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Cocaine Affects Progesterone Plasma Levels in Female Rats

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QUIÑONES-JENAB, V., L. I. PERROTTI, A. HO, S. JENAB, S. D. SCHLUSSMAN, J. FRANCK AND M. J. KREEK. *Cocaine affects progesterone plasma levels in female rats.* PHARMACOL BIOCHEM BEHAV **66**(2) 449–453, 2000.—Female Fischer rats injected with cocaine in a "binge" pattern (15 mg/kg, IP, three times a day, at 1-h intervals) for 1 day had significantly higher levels of progesterone than saline-treated controls ($p < 0.001$). When analyzed by the stage of the estrous cycle, animals in proestrus showed significantly higher cocaine-induced progesterone plasma levels than those in other stages of the cycle ($p < 0.01$). Progesterone plasma levels were also increased after a single dose of cocaine (15 mg/kg). However, 3 h postinjection progesterone plasma levels had returned to normal. Thus, cocaine modulation of progesterone plasma levels appears to be an acute effect. In ovariectomized rats pretreated with estrogen, progesterone, or estrogen + progesterone, no significant differences were observed in progesterone plasma levels after acute "binge" pattern cocaine administration. Thus, acute cocaine induced increases in progesterone plasma levels in intact female rats are probably due to an increase in secretion rates of progesterone rather than an acceleration of its biotransformation. Due to the profound effects of progesterone in the modulation of CNS plasticity, the modulation of progesterone plasma level by cocaine may have implications for reproductive processes and neuronal functions of women. Moreover, cocaine may affect the progesterone levels in women utilizing progesterone-based contraception or steroid replacement treatment after menopause. © 2000 Elsevier Science Inc.

"Binge" pattern Cocaine Female Estrus Progesterone OVX

COCAINE, a psychostimulant, is one of the most widely abused drugs in Western countries. Based on the 1998 National Household Survey on Drug Abuse, approximately 36% of an estimated 1.75 million Americans who used cocaine in a month were women. Females have a complex endocrinological profile. Female hormones alter a variety of reproductive (2,32) and nonreproductive behaviors (34) probably through their actions on the dopamine, serotonin, and opioid systems (10,11,13,26,33,42). It is well established that estrogen and progesterone hormones function in the brain to regulate neuronal activity and influence behavior in females. Because these gonadal hormones have profound effects on brain function, the female's hormonal state at the time of cocaine administration may influence cocaine-induced behaviors and molecular alterations in brain function.

Several studies suggest that gonadal hormones influence the activities of psychoactive drugs on neuronal dopamine systems. For example, significant differences have been shown in females during the different stages of their reproductive cycle in response to cocaine and amphetamine administration. Women in the follicular phase of their menstrual cycle, given a single challenge dose of cocaine by nasal route of administration, have been reported to have higher peak plasma cocaine levels than during the luteal phase (26). However, Mendelson et al. (29) reported that there are no gender or menstrual cycle differences in cocaine levels (area under the plasma concentration curve) or half-life in humans after intravenous administration. In rats, the estrous cycle influences an animal's motivation to self-administer cocaine (39), the intensity of cocaine-induced stereotypic and locomotor activity (36), and dopamine release in the striatum (3). Rats in estrus exhibit significantly higher behavioral responses to amphetamine than at other stages of the estrous cycle. Sensitivity to amphetamine has been reported to be augmented during estrus (3,12,20,38). Estrous cy-

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cle variations are also found in levels of striatal dopamine and its metabolite DOPAC (9,17), and in amphetamine-stimulated dopamine release (4). Because estrogen and progesterone levels fluctuate during the estrous cycle, it is possible that ovarian hormones modulate cocaine's effects in the CNS. This modulation may both underlie differences during the estrous cycle, and play a role in the gender differences observed in neurobiological effects of cocaine.

Little is known of the possible interaction of progesterone with cocaine or other drugs of abuse. It has been demonstrated that RU486, a progesterone antagonist, decreases cocaine toxicity in rats (14,40,41). We have previously observed that cocaine increases progesterone plasma levels in pregnant rats (37). Furthermore, cocaine induces lordotic behaviors in rats, which can be blocked by RU486 (1). Progesterone plasma levels are also increased after amphetamine treatment in male rats (7). Progesterone administration in OVX rats also affects stimulation of locomotor response to amphetamine (31). Thus, the progesterone system may be an important component in the cascade of events following administration of cocaine or other psychostimulants.

This study was designed to determine the effects of cocaine on progesterone plasma levels in female rats. Elucidating the response to cocaine across the reproductive cycle of female rats may have implications for the prevention and treatment of substance abuse in humans. This study extends our understanding of differences between gender and across the estrous cycle in the CNS response to cocaine.

METHOD

Animals

Eight-week-old female Fischer rats were purchased from Charles River, and were single housed in a standard cage with free access to food and water, and maintained on a 12 L:12 D cycle (lights on at 0930 h) in a room with access only by the experimenters.

Estrous Cycle Determinations

For estrous cycle studies, animals were acclimated for 10 days before the start of the experiment with daily handling for approximately 5 min. Vaginal lavage (30 min after lights on) of each rat for 10 consecutive days was used to determine its stage of the estrous cycle, as previously described (36). Two separate cohorts (each with 24 animals) were studied. In the first cohort, rats were randomly assigned to either cocaine or saline treatment groups. To ensure that there were enough animals in each stage of the estrous cycle, animals from the second cohort were assigned to cocaine or saline groups according to the smear from the previous day. Some animals (four in the cocaine-treated group and six in the saline-treated group) did not exhibit a clear metestrous phase during the course of the experiment. To include these rats in the final data analysis, all the subjects in metestrus and diestrus were grouped together (metestrus/diestrus) for each drug treatment group. A total of three animals (one in the saline-treated group and two in the cocaine-treated group) could not be reliably staged. These animals were not included in any data analysis of the estrous cycle effects. The locomotor and stereotypic activity of animals used for estrous cycle determinations have been reported previously (36).

For 5 days before cocaine or saline treatment, animals received three IP injections of 0.9% saline at 1-h intervals (starting 30 min after lights on) immediately following lavage. On the sixth day, animals received three hourly IP injections of cocaine (15 mg/kg of body weight dissolved in 0.9% saline at a concentration of 15 mg/ml) or 0.9% saline (1 ml/kg of body weight). This "binge" dosing schedule was chosen to mimic the manner in which cocaine is often self-administered by humans both in terms of temporal pattern and in relation to circadian rhythm, and has been used in many studies (6,35–37). Throughout the study all injections were give in the animal's home cage. Neither necrosis nor convulsions were expected or observed with this treatment of cocaine or saline injections.

Single Injections in Intact Females

Intact 8-week-old female rats were pretreated for 5 days with "binge" pattern saline administration 1 week after arrival in our animal facility. On the sixth day, animals received a single injection of cocaine (15 mg/kg of body weight dissolved in 0.9% saline at a concentration of 15 mg/ml) or saline 30 min after lights on ($n = 5$ per experimental group). This dose was the equivalent to one injection of the "binge" administration paradigm. Animals were sacrificed either 30 min or 3 h after this single cocaine or saline administration.

OVX Females

Fourteen-day post-OVX rats were pretreated for 5 days with "binge" pattern saline administration. Forty-eight hours before cocaine administration, animals received either vehicle (sesame oil) or estrogen benzoate (50 μg, SC). Forty-four hours after estrogen administration, animals received 500 μg of progesterone or vehicle (sesame oil). Four hours after progesterone (48 h after estrogen), animals received three IP injections of cocaine (15 mg/kg of body weight dissolved in 0.9% saline at a concentration of 15 mg/ml) 1 h apart or 0.9% saline (1 ml/kg of body weight). These doses and the injection paradigm were chosen because they have been shown to induce reproductive behaviors in OVX rats (25). Thirty minutes after the last injection, animals were sacrificed and trunk blood was collected.

Plasma Levels of Progesterone

Blood was allowed to clot and centrifuged at 3,000 RPM for 15 min at 4°C. Plasma was collected and stored at −40°C until analyzed by radioimmunoassay (RIA) for progesterone. Samples (100 μl) were analyzed with a RIA Kit (National Diagnostic; San Diego, CA) with internal standards containing known amounts of progesterone run to correct for extraction losses. Intraassay coefficients of variation averaged 7.0 ± 1.0%. Results for these assays were determined using a log-logit computer program. Progesterone levels are expressed as ng/ml.

Data Analysis

To determine whether plasma levels were significantly different between cocaine and saline treatment groups in each hormonal replacement condition, *t*-tests were used. To examine the effects of the phase of the estrous cycle and steroid replacement on plasma levels of progesterone, an analysis of variance (ANOVA) was used, followed by Newman–Keuls post hoc tests. Significance in all cases was considered to be $p < 0.05$.

RESULTS

Progesterone plasma levels were significantly higher in intact female rats after acute "binge" pattern cocaine administration than saline-treated animals, $t(42) = 6.49$, $p = 0.003$ (Fig. 1).

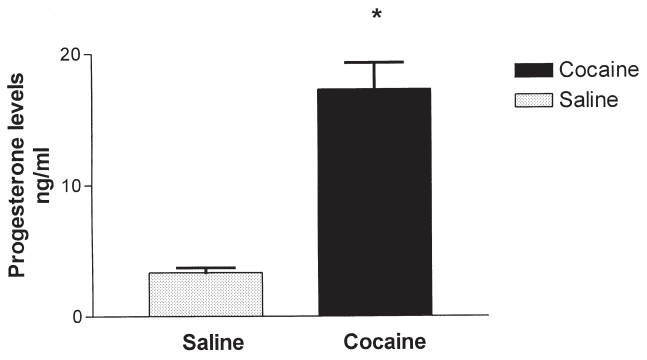

FIG. 1. Mean (+SEM) progesterone levels in female rats after "binge" pattern cocaine or saline administration. All animals ($n = 24$/group) received 5 days of saline pretreatment, followed by 1 day of cocaine or saline administration (3×15 mg/kg 1 h apart), $p = 0.003$.

To examine whether cocaine effects on progesterone plasma levels were due to a cumulative effect of cocaine after "binge" pattern administration, we examined cocaine effects on progesterone plasma levels after a single dose of cocaine, both 30 min and 3 h after injection. Similar to what was found 30 min after "binge" pattern cocaine administration, 30 min after an acute single dose of cocaine (15 mg/kg), progesterone levels were significantly higher in cocaine-treated animals than controls, $t(10) = 4.20$, $p = 0.002$ (Fig. 2). However, 3 h after a single cocaine administration, plasma progesterone levels had returned to levels comparable to those of the saline treated group, $t(10) = 1.5$, $p = 0.082$ (Fig. 2). There were no differences between groups after saline injections.

When progesterone levels were analyzed according to estrous cycle stage, plasma levels of progesterone after cocaine administration varied significantly during the estrous cycle, $F(2, 16) = 4.19$, $p = 0.034$. Progesterone plasma levels were significantly higher in cocaine-treated animals during proestrus than during estrus ($p = 0.028$) and during proestrus just failed to be significantly higher than during metestrus/diestrus ($p = 0.054$; Fig. 3). Administration of "binge" pattern cocaine did not alter progesterone plasma levels in OVX rats treated with progesterone or estrogen + progesterone, $F(1, 20) = 0.067$, $p = 0.680$; Fig. 4).

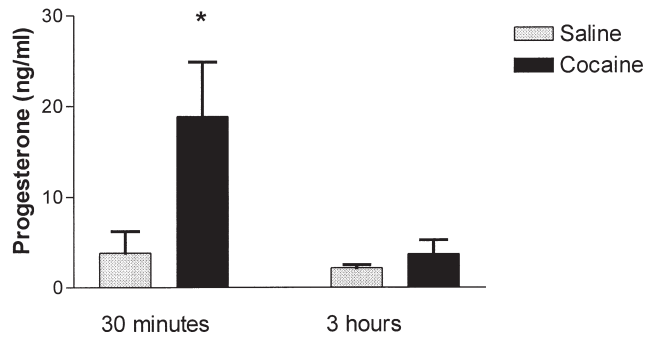

FIG. 2. Effects on progesterone plasma levels of an acute administration of 15 mg/kg cocaine or saline in female rats. Animals received a single IP injection and were sacrificed 30 min or 3 h later ($n = 5$/group); $p < 0.001$.

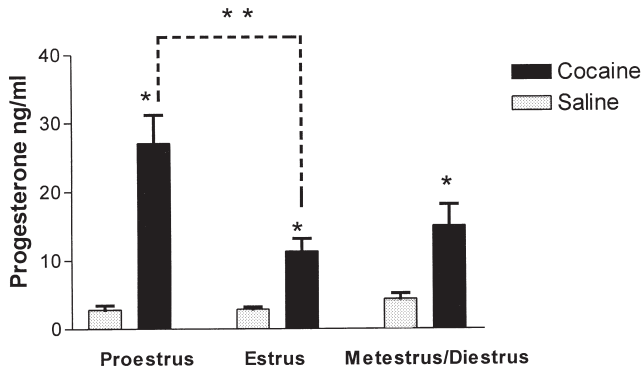

FIG. 3. Progesterone levels in female rats after "binge" pattern cocaine or saline administration in different stages of the estrous cycle. The values represent mean + SEM of the same females as in Fig. 1; *cocaine vs. saline, $p < 0.05$; **proestrus vs. estrus; $p < 0.03$ ($n = 6$/group).

DISCUSSION

We observed that acute-repetitive or single dose cocaine administration significantly increased plasma levels of progesterone in intact female rats. Cocaine modulation of progesterone plasma levels, therefore, does not depend on cumulative cocaine levels after "binge" pattern administration, because a single dose of cocaine significantly increased progesterone plasma levels in intact females. Three hours after an acute-single dose of cocaine, progesterone plasma levels returned to control levels. These results suggest that cocaine has an acute, short-lived effect on progesterone plasma levels.

We have previously shown that chronic "binge" cocaine administration doubled progesterone levels in pregnant rats (37). The magnitude of the increase in progesterone levels in this study after acute and "binge" pattern cocaine administration is comparable to that seen in pregnant rats. Amphetamine administration has been shown to increase progesterone levels in male rats (7). Other reports have implicated progesterone in the modulation of the CNS response to drug exposure (7,43,14,37,1,31). Progesterone plays a major role in female reproductive functioning, including the control, reward and locomotor aspects of reproduction. It has been reported that cocaine interrupts the menstrual/estrous cycle in humans, rabbits, monkeys, and rats (5,8,19,23,28,42). Furthermore, cocaine can interrupt the progress of pregnancy and development of maternal behaviors in humans and animal models (15,16,18,21,22,24,27,30,35,43–45). The modulation of progesterone plasma levels by cocaine may explain the profound effect of cocaine on different aspects of the female reproductive cycle, including effects on the menstrual cycle and pregnancy.

When progesterone levels were analyzed according to the stage of the estrous cycle, we observed cocaine-induced increases of progesterone levels in each stage of the rat's cycle. However, cocaine induction of progesterone plasma levels were even higher at proestrus (when progesterone levels are normally the lowest). Thus, the effect of cocaine on progesterone levels may be affected by the endocrinological profile of the female rat. The interruption or cessation of the menstrual/estrous cycle by cocaine in monkeys, rabbits, and rodents may be due to this disregulation of the plasma levels of progesterone (5,8,19,42). The endocrinological profile of female rats also affects other aspects of cocaine responses, including cocaine-induced alterations in locomotor and stereo-

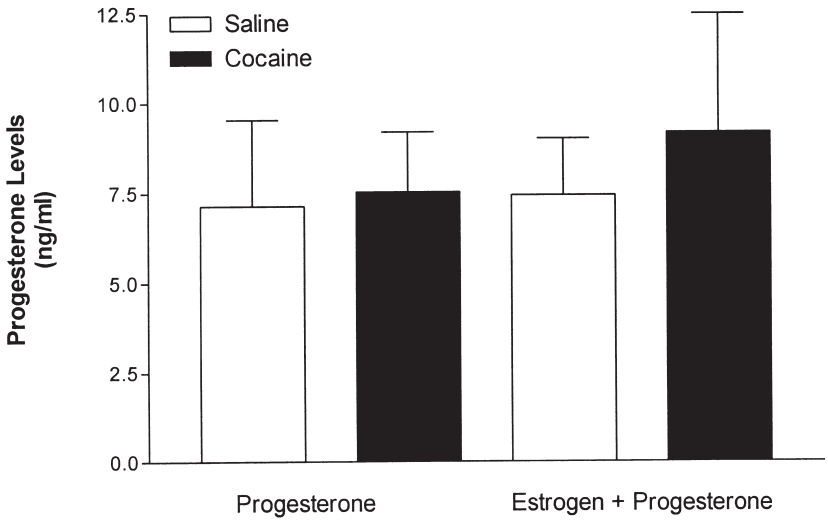

FIG. 4. Mean (+SEM) progesterone levels resulting from exogenous administration of steroids in ovx female rats after binge pattern cocaine or saline administration with different steroid replacement treatments (n = 6/group).

typic behaviors, and the levels of cocaine metabolites in the female rat (36).

There are two major mechanisms whereby cocaine modulation of progesterone levels may occur. Cocaine may either stimulate progesterone secretion or it may affect the metabolism or biotransformation of this steroid. Because we did not observe higher levels of progesterone in OVX rats after coadministration of cocaine and "replacement" steroids, it is likely that the effect of cocaine is due to the secretion of progesterone rather than to its biotransformation and clearance. However, the mechanisms underlying these effects remain to be elucidated.

Results presented here suggest that the progesterone system is an important component in the cascade of events following the administration of cocaine or other psychostimulants in females. The modulation of progesterone plasma levels by cocaine may play an important role in the effects of cocaine on different aspects of the reproductive cycle. Of further clinical importance, cocaine may affect the progesterone levels of women utilizing progesterone based contraception or steroid replacement treatment after menopause. These important issues affecting womens health need further study.

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