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Pharmacology, Biochemistry and Behavior 72 (2002) 431–435

PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR

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Effects of progesterone treatment on smoked cocaine response in women

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Received 27 June 2001; received in revised form 29 November 2001; accepted 7 December 2001

Abstract

The effects of female sex hormones on responses to cocaine have not been systematically investigated in women. In this study, the safety and efficacy of acute progesterone treatment on smoked cocaine response was examined in female cocaine users. Five women had two experimental sessions during the early follicular phase, within 3–9 days after the beginning of their menses. In each experimental session, subjects received a single 200-mg dose of progesterone or placebo orally. Starting 2 h after the medication treatment, subjects received three deliveries of 0.4-mg/kg smoked cocaine 30 min apart. Progesterone treatment, compared to placebo, did not affect the blood pressure and heart rate changes in response to cocaine deliveries. For subjective responses to cocaine, the average of five-item Cocaine Effects Questionnaire (CEQ) was attenuated under progesterone treatment compared to placebo. For individual items of CEQ, progesterone treatment was associated with diminished rating of ''feel the effect of last dose'' in response to cocaine. These preliminary results suggest that acute progesterone treatment, given during the early follicular phase, may attenuate some of the subjective effects of cocaine. Further studies are warranted to examine the effects of progesterone treatment on cocaine dependence.

Keywords: Progesterone; Micronized progesterone; Crack cocaine; Cocaine; Menstrual cycle; Early follicular phase

1. Introduction

We recently reported that female cocaine users in the luteal phase of their menstrual cycle, compared to those in the follicular phase, had an attenuated subjective response to cocaine (Sofuoglu et al., 1999). Similarly, women in the luteal phase, compared to those in the follicular phase of the menstrual cycle, showed attenuated subjective response to oral amphetamine (Justice and de Wit, 1999). Since, compared with the follicular phase, the luteal phase is characterized by higher progesterone levels, it was of interest to examine whether the attenuation of cocaine response in luteal phase was due to the effects of progesterone. In order to test this hypothesis, the effects of progesterone treatment on responses to repeated smoked cocaine deliveries was investigated. Progesterone treatment was given during the early follicular phase, which is characterized by low endogenous estradiol and progesterone levels. These low estradiol and progesterone levels make the early follicular phase a useful period to administer exogenous sex hormones. This study will extend our recent report on the effects of progesterone treatment on smoking behavior in female smokers (Sofuoglu et al., 2001).

2. Method

2.1. Subjects

Five female crack-cocaine users with an average age of 34 (4.6) participated in the study. Three subjects were African American, one was Caucasian and one was Hispanic. Subjects had an average (S.D.) of 8.1 (9.8) years of cocaine use. Their average (S.D.) self-reported frequency and amount of cocaine use were 3.4 (2.2) days/week and 2.4 (1.2) g/day, respectively. All the experimental sessions were carried out in the General Clinical Research Center. Before the study participation, drug use was confirmed with urine analysis. Reported use of other drugs within the past month were cigarettes ($n=4$), alcohol ($n=4$) and marijuana ($n=4$). Subjects had normal physical, laboratory and psychiatric examinations and regular menses. Potential subjects who were dependent on alcohol or drugs other than cocaine or nicotine were excluded from the study (APA, 1994). Sub-

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0091-3057/02/$ – see front matter
PII: S0091-3057(02)00716-5

jects were instructed not to use drugs during the study, other than the ones provided during the sessions. Before each session, subjects provided urine samples for urine drug screening. Randomly selected urine samples were tested for drug use and found to be negative, indicating compliance. Subjects were allowed to smoke just before and after the sessions but not during the sessions. Subjects signed informed consent before participation and were paid for participation. This study was approved by the Institutional Review Board of the University of Minnesota.

2.2. Study procedure

This outpatient, double-blind, placebo-controlled, crossover study consisted of one adaptation and two experimental sessions. Within 1 week before the first day of their expected menses, subjects had an adaptation session. The goal of the adaptation session was to orient the subjects to the laboratory procedures. In the adaptation session, subjects received a single 0.4-mg/kg dose of smoked cocaine to familiarize them with the dose that they would receive during the experimental sessions. Two experimental sessions were held within Days 3–9 of the menstrual cycle, Day 1 being the first day of menstrual cycle. These sessions were at least 2 days apart to minimize the carryover effect from the study medication. In each of the experimental sessions, subjects received the study medication (200-mg progesterone or placebo) followed by a light meal. Starting 2 h after medication administration, when peak levels of progesterone were expected, subjects received three doses of 0.4 mg/kg of smoked cocaine 30 min apart. Physiological and subjective measures were taken before and after each dose. Cardiac rhythm was monitored continuously during sessions. Twelve-lead ECGs were taken before the session and after each cocaine delivery. Subjects were asked to remain in the laboratory until all vital signs returned to baseline levels. Following each session, subjects were examined by the study physician and discharged home. For blood drawing and safety reasons, before each session, subjects had an indwelling intravenous catheter placed in an antecubital vein.

2.3. Cocaine and progesterone administration

The device used to deliver smoked cocaine base has been described previously (Hatsukami et al., 1990) and shown to deliver precise and reliable doses of cocaine. Briefly, specific amounts of cocaine base were applied to wire coil devices at least 24 h prior to experimental sessions. After weighing, a coil device was inserted into a glass mouthpiece and connected through a smoking chamber to a power supply. When the subject inhaled using the mouthpiece, it caused a change in air flow across the coil device that triggered the electrical heating of the coil. This process led to rapid volatilization of cocaine. Our previous analysis showed that the smoke produced consisted of more than 96% cocaine (Thompson and Hatsukami, unpublished). Subjects were told to inhale for 10 s and then hold the vapor for an additional 15 s. After the delivery, coils were reweighed to verify the amount of cocaine that was volatilized.

Cocaine hydrochloride was obtained from the National Institute on Drug Abuse and converted to cocaine base. The cocaine dose was 0.4 mg/kg, a dose that is reliably self-administered and considered safe (Hatsukami et al., 1990; Hatsukami et al., 1994).

During each session, subjects were given micronized progesterone (Prometrium, Solvay Pharmaceuticals, GA) or placebo. After oral administration, micronized progesterone reaches its peak plasma levels in 2–3 h and has an elimination half-life of 3–4 h (de Lignieres, 1999; Simon, 1995).

2.4. Outcome variables

The main outcome variables were biochemical, physiological and subjective measures. Biochemical measures were plasma estradiol, progesterone and cocaine levels. Samples for plasma estradiol and progesterone levels were taken before each experimental session to verify that subjects were in early follicular phase of their menstrual cycle. Plasma progesterone levels were also measured from 1 to 4 h after progesterone or placebo administration. Plasma cocaine levels were measured just before the first dose and 6 min after the first and the third dose. Physiological measures, heart rate and systolic and diastolic blood pressure were obtained 2 min before and 2.5, 4.5, 9.5 and 14.5 min after each cocaine delivery.

The subjective measures were Cocaine Effects Questionnaire (CEQ) 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)

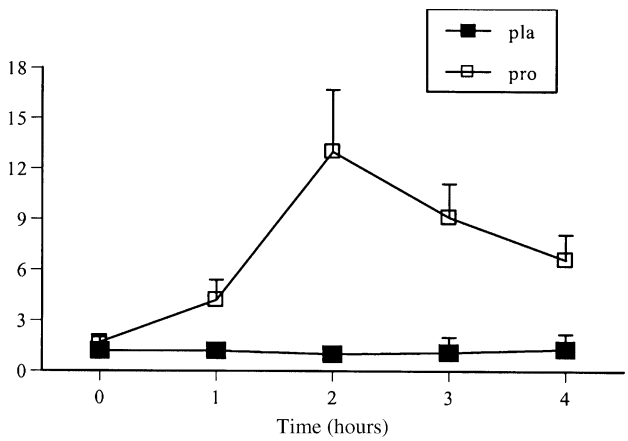

Fig. 1. The average (S.E.M.) plasma progesterone (ng/ml) following 200-mg progesterone or placebo treatment of five female cocaine users.

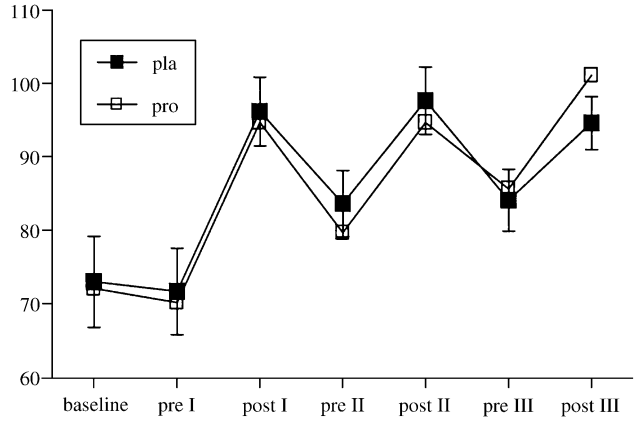

Fig. 2. The average (S.E.) heart rate (bpm) response to three deliveries of 0.4-mg/kg smoked cocaine under progesterone and placebo treatment conditions. Some S.E. bars were eliminated for clarity.

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.

2.5. Statistical analysis

Repeated-measures analysis of the primary physiological and subjective responses was conducted to assess treatment effects. In these analyses, effects for treatment (placebo or progesterone), dose of cocaine (1–3), time from cocaine delivery and the interaction of these effects were included. Huynh–Feldt adjustments were used to correct for possible violations of sphericity assumption. For all these analyses, a significance level of .05 was used.

3. Results

3.1. Biochemical measurements

Changes in progesterone levels in response to progesterone and placebo treatment together are shown in Fig. 1. Following progesterone treatment, plasma progesterone levels increased significantly compared to placebo [$F(4,16)=6.0$, $P<.005$]. To address whether the interval between the two sessions was associated with changing baseline sex hormone levels, plasma estradiol and progesterone levels measured before each session were compared. The average plasma estradiol levels were 40.6 (7.1) and 46.0 (20.8) pg/ml for the first and second sessions ($P>.05$). The corresponding figures were 1.4 (0.3) and 1.5 (0.8) ng/ml for the progesterone levels ($P>.05$).

No treatment effects were observed for the changes in plasma cocaine concentrations with cocaine deliveries ($P>.05$). The average (S.D.) cocaine concentrations after the first and third cocaine deliveries were 235 (127) and 469 (133) ng/ml under progesterone treatment. The corresponding figures were 251 (55) and 472 (127) ng/ml under placebo treatment, respectively.

3.2. Physiological measurements

Heart rate and systolic and diastolic blood pressure responses to three deliveries of cocaine (Fig. 2) were not significantly different under progesterone and placebo conditions ($P>.05$).

3.3. Subjective measurements

For the subjective response to three cocaine deliveries, significant time effects were found for all five CEQ items, as expected (Fig. 3). The average of the five items of CEQ showed a Treatment × Time interaction [$F(7,168)=2.7$, $P<.05$], with reduced response under the progesterone treatment condition. Significant and similar Treatment × Time interactions were found for item "feel the effects of last dose" [$F(7,28)=3.2$, $P<.05$]. Pairwise comparisons showed significant group differences after the third delivery ($P=.02$). For "feel high," there was a trend for attenuation of subjective response to cocaine with progesterone, which did not reach statistical significance ($P=.1$). For POMS,

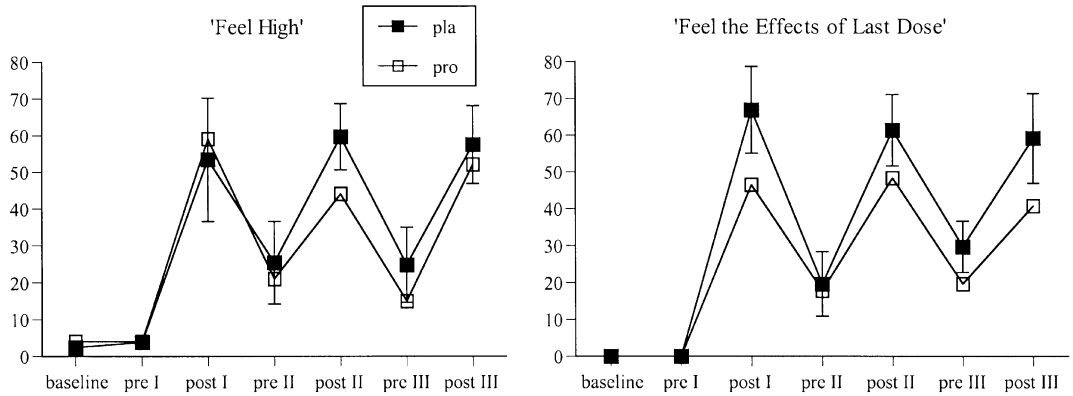

Fig. 3. The average (S.E.) subjective response to three deliveries of 0.4-mg/kg smoked cocaine under progesterone and placebo treatment conditions for selected items. Some S.E. bars were eliminated for clarity.

there was no significant Treatment × Time effect on any of the subscales ($P > .05$).

4. Discussion

In this study, progesterone treatment was well tolerated and increased plasma progesterone levels to the range found during the luteal phase of the menstrual cycle (3–30 ng/ml) in cocaine-using women. These results are similar to those reported in our recent study on progesterone effects on smoking behavior in female smokers (Sofuoglu et al., 2001) and further support the feasibility of progesterone treatment during the early follicular phase of the menstrual cycle. The early follicular phase is characterized by low and stable levels of endogenous estradiol and progesterone compared to the other phases of the menstrual cycle, which may minimize the risk of menstrual cycle disruption from sex hormone treatment. The results of this and several other studies, which used early follicular phase to administer exogenous estradiol or progesterone to women (Justice and de Wit, 2000; Tan et al., 1996; Tan et al., 1997), suggest that early follicular phase of the menstrual cycle is a useful period to investigate the short-term effects of exogenous sex hormones in normally menstruating women.

In this study, progesterone treatment attenuated some of the subjective responses to repeated deliveries of cocaine in female cocaine users. These results suggest that progesterone may mediate the attenuated subjective response to cocaine during the luteal phase of the menstrual cycle effects. In a recent study with female smokers, we observed that progesterone treatment attenuated subjective effects from smoking (Sofuoglu et al., 2001), suggesting that progesterone treatment may affect the subjective response to stimulant drugs. Preclinical studies provide possible mechanisms to explain these findings. Progesterone has wide-ranging effects in the brain including the activation of GABA type A receptors (Majewska, 1990). Another effect of progesterone is on the dopaminergic system, a neurotransmitter system that is implicated to be an important neural substrate for both the reinforcing and motoric effects of stimulants. Preclinical studies suggest that estradiol and progesterone may have opposing effects on the dopaminergic system. While estradiol has a stimulatory effect on the dopaminergic system, progesterone may have inhibitory effects (Dluzen and Ramirez, 1987; Fernandez-Ruiz et al., 1990; Michanek and Meyerson, 1982; Roberts et al., 1989; Shimizu and Bray, 1993). These preclinical studies suggest that progesterone may potentially modulate the actions of cocaine through its effects on the dopaminergic system.

Progesterone treatment did not alter the cardiovascular response to three repeated deliveries of cocaine in contrast to attenuation of some of the subjective effects of cocaine (Wise, 1996). This discrepancy may be due to differences in neurotransmitter systems that mediate the physiological and subjective effects of cocaine. In previous preclinical studies, progesterone treatment was reported to increase the cardiovascular toxicity of cocaine (Plessinger and Woods, 1990). In addition, the increased toxicity of cocaine in pregnant animals was attributed to the increased progesterone levels during pregnancy (Sharma et al., 1992). However, these earlier reports of increased cardiac toxicity of cocaine by progesterone could not be replicated in later studies (Glantz and Woods, 1995; 1994; Kurtzman et al., 1994). Our study also did not support increased cardiovascular effects of cocaine by acute progesterone treatment in cocaine using women.

In this study, there was no treatment effect on any subscales of POMS in contrast to our recent study in which progesterone treatment was associated with increased sedation subscale of POMS (Sofuoglu et al., 2001). Whether this discrepancy between two studies is due to differences in baseline characteristics of subjects in these studies or some other factors needs to be further investigated.

This study has several limitations. First, the sample size was small: only five female cocaine users. Second, only a single dose size of progesterone was administered acutely. 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 dose-dependent effects of progesterone. Third, the progesterone treatment duration was brief, with only a single progesterone administration. Fourth, multiple doses of cocaine including a placebo condition were not used. Future studies with longer treatment durations using multiple doses of progesterone and cocaine will be needed to investigate the effects of progesterone on cocaine responses and dependence measures. Finally, this study did not examine the estradiol and progesterone interactions in cocaine response, which should be investigated in future studies.

To summarize, progesterone treatment was associated with attenuated subjective effects from smoked cocaine in female cocaine users. These results also suggest that the early follicular phase of the menstrual cycle may be a useful interval to investigate the effects of exogenous progesterone in female cocaine users. Further studies are warranted to examine the effects of progesterone on various aspects of cocaine dependence.

Acknowledgments

This research was supported by grants from National Institute on Drug Abuse (P-50 DA09259) and from the National Center for Research Resources (MO1-RR00400).

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