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Effects of progesterone treatment on cocaine responses in male and female cocaine users

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Abstract

We recently reported that progesterone treatment attenuated some of the subjective effects of smoked cocaine in female cocaine users. In this study, we further examined the interaction between progesterone and cocaine in both male and female cocaine users using subjective, physiological and behavioral outcomes. A total of 10 subjects, 6 male and 4 female cocaine users, had two experimental sessions. Before each session, participants received either two oral doses of 200 mg of progesterone or placebo. Two hours after the second dose of medication treatment, the participants received a 0.3 mg/kg dose of cocaine intravenously and started the self-administration period, in which five optional doses of cocaine were available. Progesterone treatment attenuated the cocaine-induced diastolic blood pressure increases without affecting the systolic blood pressure and heart rate increases. Progesterone treatment also attenuated the subjective ratings of *high* and *feel the effect of last dose* in response to cocaine but did not affect cocaine self-administration behavior. These results suggest that progesterone attenuates some of the physiological and subjective effects of cocaine in both male and female participants. The effects of progesterone treatment on cocaine dependence need to be further studied in controlled trials.

Keywords: Cocaine; Progesterone; Self-administration

1. Introduction

Accumulating evidence suggests that the female sex hormones, estradiol and progesterone, have wide ranging effects on brain functioning, including modulation of the effects of drugs of abuse (Becker et al., 2001; Cyr et al., 2001; Sundstrom Poromaa et al., 2003). In women, fluctuation of estradiol and progesterone levels during the course of the menstrual cycle is associated with changes in responses to stimulant drugs. In two studies, female cocaine users who were in the luteal phase of their menstrual cycle showed attenuated responses to the subjective effects of cocaine, compared with those who were in the follicular phase (Sofuoglu et al., 1999; Evans et al., 2002). Similar menstrual cycle phase effects on the subjective response to amphetamines were observed in nonaddicted women (Justice and De Wit, 2000). Because the luteal phase is characterized by higher progesterone levels than the follicular phase is, we examined the role of progesterone in attenuating the cocaine response during the luteal phase of the menstrual cycle. As a first step, we examined the interaction between progesterone and cocaine in female cocaine users. In that study, a single oral dose of 200 mg progesterone attenuated some of the subjective effects from repeated smoked cocaine deliveries compared with placebo (Sofuoglu et al., 2002). These results were consistent with preclinical studies that examined progesterone and cocaine interactions. In two recent studies, progesterone treatment blocked the conditioned place preference for cocaine in mice (Romieu et al., 2003; Russo et al., 2003) and rats (Russo et al., 2003), further supporting the inhibitory effects of progesterone on cocaine responses.

In this study, we further examined the interaction between progesterone and cocaine in male and female cocaine users. The goals of this study were to determine (1) the safety and tolerability of progesterone treatment in male and female cocaine users and 2) the interaction between progesterone and cocaine using behavioral, subjective and physiological outcome measures. This study extended our pre-

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vious study by (1) including both male and females, in contrast to females alone in our previous study, and 2) using a laboratory model that also examined cocaine self-administration behavior.

2. Methods

2.1. Subjects

Participants were six males and four females, non-treatment-seeking, crack cocaine users, and were dependent on cocaine as defined by *DSM-IV* (American Psychiatric Association, 1994). Five participants were African-American, five were Caucasian. Two additional participants were enrolled but dropped out of the study for noncompliance with study procedures and were not included in the analyses. The average age and standard deviation was 38.5 (5.7) years, and average schooling was 12.8 (1.8) years. The participants weighed an average of 73.6 (11.2) kg. Within the month before admission, the average frequency of cocaine use was 16.8 (9.7) days and the amount spent on cocaine was US$328 (334) /week. The average duration of cocaine use was 17.3 (5.7) years. Current use of other drugs included cigarettes ($n=9$), alcohol ($n=6$) and marijuana ($n=7$). The participants had to meet the following inclusion criteria: (1) males and females between the ages of 20 and 45; (2) history of smoked or intravenous cocaine use on the average of at least once a week over a 6-month period; (3) current history of good health and normal ECG; and (4) not pregnant, as determined by pregnancy screening, nor breast feeding, and using acceptable birth control methods other than hormonal contraceptives. Participants were excluded from participation if they had (1) current problems with major psychiatric illnesses, including bipolar disorder, schizophrenia or major depression; (2) current dependence on alcohol or on drugs other than cocaine or nicotine; (3) for women, amenorrhea or current use of oral or other types of hormonal contraceptives; (4) currently interested with treatment for cocaine dependence; and (5) allergy to peanut oil because progesterone capsules included peanut oil, those with peanut allergy were also excluded. Before study participation, drug use history was confirmed with urine toxicology screening. This study was approved by the VA Connecticut Healthcare System Human Subjects Subcommittee. Before study participation, the participants signed an informed consent, and participants were paid for study participation.

2.2. Study procedure

This double-blind, placebo-controlled crossover study had one adaptation and two experimental sessions. The participants were housed for five days in a hospital ward, and the sessions were conducted in the Biostudies Unit both located at the VA Connecticut Healthcare System. On the day of the admission, the participants underwent an adaptation session to orient them to the laboratory procedures. Two indwelling intravenous catheter were placed, one on each arm, for injection and blood drawing. Afterwards, baseline measures, including blood pressure, heart rate, ECG and subjective measures, were obtained. The participants then received an intravenous saline injection and, 30 min later, a 0.3 mg/kg dose of intravenous cocaine to familiarize them with the intravenous and cocaine injection procedures, respectively.

To control for menstrual cycle phase, female participants were admitted within 5 days from the beginning of their menses. During the early follicular phase, the endogenous estradiol levels are low and remain stable, below 85 pg/ml, while the progesterone levels remain low throughout the follicular phase, below 2.0 ng/ml (Yen et al., 1999), which minimizes the interaction between the endogenous sex hormones and progesterone treatment. In addition, the disruption of the menstrual cycle or withdrawal bleeding due to progesterone treatment is less likely to occur when the endogenous estradiol levels are low as in the early follicular phase. The feasibility of administering sex hormones to women during the early follicular phase of the menstrual cycle has been demonstrated in a number of studies (Tan et al., 1996, 1997; Justice and De Wit, 2000; Sofuoglu et al., 2001, 2002).

For each of the two experimental sessions, participants received the assigned medication treatment at 10 p.m. the night before and at 8 a.m. on the day of the experimental session. Two hours after the a.m. medication treatment, the participants started the self-administration period, when peak levels of progesterone were expected (de Lignieres, 1999; Sofuoglu et al., 2001). During the self-administration period, a maximum of six cocaine doses were administered, one sampling and five with cocaine tokens. Following a 1-day washout, the participants were crossed over to the alternative treatment. They were asked not to use any illicit drugs or alcohol during the study, and their compliance was checked with urine drug screening and breathalyzer before the sessions. They were not permitted to eat or smoke for approximately 5 h during the sessions.

This cocaine self-administration model was originally developed for smoked cocaine administration and has been used in multiple studies to test the effects of potential medication for cocaine dependence (Hatsukami et al., 1994; Sofuoglu et al., 1999, 2000). The self-administration period started 2 h after the medication treatment, around 10 a.m. The participants first received a sampling dose of 0.3 mg/kg of intravenous cocaine. The size of the sample dose was identical to the doses that could be purchased during the session. Before the sessions, the participants were given five tokens, each worth US$5. During the cocaine-option period, there were five times that the participants could purchase a delivery of cocaine or save their token for its monetary value. The participants could not receive a delivery of cocaine more frequently than every 30 min to provide

enough time for the subjective and physiological effects of cocaine to wear off. This procedure continued until either five deliveries had been administered or 2.5 h had been elapsed. If the participants choose not to self-administer, they receive cash back at the end of the study, US$5 for every token saved.

2.3. Drugs

Cocaine hydrochloride was obtained from Sigma-Aldrich (St. Louis). The cocaine dose was 0.3 mg/kg iv injected over 60 s. This dose is comparable with the 0.4 mg/kg smoked cocaine dose used in our previous studies and is within the safe and reinforcing dose range, i.e., self-administered by cocaine users in laboratory settings (Ward et al., 1997; Haney et al., 1998; Smith et al., 2001).

During each session, the participants were given micronized progesterone (Prometrium, Solvay Pharmaceuticals, Georgia) or placebo. After oral administration, micronized progesterone reaches its peak plasma levels in 2 to 3 h and has an elimination half-life of 3 to 4 h (Simon, 1995; de Lignieres, 1999). The dose of progesterone was 200 mg, given orally twice. This dose has been shown to achieve luteal phase plasma progesterone levels in female cocaine users (Sofuoglu et al., 2002).

2.4. Medical monitoring and safety

Cardiac rhythm was monitored continuously during sessions. Twelve lead ECGs were obtained prior to cocaine administration and at the end of each session. The participants remained in the laboratory until all vital signs returned to baseline levels. A physician was present during all the sessions.

2.5. Outcome variables

The main outcome variables were physiological, behavioral, subjective and biochemical measures. The behavioral measure was the number of cocaine deliveries self-administered under the two treatment conditions. Physiological measures were heart rate and systolic and diastolic blood pressure, which were taken at −2, 3, 5, 10 and 15 min in relation to cocaine deliveries. The subjective effects of cocaine were measured by the Cocaine Effects Questionnaire (CEQ; Dudish-Poulsen and Hatsukami, unpublished) on visual analog scale (VAS) and profile of mood states (POMS). The CEQ consists of five items: feel high, feel stimulated, crave cocaine, heart racing/pounding and feel the effects of last dose. The CEQ was given 4.5 min before and 2.5 min after each dose. Additional measures were also obtained at 10 and 15 min after the first dose. POMS, a 72-item rating scale (McNair et al., 1971), was used to measure the effects of progesterone on the subjective aspects of mood. POMS has six subscales: (1) composed–anxious, (2) agreeable–hostile, (3) elated–depressed, (4) confident–unsure, (5) energetic–tired, and (6) clear headed–confused. POMS was given before medication treatment and at the end of each experimental session. Biochemical measures were plasma cocaine and progesterone levels. Samples for plasma cocaine concentrations were taken just before and 5 min after the first dose. For progesterone levels, samples of blood were taken at baseline and 2 h after progesterone or placebo treatment.

2.6. Statistical analysis

To assess treatment effects, repeated-measures ANOVA was conducted. These analyses included a fixed main effect for treatment (placebo or progesterone) and time (in relation to cocaine administration) and the interaction of these two effects. Either a significant main effect for treatment or interaction of treatment-by-time indicated treatment effect. For the subjective and physiological measures, the analysis focused on the sample dose response because the rest of the doses were optional and were not taken in approximately half of the opportunities. In addition, secondary analyses examining gender differences were conducted. In these analyses, gender was included as a covariate, in addition to treatment and treatment-by-gender interactions. In all analyses, standard F tests indicated significant treatment effects at an alpha level of .05. Huynh–Feldt adjustments were used

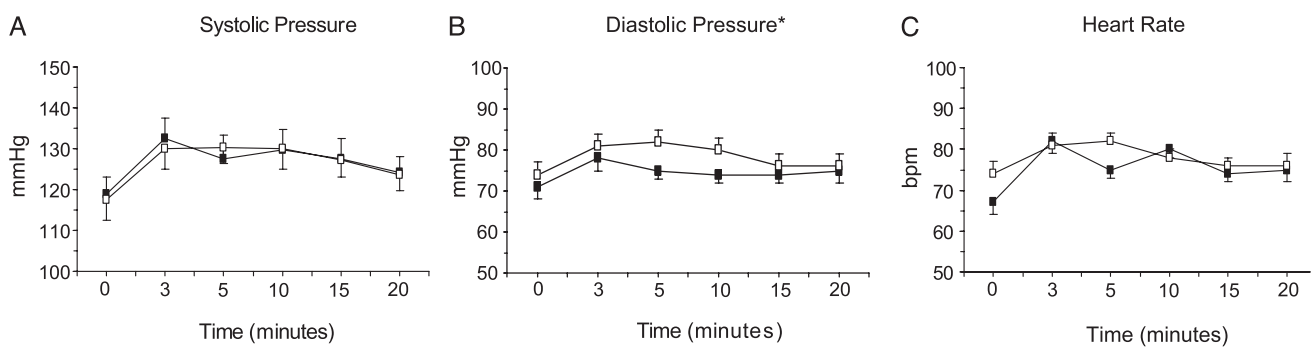

Fig. 1. Systolic blood pressure (A), diastolic blood pressure (B) and heart rate (C) responses to 0.3 mg/kg iv cocaine injection. Data are the average values (S.E.M.) under progesterone (■) or placebo (□) treatments. Measures that show significant group difference ($P < .05$) are indicated by asterisks (*).

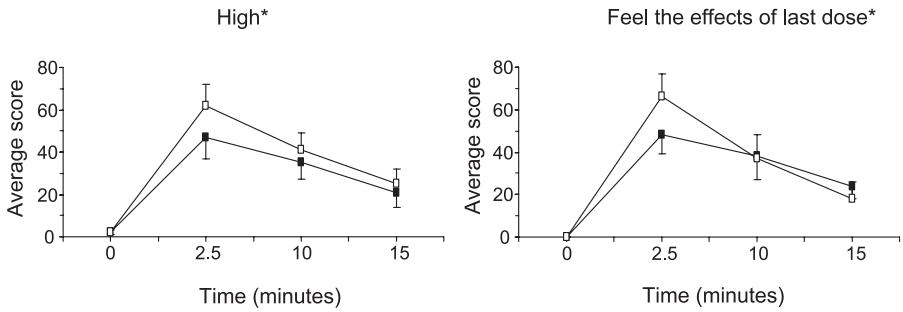

Fig. 2. Subjective ratings of selected items in response to 0.3 mg/kg iv cocaine injection. Data are the average values (S.E.M.) under progesterone (■) or placebo (□) treatments. Measures that show significant group difference ($P<.05$) are indicated by asterisks (*).

to correct for possible violations of sphericity assumption. For all these analyses, a significance level of .05 was used.

3. Results

3.1. Physiological response

In response to the sample dose of cocaine, there were no significant treatment effects for the heart rate [$F(1,54)=1.7$; $P=.1$] and systolic blood pressure [$F(1,54)=0.6$; $P=.7$] measurements (Fig. 1). Diastolic blood pressure showed significant treatment effects [$F(6,54)=3.4$; $P<.01$], with the progesterone condition showing reduced blood pressure when compared with the placebo condition. As expected, all three measures showed a significant effect of time ($P<.01$) without significant treatment-by-time interactions.

3.2. Behavioral response

The participants exchanged 24 out of 50 tokens for cocaine deliveries under the placebo treatment and 26 out of 50 tokens under the progesterone treatment. The average (S.D.) token exchange per session was 2.4 under placebo and 2.6 under progesterone treatment, with no significant group differences [$t=0.7$; $P=.5$].

3.3. Subjective response

Two of the five items of the CEQ showed significant response to treatment (either a main effect or any interaction effect with time), with attenuated responses under progesterone treatment (Fig. 2). For the rating of *high*, there was a significant main effect for treatment [$F(1,27)=6.0$; $P<.05$] and for the rating of *feel the effects of last dose* there was significant treatment-by-time interaction [$F(3,27)=4.7$; $P<.01$]. The main effect for treatment was close to significance for the rating of *feel stimulated* [$F(1,27)=4.2$; $P=.07$] and *heart racing/pounding* [$F(1,27)=4.2$; $P=.07$]. There were no treatment effects for the rating of *crave cocaine* [$F(1,27)=2.8$; $P=.13$]. For all five CEQ items, there was a significant time effect (all $P<.001$) in response to cocaine. For POMS, there was no significant Treatment × Time effect on any of the subscales ($P>.05$).

3.4. Biochemical measurements

Changes in plasma cocaine concentrations with cocaine injection did not show any treatment effect. The average (S.D.) peak cocaine concentrations under the progesterone and placebo conditions were 326 (240) and 264 (136) ng/ml, respectively.

Plasma progesterone levels 2 h after placebo or progesterone administration were 1.1 (0.72) and 15.0 (7.9) ng/ml.

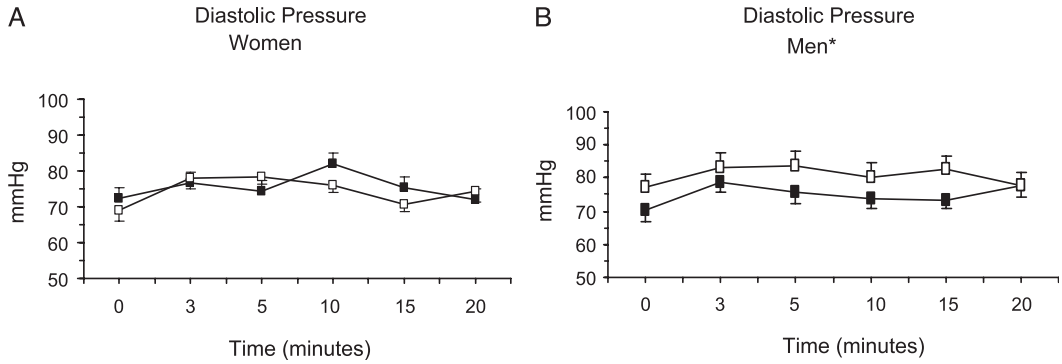

Fig. 3. Diastolic blood pressure response to 0.3 mg/kg iv cocaine injection in female (A) and male (B) cocaine users. Data are the average values (S.E.M.) under progesterone (■) or placebo (□) treatments. Measures that show significant group difference ($P<.05$) are indicated by asterisks (*).

The correlation between the peak progesterone levels and cocaine-induced diastolic blood pressure change was .35 ($P>.05$). The corresponding value for the rating of *high* was .23 ($P>.05$).

For female participants, the average baseline plasma progesterone was 1.3 (0.8) and 1.2 (0.7) ng/ml for the first and second sessions ($P>.05$), respectively, suggesting that they were in the follicular phase of the menstrual cycles.

3.5. Gender differences

No gender or gender-by-treatment interactions were found in subjective and behavioral measures and systolic blood pressure and heart rate measures. For diastolic blood pressure (Fig. 3), there was a significant treatment-by-time-by-gender effect [$F(5,8)=10.2$; $P<.05$].

4. Discussion

Our study found attenuation of some of the subjective effects of cocaine with progesterone treatment in both male and female cocaine users. This extends our previous study with only female cocaine users, whose subjective ratings of *high* and *feel the effect of last dose* were attenuated with progesterone treatment. These findings are consistent with a number of preclinical studies that suggest the attenuation of cocaine effects by progesterone, in contrast to enhancement of cocaine effects by estradiol (Dluzen and Ramirez, 1987; Becker and Cha, 1989; Michanek and Meyerson, 1982; Roberts et al., 1989; Fernandez-Ruiz et al., 1990; Peris et al., 1991; Morissette and Di Paolo, 1993; Shimizu and Bray, 1993). Some preclinical studies suggest that progesterone may not directly affect cocaine responses but may block the stimulation of the dopaminergic system by high levels of estradiol (Michanek and Meyerson, 1982; Fernandez-Ruiz et al., 1990; Morissette and Di Paolo, 1993; Peris et al., 1991). However, women in the early follicular phase and men have overlapping values of serum estradiol (30–100 and 10–60 pg/ml, respectively) and progesterone (0.25–2.0 and 0.1–0.65 ng/ml, respectively; Yen et al., 1999). Thus, in our study, progesterone actions on cocaine responses were observed in men and in women during periods of low endogenous estradiol levels. These results suggest that progesterone effects are likely to be direct rather than through the blockage of estradiol effects, as supported by some preclinical studies.

Progesterone's attenuation of diastolic blood pressure response to cocaine is consistent with both preclinical and clinical studies. In one study, progesterone particularly lowered diastolic blood pressure in hypertensive men and postmenopausal women (Rylance et al., 1985). Blood pressure decreases may involve sympathetic system activity because 400 mg/day of progesterone decreased venous norepinephrine levels in normotensive men (Tollan et al., 1993). This decrease appears to be greater in men than in women. Higher estradiol levels in women than in men is not a likely explanation because estradiol is not known to increase blood pressure (Dubey et al., 2002).

Progesterone did not attenuate cocaine self-administration. Changing cocaine use behavior may require higher doses and longer treatments than may be needed to change subjective response to cocaine. An outpatient clinical trial with cocaine users may provide a better setting to examine the effect of progesterone treatment on cocaine use behavior.

Similar with the previous studies with micronized progesterone, the peak plasma progesterone levels after treatment showed significant variation and poor correlation with various cocaine responses. Progesterone, however, has active metabolites like pregnenolone and allopregnenolone, which may attenuate cocaine reward by modulating the $GABA_A$ and NMDA receptors (Majewska et al., 1986; Smith, 1991; Cyr et al., 2001). In a previous study with women who were placed on oral contraceptives, following progesterone treatment measures of fatigue, confusion and immediate recall were better correlated with plasma allopregnenolone levels than with progesterone (Freeman et al., 1993). Future studies might measure allopregnenolone.

Our results further support the safety and tolerability of progesterone, without significant interactions with cocaine, in both male and female cocaine users. Sedation, a common side effect of progesterone, was not observed on the POMS sedation scale. Women also did not have withdrawal bleeding following progesterone treatment. However, longer treatment with progesterone is likely to cause menstrual irregularities, including inhibition of ovulation and withdrawal bleeding, because it would then be given during the luteal phase, when endogenous estradiol levels are high (Yen et al., 1999). A number of clinical trials have been conducted using progesterone for hypertension, COPD and benzodiazepine withdrawal in men, but typically select only postmenopausal women (Freeman et al., 1995; McAuley et al., 1995; Gron et al., 1997; Rylance et al., 1985; Tollan et al., 1993; Schweizer et al., 1995). Given the safety of progesterone in conjunction with cocaine, and the attenuation of cocaine effects with progesterone, long-term studies with progesterone for cocaine dependence are indicated.

This study has several limitations. First, the study did not examine the dose–effect relationship for progesterone effects on cocaine responses. Our goal was to reach the plasma progesterone levels found during the luteal phase of the menstrual cycle, which was achieved with a 200-mg dose. In future studies, using multiple doses of progesterone would be helpful to investigate the dose-dependent effects of progesterone. Second, the duration of treatment was brief, with only two doses of progesterone treatment. It is possible that a longer duration of progesterone may have different effects on our outcomes. Third, most of the participants were mainly crack cocaine users and had no previous experience with intravenous cocaine. It is possible that crack cocaine users may respond differently to cocaine than to intravenous cocaine users. However, a previous human

study suggests that the subjective and physiological effects of intravenous and smoked cocaine are very similar (Foltin and Fischman, 1991). Fourth, the study sample was small, especially to examine gender differences in progesterone responses.

To summarize, progesterone treatment attenuated some of the subjective effects of cocaine, as well as diastolic blood pressure response to cocaine. Further studies are warranted to examine the therapeutic effects of progesterone on cocaine dependence.

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