Published in final edited form as:
Horm Behav. 2011 February ; 59(2): 227–235. doi:10.1016/j.yhbeh.2010.12.009.

The Effects of Oral Micronized Progesterone on Smoked Cocaine Self-Administration in Women

Stephanie Collins Reed, **Suzette M. Evans**, **Gillinder Bedi**, **Eric Rubin**, and **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 120, New York, NY 10032 USA

Abstract

There are currently no FDA-approved pharmacotherapies for cocaine abuse. Converging preclinical and clinical evidence indicates that progesterone may have potential as a treatment for cocaine-abusing women, who represent a growing portion of cocaine users. We have previously shown that oral progesterone reduced the positive subjective effects of cocaine in female cocaine users during the follicular phase of the menstrual cycle, when endogenous progesterone levels were low. To extend these findings, the present study assessed the effects of oral progesterone (150 mg BID) administered during the follicular phase on smoked cocaine self-administration in women relative to the normal follicular and luteal phases. Healthy, non-treatment seeking female cocaine smokers (N = 10) underwent three 4-day inpatient stays, during: 1) a normal follicular phase; 2) a normal luteal phase; and 3) a follicular phase when oral progesterone was administered. During each stay, participants completed 4 self-administration sessions in which they first smoked a sample dose of cocaine (0, 12, 25 or 50 mg) and then had 5 opportunities at 14-minute intervals to self-administer that dose at a cost of $5 per dose. Expected cocaine dose effects on self-administration, subjective effects, and cardiovascular effects were observed. However, there was no effect of oral progesterone administration or menstrual cycle phase on cocaine self-administration. Thus, oral progesterone was not effective in reducing cocaine use in women under the current conditions. However, based on previous literature, further research assessing the role of oral progesterone for the treatment of cocaine dependence in women is warranted.

Keywords

cocaine; cardiovascular effects; humans; progesterone; menstrual cycle; self-administration; subjective effects; women

Introduction

Cocaine abuse continues to be a prominent public health problem, with an estimated 1.9 million current cocaine users in the United States (SAMHSA, 2009). Although cocaine abuse remains more prevalent among men, the gender gap is narrowing (SAMHSA, 2008).

*Corresponding author. Tel.: +1 212 5435181; fax: +1 212 5436018, sc2432@columbia.edu (S.C. Reed).

Based on the 2006 Treatment Episode Data Set (TEDS) the majority (71%) of all cocaine treatment admissions were for smoked cocaine, and of those, 42% were women (SAMHSA, 2008). Women exhibit more rapid progression from initiation of use to cocaine dependence (O Brien & Anthony, 2005; Ridenour et al., 2005), are more likely to be dependent on cocaine (Wu et al., 2010), and have poorer treatment outcomes than men (Tuchman, 2010). For instance, women drop out of treatment (Siqueland et al., 2002: Sayre et al., 2002) and relapse to cocaine use (Hyman et al., 2008) earlier than men. These findings highlight the need for better treatment strategies for cocaine-abusing women.

Numerous studies have shown that, in laboratory animals, females are more vulnerable to the behavioral effects of cocaine than are males (e.g., Carroll et al., 2002, Hu et al., 2004; Hecht et al., 1999; Lynch & Carroll, 1999; Roberts et al., 1989). Many of these sex differences are due, in part, to fluctuations in gonadal hormones (Becker et al., 2001; Carroll et al., 2004; Festa & Quiñones-Jenab, 2004; Becker & Hu, 2008). For instance, during the rat estrus phase of the estrous cycle, when progesterone levels are minimal, females work harder to self-administer cocaine (Roberts et al., 1989; Hecht et al., 1999), show greater disruptions in the regulation of cocaine self-administration (Lynch et al., 2000), and show greater cocaine-seeking behavior (Feltenstein & See, 2007) than they do during other phases of their cycle. More recently, several preclinical studies have shown that progesterone administration reduces the reinforcing effects of cocaine, and may reduce reinstatement of drug-self administration (relapse), particularly in female rats (Frye, 2007; Evans & Foltin, 2010; Anker & Carroll, 2010a; Hudson & Stamp, 2010). For example, progesterone attenuated cocaine-induced increases in locomotor activity (Niyomchai et al., 2006), cocaine-induced conditioned place preference (Russo et al., 2008), reinstatement of cocaine-seeking behavior (Anker et al., 2007; Feltenstein et al., 2009), and cocaine self-administration (Jackson et al., 2006; Larson et al., 2007) in female rats. In contrast, progesterone failed to reduce cocaine-induced locomotor activity or conditioned place preference in male rats (Russo et al., 2010). Similarly, an active metabolite of progesterone, allopregnanolone, reduced both cocaine-induced (Anker et al., 2009) and stress-induced (Anker and Carroll, 2010b) reinstatement of cocaine seeking in female, but not male, rats.

Sex differences in response to cocaine, and the involvement of gonadal hormones in such differences, have also been demonstrated in humans and non-human primates (e.g., Lynch et al., 2002; Mello & Mendelson, 2002; Terner & de Wit, 2006; Carroll & Anker, 2010; Evans & Foltin, 2010). However, existing evidence on the effects of progesterone on cocaine in humans is limited (Evans, 2007; Anker & Carroll, 2010a). In a previous study (Evans & Foltin, 2006), we showed that oral micronized progesterone attenuated the positive subjective effects of smoked cocaine in women, but not in men. Two studies by Sofuoglu and colleagues have also demonstrated that oral progesterone reduced some subjective effects of smoked cocaine in women (Sofuoglu et al., 2002) and intravenous (i.v.) cocaine in a mixed male and female sample (Sofuoglu et al., 2004).

In combination, these findings in laboratory animals and humans suggest that progesterone may have potential as a treatment for cocaine abuse, particularly in women. However, although oral progesterone has been shown to attenuate the positive subjective effects of cocaine, particularly in women, it remains unclear whether progesterone administration would also decrease cocaine use in humans. Similar to cocaine self-administration procedures used in laboratory animals, human cocaine self-administration studies can assess both the reinforcing effects of cocaine and the ability of potential pharmacotherapies to reduce cocaine taking (e.g., Haney, 2009; Haney & Spealman, 2008). This is important because the effect of a medication on self-reported cocaine craving or the subjective effects of cocaine may differ from its ability to decrease cocaine self-administration in the laboratory or in clinical applications (e.g. Haney et al., 1998, 2005, 2006; Hart et al., 2004,

2006). Moreover, the effect of medication on self-administration in the laboratory has good predictive validity with regards to efficacy in the clinic (see Haney, 2009). Only one study has assessed whether oral progesterone alters cocaine self-administration in the laboratory in humans (Sofuoglu et al., 2004) and one other study has evaluated its efficacy in a clinical setting (Sofuoglu et al., 2007). In the laboratory study, although oral progesterone (200 mg) reduced subjective ratings of high , participants self-administered the same number of i.v. cocaine doses regardless of whether they were pretreated with progesterone or placebo. There were no reported differences between men (n = 6) and women (n = 4; Sofuoglu et al., 2004). In addition, the one placebo-controlled clinical trial undertaken to date failed to show that oral progesterone (600 mg/day) was more effective than placebo for reducing cocaine use among opioid- and cocaine-abusing men maintained on methadone (n = 45; Sofuoglu et al., 2007). Both of these studies used either a mixed-gender sample or only men; it therefore remains unknown whether oral progesterone would decrease cocaine use in a sample of cocaine-abusing women.

The purpose of the present study was to extend the findings of our previous study (Evans & Foltin, 2006) to determine whether oral progesterone administration would not only reduce the positive subjective effects of cocaine, but would also decrease cocaine self-administration using a cocaine self-administration procedure developed in our laboratory. Since existing literature suggests that progesterone is more effective at altering the behavioral effects of cocaine in females than in males, this study was conducted only in a sample of non-treatment seeking cocaine-abusing women. We used a design similar to our previous study (Evans & Foltin, 2006); women were tested twice in the follicular phase (once in the presence of oral micronized progesterone and once during a normal follicular phase) and once in the normal midluteal phase of the menstrual cycle. A full dose-response function of smoked cocaine (0, 12, 25 and 50 mg cocaine base) was assessed during each phase. Further, since a previous study (Hart et al., 2008) demonstrated that modafinil significantly reduced cocaine self-administration when participants had to purchase the cocaine doses with their own study earnings, this methodological modification to our previous laboratory self-administration procedures (e.g., Evans et al., 1998; Haney et al., 2006) was used in the present study. We hypothesized that cocaine self-administration and the subjective and cardiovascular effects of cocaine would be 1) lower in the normal luteal phase compared to the normal follicular phase and 2) within the follicular phase, attenuated by oral progesterone compared to placebo.

Methods

Participants

Ten female research volunteers (9 Black and 1 Native American), 36 43 (mean = 41) years of age, with current reports of smoking cocaine were solicited through newspaper advertisements in New York, NY. Females reported currently spending an average of $258 per week on cocaine (range of $65 450/week), currently smoking cocaine an average of 5 days each week (range of 3 7 days/week), and smoking cocaine for an average of 19 years (range of 7 25 years). Seven women reported smoking tobacco cigarettes, an average of 7 cigarettes/day. Women had a mean education level of 12 years (range of 10 14 years) and a mean body mass index (BMI) of 27 (range of 18 - 35). All participants were medically healthy based on a physical examination, electrocardiogram, chest X-ray, complete blood chemistries (including pseudocholinesterase levels), and urinalysis. None of the participants were using hormonal contraceptives, or any other prescription medication. Participants were not pregnant (based on blood pregnancy tests) or nursing, nor had they undergone an abortion or been pregnant within the previous 6 months. All participants had normal menstrual cycles. Psychiatric status was assessed with the structured clinical interview for DSM-IV Axis I disorders (SCID I; First et al., 1994). No participants suffered from

premenstrual dysphoric disorder or other major mood or anxiety disorders. None were receiving psychiatric treatment or seeking treatment for their drug use.

Each participant signed a consent form, approved by the Institutional Review Board of the New York State Psychiatric Institute (NYSPI). The consent form described the study, outlined possible risks, and indicated that during inpatient phases, there would be opportunity for cocaine self-administration, possibly on a daily basis. Participants were paid for their participation at the end of the study in multiple weekly payments of up to $300 each week.

Design and Experimental Procedures

Participants were informed that the purpose of the study was to assess the effects of the hormone progesterone on their response to smoked cocaine at different phases of the menstrual cycle. After providing informed consent, all participants began filling out daily rating forms as outpatients (see Evans et al., 1998 for details); they were paid to report to the laboratory twice a week to return completed forms and collect new forms. This ensured consistent outpatient contact and allowed us to monitor the menstrual cycle for accurate timing of inpatient phases. Using the forms, participants reported on various aspects of daily mood and physical symptoms known to vary across the menstrual cycle and indicated whether or not they were menstruating. Participants were 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 instructed to notify the research nurse when menstruation started. During the midfollicular phase, participants provided daily urine samples to determine the time of ovulation using OvuQuick® (QUIDEL Corp., San Diego, CA; Martini et al, 1994). This 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 midluteal admission.

Participants were admitted to the NIH-funded Irving Institute for Clinical and Translational Research for the inpatient phases. While residing on the Clinical Research Center, participants had a private room with access to television, radio, and video-taped movies; they were not permitted to leave the unit unless accompanied by a staff member. Participants who smoked tobacco cigarettes were allowed to smoke as normal throughout each inpatient stay, with the exception that cigarette smoking was not allowed during experimental sessions, which lasted approximately 2.5 h each. Participants were admitted to the unit for 4 days (3 nights) on 3 separate occasions. Two inpatient admissions were scheduled during the follicular phase such that cocaine self-administration sessions occurred between 6 10 days after the onset of menstruation. One follicular phase was normal (elevated estradiol and negligible progesterone levels), and the other follicular phase was modified to mimic a mid-luteal phase by administering oral micronized progesterone (here referred to as the PROG phase). The third inpatient admission was scheduled during a normal mid-luteal phase (approximately 7 12 days after ovulation, as indicated by the urinary ovulation tests) characterized by elevated estradiol and progesterone levels. Starting the day following each inpatient admission, participants engaged in laboratory cocaine self-administration sessions twice each day for 2 days. They were discharged on the fourth inpatient day.

Progesterone Dosing

We selected a dose of 150 mg progesterone because that dose produced progesterone levels similar to natural mid-luteal levels in our previous study (8.2 vs. 7.4 ng/ml, respectively; Evans & Foltin, 2006). Oral micronized progesterone was compounded and provided free of charge by the Women s International Pharmacy (Madison, WI) as 50 mg capsules. Steady-state serum levels of progesterone are reached after the second dose of this formulation (de

Lignières, 1999). Therefore, during each inpatient phase, participants were administered 150 mg oral micronized progesterone or matching placebo capsules at 2300 h on the evening before the first cocaine session. Then, on the next 2 consecutive days, participants were administered 150 mg oral micronized progesterone or matching placebo capsules at 0700 and 1100 h, approximately 2 h before each cocaine session, because oral micronized progesterone levels peak in 1 3 h (Simon et al., 1993). Although the mean terminal half-life for doses between 100 300 mg oral micronized progesterone is between 16 18 h (Simon et al., 1993), dosing was done before each session since some studies have shown that progesterone levels can start declining within 4 h after administration (Maxson & Hargrove, 1985).

Experimental Sessions

During each inpatient phase, cocaine self-administration sessions occurred at 0900 h and again at 1300 h on 2 consecutive days, for a total of 4 sessions. During experimental sessions, participants were seated in the research laboratory in a comfortable lounge chair facing a computer monitor on which subjective-effects questions were displayed. A computer mouse was used for completion of subjective-effects questionnaires. An 18-gauge catheter (Quik-Cath®, Travenol Laboratories, Deerfield, IL) was inserted into a subcutaneous vein in one arm for blood collection. An electrocardiogram was continuously monitored via chest electrodes (MAC PC_S, Marquette Electronics, Milwaukee, WI), while heart rate and blood pressure were recorded every 2 min (Sentry IIFModel 6100 automated vital signs monitor, NBS Medical, Costa Mesa, CA) beginning 20 min prior to drug administration. A Macintosh computer located in an adjacent room was used for automated data collection.

Each cocaine self-administration session began with baseline vital signs starting at −20 min and baseline subjective-effects questionnaires at −10 min. At the start of each session, participants were provided with $25 from their study earnings (five $5 bills, one for each choice opportunity). After smoking the sample dose of cocaine base (0, 12, 25, or 50 mg) available that session, participants were given five opportunities, at 14-min intervals, to purchase for self-administration the same dose of cocaine as the sample dose, at a cost of $5 per dose. The outcome measure for self-administration was the number of cocaine doses purchased during each cocaine session. Money used to purchase cocaine was deducted from participants total study earnings at the end of the study. The dose order within each phase was randomized and the dose order across phases was not identical for a given individual. Pretreatment during the follicular phases (placebo or oral progesterone) was counterbalanced across participants. Order of menstrual cycle phase varied among participants.

Volatization of the cocaine base was accomplished by the nurse holding the flame from a pipe lighter on the cocaine in the glass stem. Participants were instructed to take one large inhalation and to hold the inhalation as long as they normally would outside of the laboratory. Participants were blindfolded during cocaine administration so they could not see the size of the cocaine dose. When 0 mg cocaine (placebo) was administered, a flame was applied to an empty glass stem and participants inhaled warm air.

Throughout the session, subjective-effects questionnaires (described below) were administered 4 min following delivery of each selected option (cocaine or $5) and 15 min following the last selected option of the session. Cocaine was not given on any trial for which any cardiovascular measure exceeded our criteria for safe drug administration (systolic pressure > 160; diastolic pressure > 100 or a heart rate ≥ 220 - subject age x 0.85, sustained for more than 6 min prior to the next scheduled dose administration). Also, participants understood that they could always refuse a cocaine dose. During all sessions, a

research nurse and a physician located in the adjacent room continuously monitored participants via a one-way mirror. Participants could communicate with staff via an intercom system.

In each session, blood was drawn at baseline (i.e., before administration of the first cocaine dose each session) to verify progesterone and estradiol levels and menstrual cycle phase.

Subjective-Effects Questionnaires

A computerized questionnaire was completed repeatedly throughout each session: at baseline, 4 min after the sample dose, 4 min after each selected option (cocaine or $5), and 15 min after the last selected option (cocaine or $5). The questionnaire consisted of a series of 100 mm visual analog scales (VAS) labeled not at all (0 mm) at one end and extremely (100 mm) at the other end. Twenty VAS items were scored into five clusters, based on previous factor analysis (e.g., Evans et al., 2002). Bad drug effect consisted of seven items related to negative drug effects (e.g., bad drug effect , anxious), self-esteem consisted of five items (e.g., self-confident , friendly), focused/calm consisted of two items (calm and able to concentrate), good drug effect consisted of three items (high , good drug effect , and stimulated), and drug quality consisted of three items related to the cocaine dose the participant had just received (drug quality , drug potency , and drug liking). Three VAS were used to operationalize drug craving, and were labeled I want& , & cocaine , & alcohol , and & nicotine . A final question asked participants How much would you pay for the dose you just received? with a range of $0 25.

Drugs

Cocaine base, derived from cocaine hydrochloride (provided by The National Institute on Drug Abuse) as described in Foltin et al. (1990), was prepared by the NYSPI research pharmacy. Oral micronized progesterone and matching placebo capsules were provided by the Women s International Pharmacy. Progesterone capsules contained 50 mg each of micronized progesterone suspended in olive oil and the placebo capsules contained lactose suspended in olive oil. Participants were administered three capsules (total of 150 mg) at each dosing time (described above).

Hormone Assays

Each experimental day, before cocaine administration, venous blood (approximately 6 ml) for estradiol and progesterone levels was drawn from an indwelling catheter into tubes containing SST® gel and clot activator. Samples were centrifuged within 30 min of collection, yielding approximately 3ml of plasma, and stored frozen until the time of analysis. Estradiol and progesterone 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) using a commercial solid-phase, chemiluminescent immunoassay (Immulite, Diagnostic Products Co., DPC, Los Angeles, CA). For estradiol, the assay sensitivity was 4 pg/ml and the intra- and interassay coefficients of variation were 4.3 and 10.5%. For progesterone, the assay sensitivity was 0.2 ng/ml and the intra- and interassay coefficients of variation were 4.8 and 9.1%.

Data Analysis

From the vital signs collected every 2 min throughout the session, mean heart rate, systolic pressure, and diastolic pressure, were collected and averaged for 8 min epochs 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 averaged measurements within a session. Similarly, responses for each VAS were averaged for eight epochs within a session. Each

cardiovascular measure, the five VAS clusters (described above) and ratings of I want cocaine, I want nicotine, I want alcohol, and willing to pay were analyzed separately.

Because participants varied in how much cocaine was self-administered in any given session, the subjective and cardiovascular effects of the sample dose of cocaine (which was administered to all participants each session) were analyzed separately from the effects of the self-administered cocaine. Subjective and cardiovascular effects measured at baseline and after administration of the sample doses of cocaine (expressed as a change from baseline) were analyzed by two-factor repeated-measures analyses of variance (ANOVA) with phase as the first factor (follicular, PROG, luteal) and dose as the second factor (0, 12, 25, or 50 mg cocaine). Cocaine self-administration (number of doses purchased) was also analyzed using a two-factor phase by dose repeated-measures analysis of variance (ANOVA). Subjective and cardiovascular effects measured during cocaine self-administration sessions (expressed as a change from baseline) were analyzed using three-factor repeated-measures ANOVAs with phase as the first factor, dose as the second factor, and time within the session as the third factor. However, upon analysis, there was little effect of time on subjective and cardiovascular effects. Thus for clarity, only the effects of dose and phase are presented here. For all of the measures, planned comparisons were conducted to compare the effects of 1) the follicular phase to the PROG phase and 2) the follicular phase to the luteal phase for each cocaine dose (collapsed across time for the subjective and cardiovascular self-administration data, e.g. 2 comparisons at each dose), regardless of the significance of the 3-way interaction.

Progesterone and estradiol levels were analyzed separately using a one-way ANOVA with phase as the factor. Planned comparisons were conducted to compare hormone levels across the phases, as described above.

For all analyses, results were considered statistically significant if $p \leq 0.01$, using Huynh Feldt corrections as a conservative measure to control for potential violation of the sphericity assumption.

Results

Hormone Levels

All women had normal ovulatory menstrual cycles ranging from 24 to 35 days (mean 29 days). Further, the dosing regimen of oral micronized progesterone used in the present study (5 doses of 150 mg micronized progesterone over a 3-day period) did not result in a single incident of breakthrough bleeding, nor did it disrupt normal menstrual cycle function.

Hormone levels indicated that participants were tested in the appropriate menstrual phases and that the oral progesterone dosing produced expected progesterone levels. There was a phase effect for estradiol levels [$F(2,18) = 5.70$, $p = 0.01$], with estradiol significantly higher in the luteal phase compared to either the follicular ($p = 0.009$; only p-values will be presented for planned comparisons) or PROG phase ($p = 0.01$), and no differences in estradiol levels between the PROG and follicular phases ($p = 0.82$). As shown in Figure 1, there was also a phase effect for progesterone levels [$F(2,18) = 0.17$, $p = 0.0002$], with significantly higher progesterone levels in the PROG phase ($p = 0.0006$) and the luteal phase ($p = 0.0001$) compared to the follicular phase. There were no differences in progesterone levels in the PROG phase compared to the luteal phase.

Baseline Differences

There were no significant baseline phase effects on any cardiovascular or subjective measures ($p s \geq 0.01$).

Effects of the Sample Dose of Cocaine

No sample cocaine doses were withheld due to elevated cardiovascular activity during baseline. Figure 2 shows that the sample dose of cocaine produced expected dose-dependent increases in heart rate [$F(3,27) = 47.19$, $p = 0.0001$]. Although a planned comparison revealed that cocaine-induced heart rate increases were marginally lower in the PROG phase than the follicular phase following 50 mg smoked cocaine ($p = 0.08$), there was no significant main phase effect ($p \geq 0.01$). Similarly, the sample dose of cocaine produced dose-dependent increases in systolic pressure [$F(3,27) = 28.73$, $p = 0.0001$] and diastolic pressure [$F(3,27) = 25.97$, $p = 0.0001$], but there were no significant phase effects (p s≥ 0.01).

Figure 3 shows that the sample dose of cocaine produced dose-dependent increases on the good drug effect cluster [$F(3,27) = 30.98$, $p = 0.0001$] and drug quality cluster [$F(3,27) = 39.06$, $p = 0.0001$] scores. Planned comparisons revealed that there was a trend for the 25 mg sample cocaine dose to produce greater increases in both good drug effect ($p = 0.03$) and drug quality cluster ($p = 0.02$) scores during the luteal phase compared to the follicular phase. No differences were observed on good drug effect and drug quality cluster scores between the follicular phase and PROG phase in response to any cocaine dose (p s≥ 0.01). Ratings of willing to pay [$F(3,27) = 20.37$, $p = 0.0001$] were also dose-dependently increased after the sample dose of cocaine (an average of $11 ± 1 for a single 50 mg cocaine dose) and there was a trend for ratings of I want cocaine to be increased after cocaine ($F(3,27) = 5.50$, $p = 0.03$), but no phase effects were observed for either measure (p s≥ 0.01; data not shown). There were no significant effects of cocaine dose or phase on bad drug effect, focused/calm or self-esteem cluster scores or on ratings of I want nicotine or I want alcohol (p≥;s 0.01; data not shown).

Effects of Cocaine Self-Administration

No cocaine doses purchased for self-administration had to be withheld due to elevated cardiovascular activity. Figure 4 shows that active cocaine was self-administered significantly more than placebo cocaine ($F(3,27) = 37.06$, $p = 0.0001$); participants purchased an average of 3.4 (± 0.3) doses of 12 mg cocaine, 4.3 (± 0.2) doses of 25 mg cocaine and 4.0 (± 0.2) doses of 50 mg cocaine. However, there was no effect of phase on the number of cocaine doses chosen for self-administration ($p \geq 0.01$).

Figure 5 shows heart rate (mean change from baseline) during cocaine self-administration as a function of phase and cocaine dose as an example of vital sign changes during cocaine self-administration. Similar to after the sample doses of cocaine, self-administered cocaine dose-dependently increased systolic pressure ($F(3,27) = 65.72$, $p = 0.0001$), diastolic pressure ($F(3,27) = 37.67$, $p = 0.0001$) and heart rate ($F(3,27) = 53.82$, $p = 0.0001$). However, there were no effects of phase on any cardiovascular measure ($p \geq 0.01$).

Similar to the sample dose of cocaine, self-administered cocaine dose-dependently increased good drug effect cluster ($F(3,27) = 65.72$, $p = 0.0001$) and drug quality cluster ($F(3,27) = 28.64$, $p = 0.0001$) scores (Fig. 6), as well as ratings of I want cocaine ($F(3,27) = 14.24$, $p = 0.0001$) and willing to pay ($F(3,27) = 12.79$, $p = 0.0002$), but there was no effect of phase on any of these subjective effect scores or ratings (p s≥ 0.01). With regards to the other subjective measures during cocaine self-administration, there was no significant effect of phase or cocaine dose on bad drug effect and focused/calm or self-esteem cluster scores or on ratings of I want nicotine or I want alcohol (p s≥ 0.01; data not shown).

Discussion

Cocaine Self-Administration

To our knowledge, this is the first study to comprehensively assess the effects of oral micronized progesterone on the self-administration of a range of doses of smoked cocaine in women. As expected, active smoked cocaine was self-administered more than placebo, and this effect was dose dependent. Based on previous studies showing that the positive subjective effects of cocaine were lower in the luteal phase (Evans et al., 2002; Evans & Foltin, 2006; Sofuoglu et al., 1999) and after oral progesterone pretreatment during the follicular phase (the PROG phase; Evans & Foltin, 2006; Sofuoglu et al., 2002) compared to the normal follicular phase, we hypothesized that cocaine self-administration would also be lower in the luteal and PROG phases compared to the follicular phase. Contrary to our hypothesis, women self-administered a similar amount of cocaine during the luteal phase, the follicular phase, and the PROG phase. Only one other study has examined the effects of oral progesterone on cocaine self-administration in the laboratory; Sofuoglu et al. (2004) found that self-administration of 0.3 mg/kg i.v. cocaine was not altered by oral progesterone pretreatment in male and female cocaine users (nor was there a sex difference in cocaine self-administration). Although that research group used: (1) a different route of cocaine administration; (2) a slightly higher dose of oral progesterone pretreatment (400 mg/day vs. 300 mg/day, respectively); and (3) a mixed gender sample, our findings were similar. Thus, although oral progesterone has previously been shown to reduce the subjective effects of cocaine, it did not alter smoked cocaine self-administration in women in the present study.

There are a number of possible explanations for the lack of effect of oral progesterone on cocaine self-administration. First, only a moderate dose of progesterone was examined and higher doses may be necessary to decrease cocaine self-administration. However, as noted above, a slightly higher dose of progesterone (400 mg/day) did not alter i.v. cocaine self-administration (Sofuoglu et al., 2004) nor did 600 mg/day oral progesterone reduce cocaine use among men maintained on methadone (Sofuoglu et al., 2007). Second, the present study examined cocaine-abusing women who were not interested in treatment for their cocaine use. Therefore, it remains unknown whether maintenance on higher doses of oral progesterone would reduce cocaine use among a sample of treatment-seeking cocaine-dependent women.

The cocaine self-administration procedure used may have hindered the ability of progesterone to reduce cocaine choice in the laboratory. Several studies have shown that it is difficult to reduce self-administration of larger doses of cocaine, such as the 25 and 50 mg cocaine doses used in the current study (Haney, 2009). However, a previous study (Hart et al., 2008) conducted in our laboratory showed that maintenance on modafinil significantly decreased cocaine self-administration when participants had to purchase the doses of cocaine with their own study earnings. The same procedure was used in the present study since we expected that women would be less inclined to use their study earnings to purchase cocaine (women often report that they do not buy all the cocaine they use outside of the laboratory and they use money earned in research studies to help with standard living expenses). Regardless, women purchased the majority of cocaine doses at the 25 and 50 mg doses.

It is possible that a cost of $5/cocaine dose was not economically challenging enough for this population of non-treatment seekers; progesterone may have decreased cocaine self-administration if the cost to buy cocaine had been greater. Unfortunately, previous laboratory studies that have examined altering the cost of cocaine have shown little evidence that increasing costs reduces cocaine self-administration (e.g., Walsh et al., 2001; Donny et al., 2003). Alternatively, we may have observed a change in self-administration if there had

been an immediate and tangible alternative to taking cocaine: study earnings were not given to participants until they completed the entire study. Thus, during the 2-hr cocaine self-administration sessions, the immediate choice was to purchase the doses of cocaine or choose nothing. An immediate alternative such as a game of chance (Vosburg et al., 2010), vouchers (e.g., Higgins et al., 1994; Hart et al., 2000), or actual money (Stoops et al., 2010) may have been more effective at decreasing cocaine self-administration, and may more closely mimic the demands of the natural ecology, where individuals may have the option of undertaking other activities instead of using cocaine.

As in most cocaine self-administration studies in humans (e.g., Hart et al., 2008; Sofuoglu et al., 2004), in the current study the sample dose of cocaine was given shortly before participants had the opportunity to self-administer cocaine, and thus the sample dose effectively acted as a prime for taking subsequent doses. This is supported by data obtained in laboratory animals, which has long shown that a priming dose of cocaine influences subsequent responding for placebo under extinction conditions (e.g., Stewart, 1983; Lynch & Carroll, 2000; Leri & Stewart, 2001; Highfield et al., 2002). Thus, once participants sampled the initial cocaine dose and were primed, this may have increased the likelihood that they would then self-administer additional doses, particularly in the absence of alternatives (Haney, 2009). To eliminate this priming effect, it may be necessary to administer the sample cocaine dose several hours or the day before the self-administration session.

Further, in the current study, the sample cocaine dose and the choice to self-administer subsequent cocaine doses took place in the same environment, with all the cues (e.g., room, staff, monitoring equipment, cocaine smoking paraphernalia) associated with cocaine smoking in the laboratory. The environment and/or the cues associated with cocaine use can influence a range of behaviors during subsequent exposures to that environment in rats (e.g., Robinson et al., 1998; Leyton, 2007) and humans (e.g., Nagoshi et al., 1992; Foltin & Haney, 2000; Volkow et al., 2008; but see Rothman et al., 1994; Reed et al., 2009). Although a medication effect may be more apparent if participants choose whether or not to self-administer cocaine in an environment separate from, and not associated with, previous cocaine consumption (Haney, 2009), this would limit external validity since a treatment medication should also be effective in the presence of cocaine-associated stimuli. Taken together, any one, or a combination, of the above factors likely played a role in the failure to observe a reduction in cocaine self-administration in the present study.

Subjective and Cardiovascular Effects

Contrary to our hypothesis, oral progesterone did not attenuate the positive subjective effects of cocaine and, overall, there were no differences between the normal follicular and luteal phases. These findings also contrast with previous studies conducted in our laboratory and by others demonstrating that the positive subjective effects of cocaine were lower in the luteal phase (Sofuoglu et al., 1999; Evans et al., 2002; Evans & Foltin, 2006; but see Lukas et al., 1996; Mendelson et al., 1999; Collins et al., 2007) and after oral progesterone (Sofuoglu et al., 2002, 2004; Evans & Foltin, 2006) compared to the follicular phase in women (Evans & Foltin, 2010). The most parsimonious explanation for the inconsistencies between this study and previous studies with smoked cocaine is that in this study, participants had a single fixed sample dose of cocaine and then self-administered subsequent doses of cocaine, whereas in previous smoked cocaine studies a fixed-dosing design was used (Evans et al., 2002; Evans & Foltin, 2006; Sofuoglu et al., 2002). The lack of effect of oral progesterone on the single fixed cocaine dose effects in the current study is supported by a similar absence of an oral progesterone pretreatment effect on the first fixed dose of cocaine in our previous study (Evans & Foltin, 2006); the significant effects in our previous study were only apparent after repeated fixed doses of cocaine. In addition, the fact that

participants actively chose (purchased) subsequent cocaine doses after the sample dose, and were anticipating all of the expected effects of cocaine, may have overridden the ability of progesterone (either endogenous or orally administered) to attenuate cocaine s effects.

As expected, cocaine increased cardiovascular effects, but there were no differences in cocaine-induced cardiovascular measures between the follicular and luteal phases. In contrast, our previous studies did observe differences in cocaine-induced cardiovascular effects between the follicular and luteal phases (Evans et al., 2002; Evans & Foltin, 2006). Considering that the participants and much of the methodology, other than the dosing paradigm, were nearly identical to our previous studies (Evans et al., 2002; Evans & Foltin, 2006), it is likely that the inconsistent findings were again due to using the self-administration procedure as opposed to fixed dosing procedure in the previous studies. Other studies, often using different routes of cocaine administration, have failed to observe a difference in cocaine-induced cardiovascular effects between these two phases of the menstrual cycle (Lukas et al., 1996; Mendelson et al., 1999; Sofuoglu et al., 1999; Collins et al., 2007). Thus, the effect of menstrual cycle phase on cardiovascular responses to cocaine requires further investigation.

There was also no effect of oral progesterone pretreatment on cocaine-induced cardiovascular effects in the current study. Similarly, Sofuoglu and colleagues found that progesterone did not alter cocaine-induced heart rate in women after 3 fixed doses of 0.4 mg/kg smoked cocaine (Sofluoglu et al., 2002) or after a sample dose of 0.3 mg/kg i.v. cocaine (Sofluoglu et al., 2004). However, in our previous study, oral progesterone attenuated cocaine-induced heart rate after 6 fixed doses of 25 mg smoked cocaine in women (Evans & Foltin, 2006). As discussed above, oral progesterone may produce different effects on cocaine s cardiovascular response depending on what dosing procedure is used.

Strengths and Limitations

This study had a number of strengths. Laboratory studies of pharmacotherapies such as this study are important because they provide preliminary tolerability and safety data of the putative pharmacotherapy, as well as often have good predictive validity of efficacy in the clinic, as mentioned above. Even though the sample size was small, this is the largest laboratory study to date to examine the effects of oral progesterone on smoked cocaine self-administration in general, and in women. Further, similar to our previous study (Evans & Foltin, 2006) women were tested in different menstrual cycle phases and phases were tracked via hormone levels and daily rating forms prior to and throughout the study. Additionally, a range of self-administered cocaine doses was examined, and repeated doses of cocaine were available, reflecting common naturalistic patterns of smoked cocaine use.

As described above, the study also had limitations that may explain the lack of effect of oral progesterone on cocaine self-administration and the inability to replicate our previous findings. First, only a moderate dose of progesterone, comparable to natural mid-luteal phase levels, was tested. Second, participants were not provided any alternative to purchasing cocaine and the cost for each dose was not varied. Further, the sample dose of cocaine was administered shortly before the opportunity to buy cocaine and may have served as a strong stimulus to continue to use cocaine. This may also have led to a ceiling effect in the choice to self-administer the two highest doses of cocaine in some of the participants, although this should not preclude a decrease in cocaine self-administration by oral progesterone, as was hypothesized. In fact, we observed slight decreases in the number of choices of cocaine after oral progesterone that may have become significant with a much larger sample size and/or more drug choices. These considerations, combined with a modest medication effect, may have limited the ability to detect medication effects on cocaine self-

administration. Since medications that show both a decrease in the positive subjective effects of cocaine and a decrease in cocaine self-administration are the medications that have shown clinical efficacy to date (Comer et al., 2008), our laboratory and others are actively investigating approaches to refine current human laboratory self-administration procedures to improve the utility of these procedures in ongoing and future studies.

Conclusions

Based on the results of previous studies by our laboratory and others, oral progesterone appears to decrease some of the subjective effects of cocaine associated with its reinforcing properties. However, there has yet to be a demonstration that it reduces cocaine self-administration in humans. Despite not observing a decrease in cocaine self-administration after oral progesterone in the current study, the issues surrounding current human self-administration paradigms and the positive findings in previous studies suggest that oral progesterone warrants further exploration as a medication for cocaine abuse, particularly in women (Evans & Foltin, 2010). There is compelling preclinical evidence that progesterone may be effective in reducing cocaine self-administration and relapse in female rats (e.g., Frye, 2007; Evans & Foltin, 2010; Anker & Carroll, 2010a; Hudson & Stamp, 2010). Thus far, this has been more difficult to demonstrate in humans. Future studies should investigate higher doses of progesterone and explore variations on self-administration procedures that both better mimic the natural ecology, and remove possible hindrances to observing a reduction in drug taking. In addition, given that progesterone may decrease relapse in animal models (as discussed above) and the response to stress in humans (Childs et al., 2010) which has been suggested to lead to relapse (e.g., Sinha et al., 2006), progesterone may yet have clinical utility for reducing relapse to cocaine use in women, perhaps in combination with psychological treatments (e.g., Carroll et al., 2004).

Research highlights

Smoked cocaine self-administration did not differ across menstrual cycle phase. Oral progesterone did not alter smoked cocaine self-administration in women. Based on existing literature, additional clinical studies in females are warranted.

Acknowledgments

This research was supported by Grant Nos. R01 DA008105 (RWF) and K01 DA022282 (SCR) from the National Institute on Drug Abuse. The participants resided on the Irving Institute for Clinical and Translational Research at the Columbia-Presbyterian Medical Center, supported by Grant No. UL1-RR024156-02 from the National Institutes of Health. The authors gratefully acknowledge the expert assistance of the research and clinical staff, including Brenda Fay, R.N., Laura Burr, R.N, Alyce Stephens, R.N. and Alicia Couraud, R.N. The Women's International Pharmacy (Madison, WI) graciously provided the oral micronized progesterone and matching placebo. The cocaine self-administration data from the normal follicular and luteal phases presented here were also presented in a previously published review paper (Evans, S.M., Foltin, R.W., 2010. Does the response to cocaine differ as a function of sex or hormonal status in human and non-human primates? Horm. & Behav. 58, 13-21). The authors have no financial disclosures or conflicts of interest to report.

References

Anker JJ, Carroll ME. The role of progestins in the behavioral effects of cocaine and other drugs of abuse: human and animal research. Neurosci. Biobehav. Rev. 2010a doi: 10.1016/j.neubiorev.2010.04.003.

Anker JJ, Carroll ME. Sex differences in the effects of allopregnanolone on yohimbine-induced reinstatement of cocaine seeking in rats. Drug Alcohol Depend 2010b;107:264–267. [PubMed: 20005642]

Anker JJ, Holtz NA, Zlebnik N, Carroll ME. Effects of allopregnanolone on the reinstatement of cocaine-seeking behavior in male and female rats. Psychopharmacology 2009;203:63–72. [PubMed: 18998113]

Anker JJ, Larson EB, Gliddon LA, Carroll ME. Effects of progesterone on the reinstatement of cocaine-seeking behavior in female rats. Exp. Clin. Psychopharmacol 2007;15:472–480. [PubMed: 17924781]

Becker JB, Hu M. Sex differences in drug abuse. Frontiers in Neuroendocrinology 2008;29:36–47. [PubMed: 17904621]

Becker JB, Molenda H, Hummer DL. Gender differences in the behavioral responses to cocaine and amphetamine: implications for mechanisms mediating gender differences in drug abuse. Ann. N.Y. Acad. Sci 2001;937:172–187. [PubMed: 11458536]

Carroll KM, Fenton LR, Ball SA, Nich C, Frankforter TL, Shi J, Rounsaville BJ. Efficacy of disulfiram and cognitive behavior therapy in cocaine-dependent outpatients: a randomized placebo-controlled trial. Arch. Gen. Psychiatry 2004;61:264–272. [PubMed: 14993114]

Carroll ME, Anker JJ. Sex differences and ovarian hormones in animal models of drug dependence. Horm. Behav 2010;58:44–56. [PubMed: 19818789]

Carroll ME, Lynch WJ, Roth ME, Morgan AD, Cosgrove KP. Sex and estrogen influence drug abuse. Trends Pharmacol. Sci 2004;25:273–279. [PubMed: 15120494]

Carroll ME, Morgan AD, Lynch WJ, Campbell UC, Dess NK. Intravenous cocaine and heroin self-administration in rats selectively bred for differential saccharin intake: phenotype and sex differences. Psychopharmacology 2002;161:304–313. [PubMed: 12021834]

Childs E, Van Dam NT, de Wit H. Effects of acute progesterone administration upon responses to acute psychosocial stress in men. Exp. Clin. Psychopharmacol 2010;18:78–86. [PubMed: 20158297]

Collins SL, Evans SM, Foltin RW, Haney M. Intranasal cocaine in humans: effects of sex and menstrual cycle. Pharmacol. Biochem. Behav 2007;86:117–124. [PubMed: 17257663]

Comer SD, Ashworth JB, Foltin RW, Johanson CE, Zacny JP, Walsh SL. The role of human drug self-administration procedures in the development of medications. Drug Alcohol Depend 2008;96:1–15. [PubMed: 18436394]

de Lignières B. Oral micronized progesterone. Clin. Ther 1999;21:41–60. [PubMed: 10090424]

Donny EC, Bigelow GE, Walsh SL. Choosing to take cocaine in the human laboratory: effects of cocaine dose, inter-choice interval, and magnitude of alternative reinforcement. Drug Alcohol Depend 2003;69:289–301. [PubMed: 12633915]

Evans SM. The role of estradiol and progesterone in modulating the subjective effects of stimulants in humans. Exp. Clin. Psychopharmacology 2007;29:1889–1900.

Evans SM, Foltin RW. Exogenous progesterone attenuates the subjective effects of smoked cocaine in women, but not in men. Neuropsychopharmacology 2006;31:659–674. [PubMed: 16160708]

Evans SM, Foltin RW. Does the response to cocaine differ as a function of sex or hormonal status in human and non-human primates? Horm. Behav 2010;58:13–21. [PubMed: 19733571]

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. [PubMed: 11823892]

Evans SM, Haney M, Levin FR, Foltin RW, Fischman MW. Mood and performance changes in women with premenstrual dysphoric disorder: acute effects of alprazolam. Neuropsychopharm 1998;19:499–516.

Evans SM, Levin FR, Fischman MW, Foltin RW. Smoked cocaine self-administration in females and voucher incentives for abstinence. J. Subst. Abuse 1998;10:143–162. [PubMed: 9854700]

Feltenstein MW, Byrd EA, Henderson AR, See RE. Attenuation of cocaine-seeking by progesterone treatment in female rats. Psychoneuroendocrinology 2009;34:343–352. [PubMed: 18977603]

Feltenstein MW, See RE. Plasma progesterone levels and cocaine-seeking in freely cycling female rats across the estrous cycle. Drug Alcohol Depend 2007;89:183–189. [PubMed: 17240083]

Festa ED, Quiñones-Jenab V. Gonadal hormones provide the biological basis for sex differences in behavioral responses to cocaine. Horm. Behav 2004;46:509–519. [PubMed: 15555492]

First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JBW. Structured clinical interview for DSM-IV Axis I disorders - Patient Edition (SCID-I/P, version 2.0*)* Biometrics Research Department. New York State Psychiatric Institute; New York, NY: 1995.

Foltin RW, Fischman MW, Nestadt G, Stromberger H, Cornell EE, Pearlson GD. Demonstration of naturalistic methods for cocaine smoking by human volunteers. Drug Alcohol Depend 1990;26:145–154. [PubMed: 2242715]

Foltin RW, Haney M. Conditioned effects of environmental stimuli paired with smoked cocaine in humans. Psychopharmacology 2000;149:24–33. [PubMed: 10789879]

Frye CA. Progestins influence motivation, reward, conditioning, stress, and/or response to drugs of abuse. Pharmacol. Biochem. Behav 2007;86:209–219. [PubMed: 16979750]

Haney M. Self-administration of cocaine, cannabis and heroin in the human laboratory: benefits and pitfalls. Addict Biol 2009;14:9–21. [PubMed: 18855806]

Haney M, Hart CL, Foltin RW. Effects of baclofen on cocaine self-administration: opioid- and nonopioid-dependent volunteers. Neuropsychopharmacology 2006;31:1814–1821. [PubMed: 16407903]

Haney M, Spealman R. Controversies in translational research: drug self-administration. Psychopharmacology 2008;199:403–419. [PubMed: 18283437]

Hart CL, Haney M, Foltin RW, Fischman MW. Alternative reinforcers differentially modify cocaine self-administration by humans. Behav. Pharmacol 2000;11:87–91. [PubMed: 10821213]

Hart CL, Haney M, Vosburg SK, Rubin E, Foltin RW. Smoked cocaine self-administration is decreased by modafinil. Neuropsychopharmacology 2008;33:761–768. [PubMed: 17568397]

Hecht GS, Spear NE, Spear LP. Changes in progressive ratio responding for intravenous cocaine throughout the reproductive process in female rats. Dev. Psychobiol 1999;35:136–145. [PubMed: 10461127]

Higgins ST, Budney AJ, Bickel WK, Foerg FE, Donham R, Badger GJ. Incentives improve outcome in outpatient behavioral treatment of cocaine dependence. Arch. Gen. Psychiatry 1994;51:568–576. [PubMed: 8031230]

Highfield DA, Mean AN, Grimm JW, Rocha BA, Shaham Y. Reinstatement of cocaine seeking in 129X1/SvJ mice: effects of cocaine priming, cocaine cues and food deprivation. Psychopharmacology 2002;161:417–424. [PubMed: 12073170]

Hu M, Crombag HS, Robinson TE, Becker JB. Biological basis of sex differences in the propensity to self-administer cocaine. Neuropsychopharmacology 2004;29:81–85. [PubMed: 12955098]

Hudson A, Stamp JA. Ovarian hormones and propensity to drug relapse: a review. Neurosci. Biobehav. Rev. 2010 doi: 10.1016/j.neurobiorev.2010.05.001.

Hyman SM, Paliwal P, Chaplin TM, Mazure, Rounsaville BJ, Sinha R. Severity of childhood trauma is predictive of cocaine relapse outcomes in women but not men. Drug Alcohol Depend 2008;92:208–216. [PubMed: 17900822]

Jackson LR, Robinson TE, Becker JB. Sex differences and hormonal influences on acquisition of cocaine self-administration in rats. Neuropsychopharmacology 2006;31:129–138. [PubMed: 15920500]

Larson EB, Anker JJ, Gliddon LA, Fons KS, Carroll ME. Effects of estrogen and progesterone on the escalation of cocaine self-administration in female rats during extended access. Exp. Clin. Psychopharmacol 2007;15:461–471. [PubMed: 17924780]

Leri F, Stewart J. Drug-induced reinstatement to heroin and cocaine seeking: a rodent model of relapse in polydrug use. Exp. Clin. Psychopharmacol 2001;9:297–306. [PubMed: 11534540]

Leyton M. Conditioned and sensitized responses to stimulant drugs in humans. Prog. Neuropsychopharmacol. Biol. Psychiatry 2007;31:1601–1613. [PubMed: 17888557]

Lukas SE, Sholar M, Lundahl LH, Lamas X, Kouri E, Wines JD, Kragie L, Mendelson JH. Sex differences in plasma cocaine levels and subjective effects after acute cocaine administration in human volunteers. Psychopharmacology 1996;125:346–354. [PubMed: 8826539]

Lynch WJ, Arizzi MN, Carroll ME. Effects of sex and the estrous cycle on regulation of intravenously self-administered cocaine in rats. Psychopharmacology 2000;152:132–139. [PubMed: 11057516]

Lynch WJ, Carroll ME. Reinstatement of cocaine self-administration in rats: sex differences. Psychopharmacology 2000;148:196–200. [PubMed: 10663435]

Lynch WJ, Carroll ME. Sex differences in the acquisition of intravenously self-administered cocaine and heroin in rats. Psychopharmacology 1999;144:77–82. [PubMed: 10379627]

Lynch WJ, Roth ME, Carroll ME. Biological basis of sex differences in drug abuse: preclinical and clinical studies. Psychopharmacology 2002;164:121–137. [PubMed: 12404074]

Maxson WS, Hargrove JT. Bioavailability of oral micronized progesterone. Fertil. Steril 1985;44:622–626. [PubMed: 4054341]

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

Mendelson JH, Mello NK, Sholar MB, Siegel AJ, Kaufman MJ, Levin JM, Renshaw PF, Cohen BM. Cocaine pharmacokinetics in men and in women during the follicular and luteal phases of the menstrual cycle. Neuropsychopharmacology 1999;21:294–303. [PubMed: 10432477]

Nagoshi C, Kumor KM, Muntaner C. Test-retest stability of cardiovascular and subjective responses to intravenous cocaine in humans. Br. J. Addict 1992;87:591–599. [PubMed: 1591513]

Niyomchai T, Akhavan A, Festa ED, Lin SN, Lamm L, Foltz R, Quiñones-Jenab V. Estrogen and progesterone affect cocaine pharmacokinetics in female rats. Brain Res. Bull 2006;68:310–314. [PubMed: 16377436]

O Brien MS, Anthony JC. Risk of becoming cocaine dependent: epidemiological estimates for the United States, 2000-2001. Neuropsychopharmacology 2005;30:1006–1018. [PubMed: 15785780]

Reed SC, Haney M, Evans SM, Vadhan NP, Rubin E, Foltin RW. Cardiovascular and subjective effects of repeated smoking cocaine administration in experienced cocaine users. Drug Alcohol Depend 2009;102:102–107. [PubMed: 19303723]

Ridenour TA, Maldonado-Molina M, Compton WM, Spitznagel EL, Cottler LB. Factors associated with the transition from abuse to dependence among substance abusers: implications for a measure of addictive liability. Drug Alcohol Depend 2005;80:1–14. [PubMed: 16157227]

Roberts DC, Bennett SA, Vickers GJ. The estrous cycle affects cocaine self-administration on a progressive ratio schedule in rats. Psychopharmacology 1989;98:408–411. [PubMed: 2501818]

Robinson TE, Browman KE, Crombag HS, Badiani A. Modulation of the induction or expression of psychostimulant sensitization by the circumstances surrounding drug administration. Neurosci. Biobehav. Rev 1998;22:347–354. [PubMed: 9579324]

Rothman RB, Gorelick DA, Baumann MH, Guo XY, Herning RI, Pickworth WB, Gendron TM, Koeppl B, Thomson LE. Lack of evidence for context-dependent cocaine-induced sensitization in humans: preliminary studies. Pharmacol. Biochem. Behav 1994;49:583–588. [PubMed: 7862712]

Russo SJ, Sun WL, Minerly C, Weierstall K, Nazarian A, Festa ED, Niyomchai T, Akhavan A, Luine V, Jenab S, Quiñones-Jenab V. Progesterone attenuates cocaine-induced conditioned place preference in female rats. Brain Res 2008;1189:229–235. [PubMed: 18067879]

Russo SJ, Sun WL, Minerley AC, Weierstall K, Nazarian A, Festa ED, Niyomchai T, Akhavan A, Jenab S, Quiñones-Jenab V. Progesterone does not affect cocaine-induced conditioned place preference or locomotor activity in male rats. Ethn. Dis 2010;20:S1-73–7. [PubMed: 20521389]

Sayre SL, Schmitz JM, Stotts AL, Averill PM, Rhoades HM, Grabowski JJ. Determining predictors of attrition in an outpatient substance abuse program. Am. J. Drug Alcohol Abuse 2002;28:55–72. [PubMed: 11853135]

Simon JA, Robinson DE, Andrews MC, Hildebrand JR III, Rocci ML Jr. Blake ME, Hodgen GD. The absorption of oral micronized progesterone: the effect of food, dose proportionality, and comparison with intramuscular progesterone. Fertil. Steril 1993;60:26–33. [PubMed: 8513955]

Sinha R, Garcia M, Paliwal P, Kreek MJ, Rounsaville BJ. Stress-induced cocaine craving and hypothalamic-pituitary-adrenal responses are predictive of cocaine relapse outcomes. Arch. Gen. Psychiatry 2006;63:324–331. [PubMed: 16520439]

Siqueland L, Crits-Christoph P, Gallop R, Barber JP, Griffin ML, Thase ME, Daley D, Frank A, Gastfriend DR, Blaine J, Connolly MB, Gladis M. Retention in psychosocial treatment of cocaine dependence: predictors and impact on outcome. Am. J. Addict 2002;11:24–40. [PubMed: 11876581]

Sofuoglu M, Babb DA, Hatsukami DK. Effects of progesterone treatment on smoked cocaine response in women. Pharmacol. Biochem. Behav 2002;72:431–435. [PubMed: 11900816]

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;7:274–283. [PubMed: 10472516]

Sofuoglu M, Mitchell E, Kosten TR. Effects of progesterone treatment on cocaine responses in male and female cocaine users. Pharmacol. Biochem. Behav 2004;78:699–705. [PubMed: 15301924]

Sofuoglu M, Poling J, Gonzalez G, Gonsai K, Oliveto A, Kosten TR. Progesterone effects on cocaine use in male cocaine users maintained on methadone: a randomized, double-blind, pilot study. Exp. Clin. Psychopharmacol 2007;15:453–460. [PubMed: 17924779]

Stewart J. Conditioned and unconditioned drug effects in relapse to opiate and stimulant drug self-administration. Prog. Neuropsychopharmacol. Biol. Psychiatry 1983;7:591–597. [PubMed: 6686696]

Stoops WW, Lile JA, Rush CR. Monetary alternative reinforcers more effectively decrease intranasal cocaine choice than food alternative reinforcers. Pharmacol. Biochem. Behav 2010;95:187–191. [PubMed: 20109483]

Substance Abuse and Mental Health Services Administration. Office of Applied Studies. National Survey on Drug Use and Health, (NSDUH); Rockville, MD: 2009.

Substance Abuse and Mental Health Services Administration. Office of Applied Studies. Treatment Episode Data Set (TEDS); Rockville, MD: 2008.

Terner JM, de Wit H. Menstrual cycle phase and responses to drugs of abuse in humans. Drug Alcohol Depend 2006;84:1–13. [PubMed: 16413143]

Tuchman E. Women and addiction: the importance of gender issues in substance abuse research. J. Addict. Dis 2010;29:127–138. [PubMed: 20407972]

Volkow D, Wang GJ, Telang F, Fowler JS, Logan J, Childress AR, Jayne M, Ma Y, Wong C. Dopamine increases in striatum do not elicit craving in cocaine abusers unless they are coupled with cocaine cues. Neuroimage 2008;39:1266–1273. [PubMed: 18024160]

Vosburg SK, Haney M, Rubin E, Foltin RW. Using a novel alternative to drug choice in a human laboratory model of a cocaine binge: a game of chance. Drug Alcohol Depend 2010;110:144–150. [PubMed: 20346597]

Walsh SL, Geter-Douglas B, Strain EC, Bigelow GE. Enadoline and butorphanol: evaluation of kappa-agonists on cocaine pharmacodynamics and cocaine self-administration in humans. J. Pharmacol. Exp. Ther 2001;299:147–158. [PubMed: 11561074]

Wu LT, Pan JJ, Blazer DG, Tai B, Stitzer ML, Woody GE. Using a latent variable approach to inform gender and racial/ethnic differences in cocaine dependence: a National Drug Abuse Treatment Clinical Trials Network study. J. Subst. Abuse Treat 2010;38:S70–79. [PubMed: 20307798]

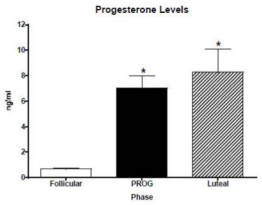

Figure 1.

Plasma progesterone levels as a function of study phase: (1) follicular phase when placebo progesterone was administered, (2) PROG (progesterone) phase when progesterone (150 mg B.I.D) was administered during the follicular phase, and (3) luteal phase when placebo progesterone was administered. Bars represent the mean + 1 SEM. * Indicates a significant difference from the follicular phase ($p \leq 0.01$).

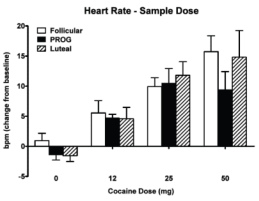

Figure 2.

Mean heart rate (expressed as change from baseline) as a function of phase and sample cocaine dose. Each bar represents the mean + 1 SEM for one administration of a sample dose of cocaine.

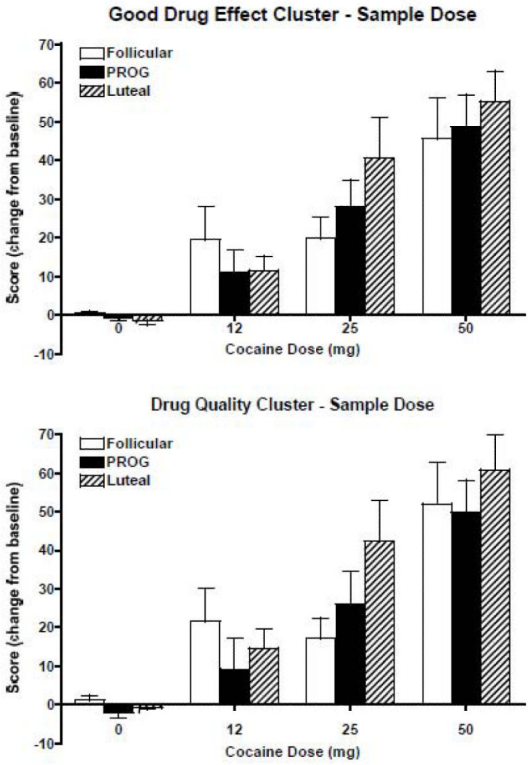

Figure 3.

Mean scores on the good drug effect and drug quality clusters (expressed as change from baseline) as a function of phase and sample cocaine dose. Each bar represents the mean + 1 SEM for one administration of a sample dose of cocaine.

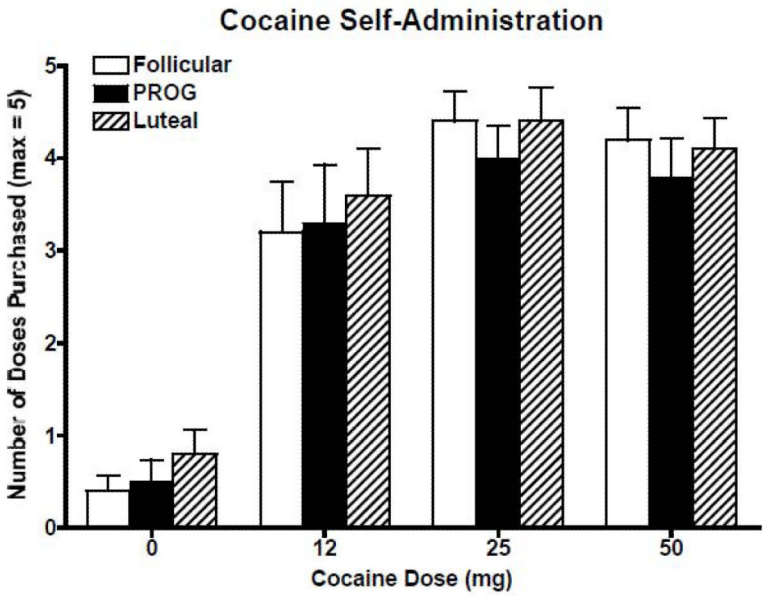

Figure 4.
Number of cocaine doses purchased as a function of phase and cocaine dose. Each bar represents the mean + 1 SEM. Portions of these data were published in Evans & Foltin (2010).

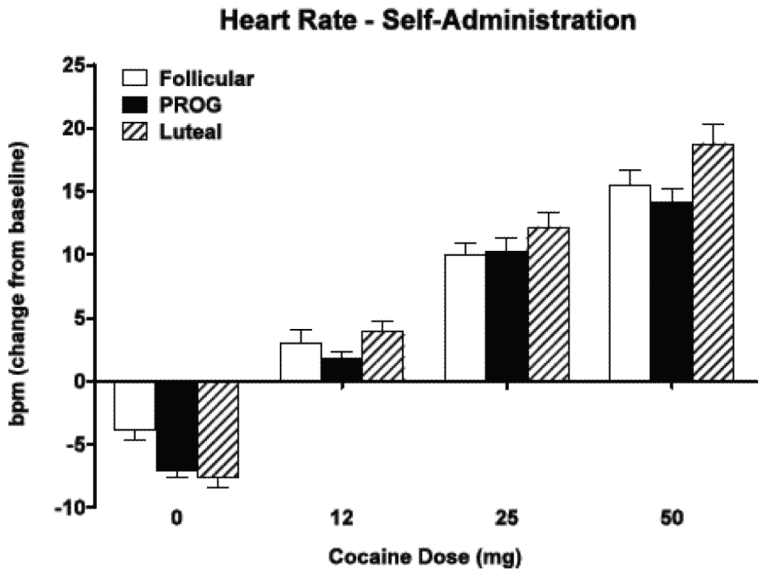

Figure 5.
Mean heart rate (expressed as change from baseline) as a function of phase and self-administered cocaine dose. Each bar represents the mean + 1 SEM collapsed across six time points during cocaine self-administration sessions.

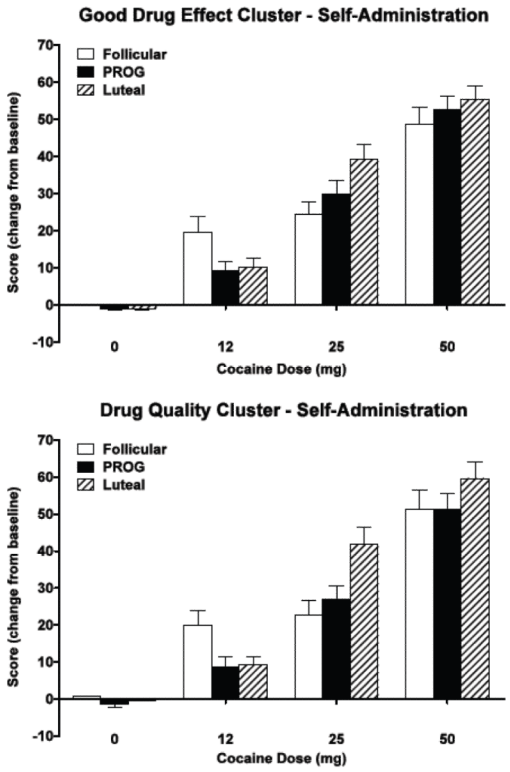

Figure 6.

Mean good drug effect and drug quality cluster scores (expressed as change from baseline) as a function of phase and self-administered cocaine dose. Each bar represents the mean + 1 SEM collapsed across six time points during cocaine self-administration sessions.