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Progesterone inhibits behavioral responses and estrogen increases corticosterone levels after acute cocaine administration

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Abstract

Accumulating evidence suggests that estrogen and progesterone contribute to the sexually dimorphic behavioral response to cocaine. In this study, we tested the hypothesis that varying the level of estrogen or progesterone affects cocaine-induced locomotive behavior in female rats. Ovariectomized (OVX) rats received estrogen (0, 5, 10, 20, or 50 μg) 48 h or progesterone (0, 50, 100, 250, or 500 μg) 24 h before acute saline or cocaine (15 mg/kg) administration. Although estrogen did not affect cocaine-induced ambulatory and rearing behaviors, it affected stereotypic behaviors regardless of cocaine administration (animals receiving 50 μg had higher stereotypic counts than did the OVX group). In contrast, progesterone affected rearing activity dose-dependently: 50 and 500 μg of progesterone inhibited, whereas 100 μg and 250 μg stimulated, rearing in response to cocaine. That estrogen and progesterone did not affect overall baseline behavioral activity suggests their effects are mediated in part through interactions with cocaine. Progesterone administration did not affect corticosterone levels in saline- or cocaine-treated rats. Estrogen administration, however, affected levels of corticosterone both at baseline and after cocaine treatment. After accounting for baseline differences, we found that rats receiving 5 or 10 μg of estrogen and cocaine had higher percentage increases in serum corticosterone levels than did the control group that did not receive estrogen. On the basis of these observations, we suggest that progesterone fluctuations during the estrous cycle impact cocaine-induced behavioral responses, whereas estrogen may affect activity in the hypothalamic–pituitary–adrenal axis. Thus, dose-dependent effects of gonadal hormones may underlie some of the reported sex differences and reproductive cycle effects of cocaine.

Keywords: Estrogen; Progesterone; Gonadal hormones; Females

1. Introduction

Recent clinical and basic studies have demonstrated sex differences in the pattern of cocaine use and in the behavioral and subjective effects of cocaine. In human studies, females appear to be more sensitive to cocaine reward (Griffin et al., 1989; Lukas et al., 1996; Robbins et al., 1999). Similarly, female rats exhibit greater hyperactivity and exaggerated behavioral responses compared to male rats (Caihol and Morméde, 1999; Chin et al., 2001, 2002; Craft and Stratmann, 1996; Festa et al., 2003, 2004; Sircar and Kim, 1999; Van Haaren and Meyer, 1991). Female rats also display cocaine-induced locomotive sensitization sooner than males rats, and they maintain this sensitized response after a withdrawal period, whereas male rats do not (Chin et al., 2001). Additionally, female rats acquire conditioned place preference (CPP) for cocaine at lower doses and with fewer pairing sessions than do males (Russo et al., 2003b).

The estrous cycle influences behavioral responses to acute cocaine administration: cocaine-induced behavioral activity is lowest during diestrus in comparison with proestrus and estrus (Quiñones-Jenab et al., 1999; Sell et

Abbreviations: CNS, central nervous system; s.c., subcutaneous; i.p., intraperitoneal; CPP, conditioned place preference; HPA, hypothalamic–pituitary–adrenal.

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al., 2000). It has been postulated that fluctuating levels of estrogen and progesterone modulate the locomotive response to acute cocaine administration. Steroid replacement paradigms have shown that estrogen enhances behavioral sensitization to cocaine, and estrogen has been found to either decrease or increase cocaine self-administration depending on the concentration and manner of administration (Grimm and See, 1997; Lynch and Carroll, 1999; Perrotti et al., 2001b; Sell et al., 2002; Zhou et al., 2002). On the other hand, most studies show that progesterone has no effect on cocaine-induced locomotive activity in rats (Perrotti et al., 2001b; Sell et al., 2000; Sircar and Kim, 1999).

Similar to the sexually dimorphic cocaine-induced behavioral findings, there are also sex differences in hypothalamic–pituitary axis (HPA) responses to cocaine. Compared to male rats, females have been reported to have higher levels of corticosterone and a more prolonged response after cocaine administration (Walker et al., 2001a,b; Chin et al., 2001, 2002; Kuhn and Francis, 1997). Ovariectomy has also been shown to affect corticosterone in that levels are higher after ovariectomy than they are in intact controls (Chin et al., 2002). In addition, levels of corticosterone vary throughout the estrous cycle of the rat; specifically, levels are highest during proestrus and lowest during diestrus (Walker et al., 2001a,b). This fluctuation suggests that endogenous ovarian hormones may modulate HPA responses to cocaine.

Although estrogen and progesterone levels fluctuate during the estrous cycle, most published studies have used a single dose to determine how these ovarian hormones interact with cocaine to affect locomotive behaviors (Benmansour et al., 1992; Perrotti et al., 2001b; Sircar and Kim, 1999). A study on how hormonal fluctuations affect important components of cocaine-induced responses (behavioral activation, HPA responses and cocaine metabolism) has yet to be conducted. Determining these effects is necessary to explain the biological basis of sex differences and estrous cycle influences in response to cocaine. The aim of the current study was to determine whether the dose of estrogen and progesterone affects cocaine-induced behavioral responses and corticosterone levels.

2. Methods

2.1. Animals

Eight-week-old OVX Fischer rats purchased from Charles River (Raleigh, NC) were individually housed in standard cages with access to food and water ad libitum. Rats were maintained on a 12-h light/dark cycle with lights on at 10:30 a.m. Rats were handled and weighed daily for 1 week before experimental manipulations. Experiments were conducted 2 weeks after ovariectomy. For all experimental groups, *n* ranged from 8 to 10. Each study consisted of at least two cohorts. All NIH guidelines for the care and use of laboratory animals were followed, and the experimental use of animals was approved by the Institutional Animal Care and Use Committee of Hunter College.

2.2. Hormone replacement

Rats received subcutaneous (s.c.) injections of either estrogen or vehicle (0, 5, 10, 20, or 50 μg) 48 h, or progesterone or vehicle (0, 50, 100, 250, or 500 μg) 24 h before administration of 15 mg/kg of cocaine or saline. In control groups, vehicle (sesame oil) was administered either 24 or 48 h before exposure to cocaine. Administration of 20 and 50 μg of estrogen and 250 μg of progesterone produces levels equal to those observed during the late proestrus stage; all other doses are representative of the fluctuating levels of the hormones throughout the cycle (Freeman, 1994; Pfaff and Schwartz-Giblin, 1995). Furthermore, these doses fall within the range of doses used in previously published studies that aimed to determine interactions between gonadal hormones and cocaine (Perrotti et al., 2001a; Quinones-Jenab et al., 2000; Sircar and Kim, 1999). The timing of progesterone administration was chosen on the basis of previous reports from our group showing that maximal behavioral alteration was observed when progesterone treatment was given 24 h before cocaine administration (Perrotti et al., 2004).

2.3. Drug administration

Cocaine solutions were prepared daily by dissolution in physiological saline (0.9%) and injected intraperitoneally at a volume of 1 mL/kg. Injections of 15 mg/kg of cocaine or saline were administered in the home cage 30 min after lights were turned on.

2.4. Behavioral activity

Behavioral measurements were performed for each rat in its home cage for 30 min after saline or cocaine administration. Locomotive activity was monitored with a Photobeam Activity System from San Diego Instruments (CA), as previously described (Perrotti et al., 2001a). Ambulatory activity represents the number of counts produced by the interruption of two consecutive photobeams in the horizontal frame. Rearing activity represents the total counts of vertical motion.

To assess stereotypic activity, rats were videotaped for 40 s, 15 and 30 min after cocaine or saline administration. The videotapes were later analyzed for behavioral stereotypy by three trained observers blinded to each animal's treatment group. The rating for cocaine-induced stereotypic behavior was based on a modification of the Creese and Iversen scale (Creese and Iversen, 1974). This scale consists of 10 scores ranging from 1, given to an animal that was asleep or inactive, to 10, given to an animal that exhibited

Table 1
Rating scale from Daunais and McGinty (1995)

Score	Behavior
1	Asleep, inactive
2	Alert, actively grooming
3	Increased sniffing in one location
4	Intermittent rearing and sniffing
5	Increased locomotion and sniffing
6	Intense sniffing in one location
7	Continuous pivoting and sniffing
8	Continuous rearing and sniffing
9	Maintained rearing and sniffing for >25 seconds
10	Splayed hind limbs

splayed hind limbs (Table 1). A score of 10 was never observed during the course of this experiment. Because no significant differences were observed in stereotypy between 15 and 30 min, only the stereotypic data recorded at 15 min after cocaine administration are presented.

2.5. Serum levels of benzoylecgonine and corticosterone

Thirty minutes after cocaine or saline administration, the rats were sacrificed by decapitation, following a brief exposure (20 s) to CO_2. Trunk blood was collected and centrifuged at 3000 RPM for 15 min at 4 °C. Serum was collected and stored at −80 °C. Serum was analyzed with Coat-A-Count radioimmunoassay kits for benzoylecgonine and corticosterone (National Diagnostic, San Diego, CA). Because we have previously determined that BE is not detected in saline-treated animals, in this study, we did not perform the analysis on these groups. Intra-assay coefficients of variation were less than 10.0±1.0%. Results for these assays were determined by a log-logit analysis within GraphPad Prism (GraphPad Software, San Diego, CA, USA). Serum levels of corticosterone and benzoylecgonine are expressed as ng/mL.

2.6. Statistical analysis

Ambulatory, rearing and corticosterone data are presented as mean±standard error of the mean. Stereotypic data are presented as median score±semi-interquartile range. To analyze locomotive activity, we used two-way analyses of variance to determine the effects of cocaine and hormone on locomotive behavior as follows: drug (saline or cocaine)×hormone (vehicle, estrogen, or progesterone). For all analyses, separate ANOVAs were performed on estrogen- and progesterone-treated groups, and comparisons were made with their respective controls. When significant interactions were obtained, Fisher LSD post hoc tests were used to assess differences between cocaine groups and their respective saline controls within each hormone group. To analyze stereotypic behavior, we used a Kruskal–Wallis test, followed by a Dunn's post hoc analysis, to assess the effects of hormone dose or cocaine treatment. A p-value of <0.05 was considered significant in all statistical analyses.

3. Results

3.1. Estrogen effects on cocaine-induced behaviors and serum levels of corticosterone and benzoylecgonine

Overall, cocaine significantly increased ambulatory, rearing and stereotypic activities following cocaine administration as compared with those of saline-treated controls ([$F(1,95)=21.240$, $p=0.0001$], Fig. 1A; [$F(1,95)=38.520$, $p=0.0001$], Fig. 1B; and [$H(1,74)=17.725$, $p=0.0001$], Fig. 1C). There was a significant effect of estrogen dose on stereotypic behavior in that animals receiving 50 μg had higher stereotypic counts than did the group receiving only sesame oil [$H(4,74)=10.255$, $p=0.0139$]. After 30 min, cocaine-induced stereotypic activity was similar to that observed at 15 min (data not shown). None of the estrogen doses altered baseline behavioral activity in saline-treated controls.

Estrogen administration affected baseline serum levels of corticosterone in saline-treated controls ([$F(4,33)=2.858$, $p=0.0388$], Fig. 2); saline-treated rats receiving 50 μg of

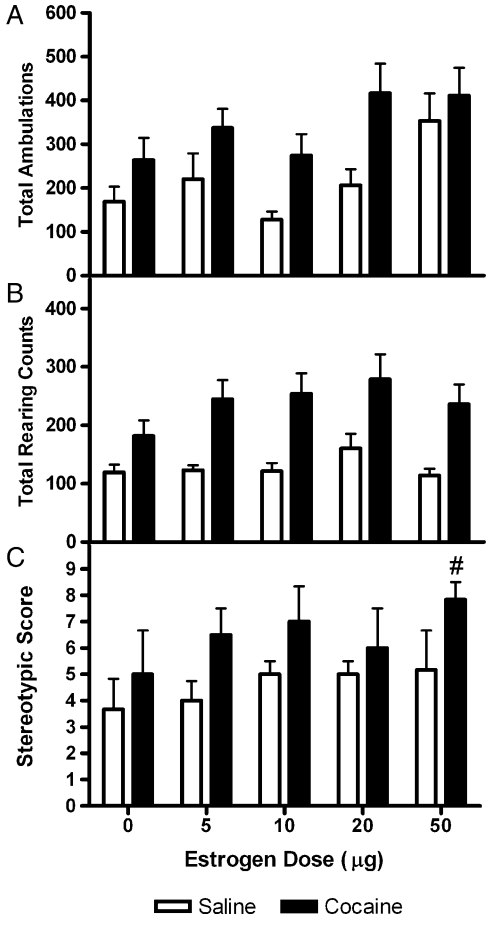

Fig. 1. Influence of estrogen dose on cocaine-induced (A) ambulatory, (B) rearing, and (C) stereotypic activities. Graphs summarize behavioral activity after administration of saline (white bars) or cocaine (solid bars) for OVX Fischer rats pretreated for 48 h with estrogen (0, 5, 10, 20, or 50 μg). Data are represented as cumulative ambulatory counts for the 30 min of behavioral testing. #Represents statistically significant differences between the vehicle- and hormone-treated groups ($p<0.05$).

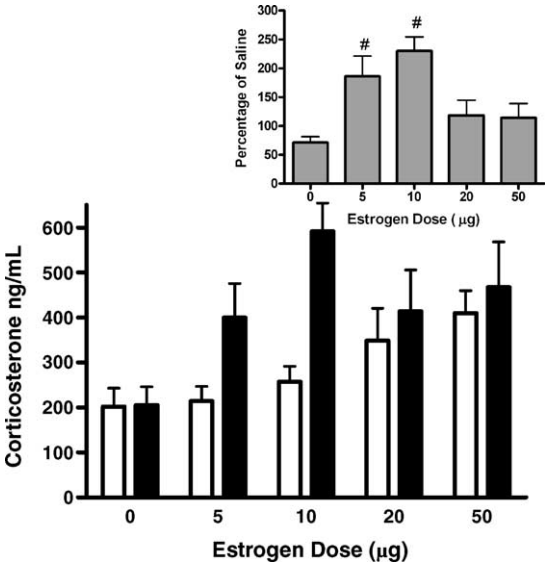

Fig. 2. Effect of estrogen replacement on serum corticosterone levels after saline or cocaine administration. Mean±S.E.M. serum levels of corticosterone (expressed as ng/mL) for cocaine- (black bars) and saline-treated (white bars) rats. The inset shows the percentage change. #Represents statistically significant differences between the vehicle- and hormone-treated groups ($p<0.05$).

estrogen had higher serum levels of corticosterone than rats receiving vehicle, 5, or 10 μg of estrogen ($p=0.0091$, $p=0.0179$, $p=0.0424$, respectively). To account for the estrogen effect on baseline corticosterone levels, data were normalized to the percentage change in reference to the respective controls where we observed an effect of estrogen dose [$F(4,38)=5.537$, $p=0.0013$]. Estrogen administration of 5 or 10 μg led to a higher percentage increase in serum levels of corticosterone after cocaine administration than was found in the hormone group receiving only sesame oil ($p=0.0032$ and $p=0.0004$, respectively) or 50 μg ($p=0.0257$ and $p=0.0035$, respectively). No significant differences in serum levels of benzoylecgonine were observed among the cocaine-treated groups ([$F(4,41)=0.5533$, $p=0.6977$], Table 2).

3.2. Progesterone effects on cocaine-induced behaviors and serum levels of corticosterone and benzoylecgonine

There was a significant interaction between cocaine administration and progesterone dose in rearing counts:

Table 2
Serum levels of benzoylecgonine (BE) after hormonal pretreatment and cocaine administration

Estrogen		Progesterone	
Dose (μg)	Serum levels (ng/mL)	Dose (μg)	Serum levels (ng/mL)
0	45.33±6.98	0	46.26±4.18
5	50.00±9.27	50	39.97±6.14
10	50.84±11.95	100	60.64±15.48
20	56.04±13.29	250	49.60±8.09
50	66.45±11.37	500	33.17±1.49

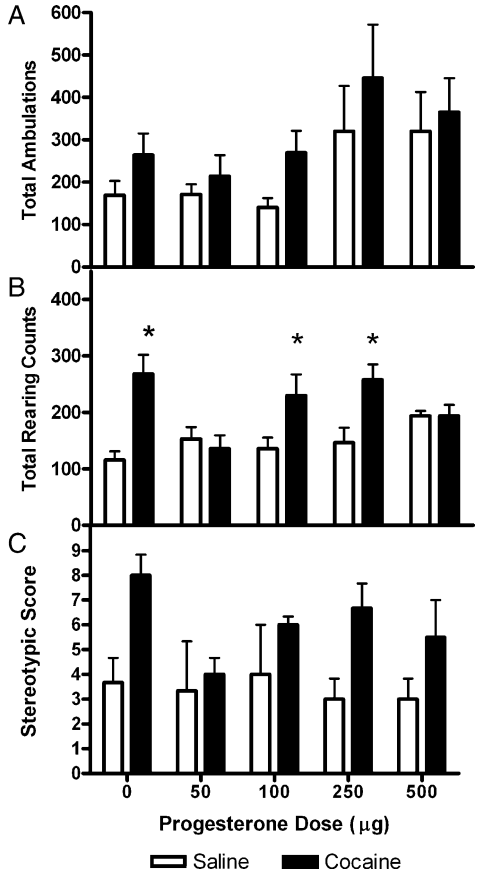

Fig. 3. Influence of progesterone dose on cocaine-induced (A) ambulatory, (B) rearing and (C) stereotypic activities. Graphs summarize behavioral activity after administration of saline (white bars) or cocaine (solid bars) for OVX Fischer rats pretreated for 24 h with progesterone (0, 50, 100, 250, or 500 μg). Data are represented as cumulative counts for the 30 min of behavioral testing. *Indicates a statistically significant difference from saline-treated control, $p<0.05$.

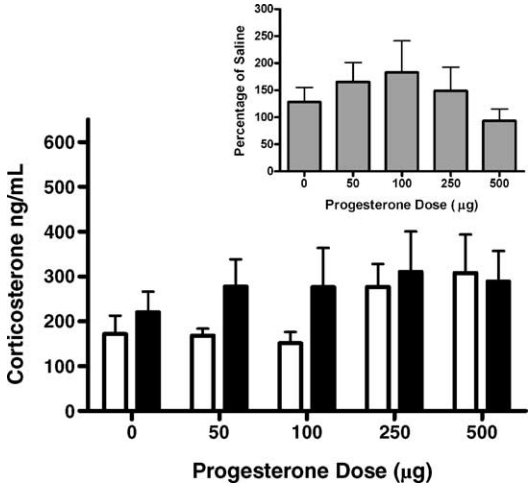

Fig. 4. Effect of progesterone replacement on serum corticosterone levels after saline or cocaine administration. Mean±S.E.M. serum levels of corticosterone (expressed as ng/mL) for cocaine- (black bars) and saline-treated (white bars) rats. The inset shows the percentage change.

groups receiving 50 and 500 μg displayed an inhibition and those receiving 100 and 250 μg exhibited an enhancement in cocaine-induced rearing [$F(4,76)=7.106$, $p=0.0001$]. Additionally, cocaine administration significantly increased rearing and stereotypic activity as compared with that of saline-treated controls ([$F(1,76)=23.123$, $p=0.0001$], Fig. 3B; and [$H(1,75)=34.039$, $p=0.0001$], Fig. 3C, respectively). Progesterone did not affect baseline activity in any of the behavioral measurements, nor did it affect baseline corticosterone levels [$F(4,35)=1.408$, $p=0.2517$]. Moreover, progesterone administration did not affect the cocaine-induced alteration of corticosterone and benzoylecgonine levels ([$F(4,76)=0.852$, $p=0.4971$], Fig. 4; and [$F(4,33)=1.003$, $p=0.4971$], Table 2, respectively).

4. Discussion

Similar to findings of past studies, we observed that cocaine increased locomotive behavior in OVX rats (Chin et al., 2002; Sell et al., 2000; Walker et al., 2001a). Consistent with previously published reports, this study found an interaction between estrogen or progesterone and cocaine on some cocaine-induced behavioral responses (Hu and Becker, 2003; Perrotti et al., 2001b; Quiñones-Jenab et al., 1999; Sell et al., 2000). However, we extend current knowledge by demonstrating that both estrogen and progesterone differentially affect behavioral and hypothalamic–pituitary–adrenal (HPA) responses to cocaine dose-dependently. Also consistent with past studies, our results show that s.c. estrogen administration does not affect ambulatory and rearing responses to acute cocaine administration (Hu and Becker, 2003; Quinones-Jenab et al., 2000; Sircar and Kim, 1999). Previous studies showed that estrogen, administered via SILASTIC capsules, potentiates cocaine-induced behavioral effects (Perrotti et al., 2001b; Sell et al., 2000). Thus, it is possible that estrogen's effects on cocaine-induced activity vary as a result of prolonged exposure to estrogen rather than a single surge. Festa and Quiñones-Jenab (2004) postulated that variations in estrogen effects after s.c. and SILASTIC administration may be attributed to different mechanisms of action, such as long- vs. short-term effects of estrogen in the central nervous system (CNS). Further studies are needed to address whether genomic and/or membrane effects may underlie the heterogeneity of reported estrogen effects on cocaine-induced behavioral responses.

It has previously been shown that progesterone administration (500 μg, 4 h before cocaine administration) has no effect on cocaine-induced behavioral responses (Perrotti et al., 2001b; Quinones-Jenab et al., 2000; Sell et al., 2000; Sircar and Kim, 1999). In the present study, however, administration of 50 and 500 μg but not 100 and 250 μg of progesterone 24 h before cocaine administration inhibited rearing responses. Thus, progesterone-dose effects on cocaine-induced rearing activity may be more complex than previously expected. It is feasible that at different doses of progesterone separate mechanisms may be activated. However, the mechanisms underlying this dose-dependent effect have yet to be determined. Russo et al. (2003a) showed that progesterone replacement via SILASTIC capsules attenuated cocaine CPP. Our results are consistent with these observations and further demonstrate that, at certain concentrations, progesterone attenuates or inhibits some cocaine-induced behavioral effects in female rats. It is possible that inconsistencies between our observations and those of others (Perrotti et al., 2001b; Quinones-Jenab et al., 2000; Sell et al., 2000; Sircar and Kim, 1999) may be attributed to differences in the route of administration and the time at which progesterone was administered.

The mechanisms by which these hormones differentially affect behavioral responses to cocaine are not well understood. Progesterone has been shown to decrease anxiety (Fernandez-Guasti and Picazo, 1995; Rodriguez-Sierra et al., 1984). Additionally, allopregnanolone, a metabolite of progesterone that interacts with the GABA-A receptor, exhibits anxiolytic effects (Bitran et al., 1993, 1995; Fernandez-Guasti and Picazo, 1995; Kokate et al., 1999; Majewska, 1992; Reddy et al., 2004). Thus, progesterone-mediated inhibition of rearing activity may, in part, be the result of anxiolytic effects resulting from GABA-A activation.

Several studies have shown that the estrous cycle influences both behavioral outcome and the animals' motivation to self-administer cocaine (Bless et al., 1997; Lynch et al., 2000; Quiñones-Jenab et al., 1999; Roberts et al., 1989; Walker et al., 2001b). In rats, cocaine-induced behavioral responses during diestrus are lower than those of rats in other stages of the cycle (Quiñones-Jenab et al., 1999; Sell et al., 2000; Walker et al., 2001b). In women, subjective effects of cocaine were also shown to fluctuate during the menstrual cycle (Sofuoglu et al., 1999). Female cocaine users had an attenuated subjective response to cocaine during the luteal phase of the menstrual cycle as compared with those in the follicular phase (Sofuoglu et al., 1999). In addition, Evans et al. (2002) demonstrated that women in the luteal phase had less desire to smoke cocaine than they did in the follicular phase. Since the luteal and diestrus phases of the cycle are characterized by higher levels of progesterone, these reports suggest that the increase of progesterone serum levels decreases the subjective effects of psychostimulants in humans. This decrease may partially be attributed to the anxiolytic effects of progesterone.

Estrogen may modulate cocaine-induced behavior through alternate pathways. For example, estrogen increases striatal dopamine turnover and produces changes in the density of striatal dopamine receptors (Becker, 1990; Di Paolo et al., 1981, 1985; Hruska and Pitman, 1982; Hruska and Silbergeld, 1980). Additionally, estrogen has been shown to increase dopamine release in the mesolimbic pathway (Becker, 1990; Thompson and Moss,

1994). Thus, an estrogen-mediated increase in dopamine activity may underlie increases in stereotypic behavior. However, since no effect of estrogen was observed in locomotor activity, it is feasible that estrogen affects various components of behavioral responses via differential modulation of CNS pathways. For example, it has been postulated that stereotypic and locomotive responses are controlled by different pathways in the CNS, as well as by differential activation of the D1/D2 dopamine receptors (Capper-Loup et al., 2002; De Jonge et al., 1986; McCreary and Marsden, 1993).

On the basis of our observations, we postulate that the transition from inhibition to potentiation of behavioral responses to cocaine in female rats during the estrous cycle is mainly derived from alterations in hormone levels. We showed that although hormonal fluctuations affect cocaine-induced responses, the magnitude of their impact on behavioral outcome was not dramatic. Indeed, ambulatory activity was not affected by either hormone. It is possible that the presence of both hormones may lead to a more robust behavioral effect than that observed after replacement of a single hormone. In a recent publication by our group, we showed that estrogen and progesterone co-administration produced a complex interaction wherein increases or decreases in behavioral outcomes varied according to temporal interactions between the hormones (Perrotti et al., 2004). The degree to which the fluctuation of ovarian hormone levels affects these phenomena remains to be elucidated.

A second aim of this report was to examine the effect of ovarian hormones on the activation of the HPA axis. The post-cocaine surge of corticosterone has been postulated to be essential for the control of cocaine-induced behavioral alterations. For example, manipulation of corticosterone levels has been shown to influence locomotive responses to cocaine (Marinelli et al., 1994, 2000) as well as the development of sensitized responses after cocaine administration (Rough-Pont et al., 1995). After acute cocaine administration, female rats have exhibited greater activation of the HPA axis than male rats (Chin et al., 2001; Festa et al., 2003; Kuhn and Francis, 1997). Moreover, cocaine-induced increases in levels of corticosterone were present in rats receiving estrogen replacement but not in OVX controls (Perrotti et al., 2001b). Our results are consistent with these findings. Additionally, we have expanded on these observations by demonstrating that estrogen, but not progesterone, affects corticosterone levels dose-dependently. The observed estrogen effects occurred at two levels. On one level, an alteration in baseline corticosterone levels was observed, namely, there was an observed three-fold increase in corticosterone levels in estrogen-treated rats in response to cocaine. Our finding is consistent with a study that reported an increase in corticosterone levels in OVX rats after estrogen replacement (Burgess and Handa, 1992). This observation strongly suggests that fluctuating levels of estrogen during the estrous cycle are potentially involved in creating a differential predisposition to cocaine-induced responses in HPA activity. On a second level, there was a cocaine–estrogen interaction wherein percentage increases in levels of corticosterone were higher at certain doses. However, it remains to be elucidated whether administration of higher doses of estrogen results in a ceiling effect that diminishes cocaine-induced increases in corticosterone levels at these doses. Based on our findings, we postulate that fluctuations of estrogen during the estrous cycle affect HPA-mediated responses to cocaine, whereas progesterone–HPA interactions play a limited role.

Taken together, our results demonstrate that ovarian hormones interact with cocaine in a multifaceted manner, both inhibiting and enhancing behavioral and endocrinological responses to cocaine. Important clinical observations can be drawn from this study. According to the findings of our dose–response study, the use of contraceptives in varying concentrations of estrogen and progesterone may differentially affect cocaine-induced effects in women. Studies delineating how hormonal interactions affect cocaine-induced responses and subjective effects are necessary to improve treatment methods developed for cocaine addiction in females.

Acknowledgments

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