suggest that some mild level of dysphoric mood is present during the luteal phase among women without clinically significant premenstrual symptoms and that cocaine can ameliorate these dysphoric mood symptoms.

Relatively low cocaine doses were tested in the present study to increase the likelihood that an effect of menstrual cycle phase on cocaine's effects would be detected. Although previous studies from our laboratory have used repeated doses of 50 mg smoked cocaine (Evans et al. 1999), this dose may have resulted in a ceiling effect with respect to the subjective effects of cocaine. Findings from previous studies have shown that the subjective effects of low cocaine doses can be attenuated more readily than high cocaine doses (Haney et al. 1998, 1999; Walsh et al. 2000). In the present study, the most robust differences between the follicular phase and the luteal phase were observed following repeated doses of 12 mg cocaine rather than at the highest dose tested (25 mg). In fact, for several measures (e.g., "I want cocaine", "amount willing to pay", "bad drug effects" cluster, and the "drug quality ratings" cluster), the direction of these phase differences shifted when the dose was raised from 12 mg to 25 mg. It is unclear why this shift occurred, but one can speculate that the improved dysphoric mood following 25 mg cocaine during the luteal phase, including a reduction in ratings on the "bad drug effects" cluster and the "on edge/miserable" cluster, may have resulted in the corresponding positive increases following this dose for the "drug quality ratings" cluster, "amount willing to pay", and "I want cocaine."

In the present study, women had remarkably regular menstrual cycles ranging from 21 days to 35 days, and all menstrual cycles were ovulatory, based on urinary ovulation kits and hormonal assays of estradiol and progesterone. Based on the preclinical literature, we had anticipated that female cocaine abusers would have had abnormal menstrual cycles. Several studies have shown that chronic cocaine use disrupts various aspects of the estrous cycle in rodents (King et al. 1990, 1993; Chen and Vandenbergh 1994; Quiñones-Jenab et al. 2000a; but see Booze et al. 1999) and the menstrual cycle in nonhuman primates (Mello et al. 1997; Potter et al. 1998, 1999) and humans (Mello 1998). In the present study, women reported spending approximately US $400 per week on cocaine and using it 3–4 days each week. It is possible that this level of cocaine use is not sufficient to disrupt the menstrual cycle. While disruptions of the menstrual cycle by cocaine have been viewed as a limitation in conducting these types of studies in humans (Sofuoglu et al. 1999), the largest difficulty posed in the present study was the recruitment of female cocaine abusers.

Despite the strengths of the present study, there were several limitations. First, the smoking procedure was not standardized with respect to controlling puff duration and inhalation duration. Thus, it is possible that similar cocaine plasma levels were obtained across the phases of the menstrual cycle due to women titrating the smoked cocaine. Second, only a limited number of blood samples were collected to determine cocaine plasma levels. Differences in plasma samples might have been observed if more frequent samples had been collected. However, two other studies have also failed to show differences in cocaine plasma levels between the follicular and luteal phases of the menstrual cycle following both smoked (Sofuoglu et al. 1999) and i.v. (Mendelson et al. 1999) cocaine. Last, since women were allowed to refuse doses, not all cocaine doses were administered. However, for each cocaine dose condition, there were no differences in the number of cocaine doses administered dur-

ing each menstrual cycle phase. Moreover, the only dose for which females did not receive the majority of doses (5–6) was when placebo was available.

The present findings are somewhat consistent with the preclinical literature that documents increased behavioral effects during estrus compared with other phases of the estrous cycle following stimulant administration (Becker and Cha 1989; Roberts et al. 1989; Lynch et al. 2000) and that the response to stimulants is attenuated in ovariectomized female rodents (Becker et al. 1982; Camp et al. 1986; Roberts et al. 1987; Haney et al. 1994; Sircar and Kim 1999). While much of the preclinical evidence supporting the role of estradiol in the enhanced behavioral effects of stimulants comes from studies that have exogenously administered estradiol to ovariectomized rats (Castner et al. 1993; Grimm and See 1997; Sircar and Kim 1999; Sell et al. 2000), both estradiol and progesterone levels are relatively low during estrus and actually peak during proestrus (Butcher et al. 1974; Smith et al. 1975). In a recent study by Quiñones-Jenab et al. (2000b), a single injection of cocaine to ovariectomized female rats pretreated with estrogen and progesterone showed an attenuation in cocaine-induced locomotor activity compared with female rats pretreated with estrogen, suggesting that progesterone may also be involved by inhibiting or attenuating the effects of estradiol.

Based on the limited human data available, including the present study, in the presence of estradiol and in the absence of progesterone (i.e., the follicular phase), the effects of cocaine or amphetamine appear to be increased compared with the luteal phase when both estradiol and progesterone levels are high. While these data suggest that the increased response is due to estradiol, the evidence supporting this in humans is not clear cut. In one study, Justice and de Wit (1999) found that the increased response to amphetamine was related to estradiol levels during the follicular phase but not the luteal phase. In fact, during the luteal phase, they found no relationship between the response to amphetamine and the estradiol level, progesterone level, or ratio of estradiol to progesterone levels. However, a subsequent study from the same laboratory (Justice and de Wit 2000a) found minimal differences in response to amphetamine between the early and late follicular phases of the menstrual cycle despite significantly higher estradiol levels during the late follicular phase. Further, exogenously administered estradiol during the follicular phase produced minimal changes in the response to amphetamine (Justice and de Wit 2000b). There is also suggestive evidence that the presence of progesterone may mask the effects of estradiol during the luteal phase. In the study by Sofuoglu et al. (1999), ratings of "high" appeared similar following smoked cocaine in men and in follicular phase women, but were significantly lower in luteal phase women than in follicular phase women.

At this time, it is unclear whether the increases in response to stimulants in females are due to estradiol and/or whether progesterone decreases the response to stimulants. Clearly the interactions between estradiol and progesterone are complex and future studies in humans need to address the possible mechanism underlying these menstrual cycle differences in response to cocaine.

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