COADMINISTRATION OF ESTROGEN AND PROGESTERONE DIFFERENTIALLY AFFECTS LOCOMOTOR RESPONSES TO COCAINE IN RATS

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Fluctuations in ovarian hormones throughout the estrous cycle may underlie sex differences in behavior. In this study, estrogen plus progesterone were coadministered at different ratios to determine whether the interaction of those hormones during the estrous cycle contributes to cocaine-induced alterations in behavior. Before cocaine (15 mg/kg) or saline administration, ovariectomized female rats received either vehicle or estrogen (10 μg or 50 μg) and progesterone (100 μg or 500 μg). Cocaine-induced locomotor activity was affected by estrogen plus progesterone ratio. While administration of 50 μg estrogen plus 500 μg progesterone increased total locomotor behavior, administration of 10 μg estrogen plus 500 μg progesterone inhibited total locomotor activity. This study suggests that alterations of estrogen and progesterone serum levels may underlie the observed changes in cocaine-induced behavior during the estrous cycle. (*Ethn Dis*. 2008;18[Suppl 2]:S2-51–S2-53)

Key Words: Cocaine, Gonadal Hormones, Sex Differences

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INTRODUCTION

Numerous reports of sex differences in cocaine-induced behavioral activation have shown that female rats display more locomotor and stereotypic behavioral responses and self-administer cocaine at higher rates than do male rats.[1–6] Female rats also condition to cocaine at lower doses and after fewer pairings than do males.[4] Fluctuations in ovarian hormones throughout the estrous cycle may underlie these sex differences in behavior. Notably, cocaine-induced behavioral responses during diestrus are lower than those of rats in other stages of the cycle.[7–9] Moreover, studies in which estrogen and progesterone are replaced in ovariectomized rats further support a role of ovarian hormones in observed sex differences. For example, whereas estrogen replacement enhances locomotor and stereotypic behaviors in response to cocaine,[8,10,11] progesterone attenuates some cocaine-induced locomotor and rewarding responses.[8,10–13]

Most studies examining the role that estrogen and progesterone play in the effects of cocaine have used a single hormone-replacement paradigm. However, females have a complex endocrinologic profile, wherein both estrogen and progesterone are always present but their concentrations fluctuate throughout the estrous cycle. Interactions between gonadal hormones, in terms of both concentrations and temporal relationships (length of time between each hormonal surge), have been postulated to be critical in the modulation of reproductive behaviors as well as neuronal activity and plasticity. Indeed, when progesterone is administered at shorter intervals in relation to estrogen and cocaine treatment, progesterone attenuates cocaine-induced motor responses.[14] Moreover, when progesterone is administered at longer intervals, it either has no effect or enhances cocaine-induced motor alterations.[14] However, whether the outcome of coadministration of estrogen and progesterone is also affected by the doses used has yet to be determined. The aim of this study was to test that possibility.

METHODS

Animals

Eight-week-old ovariectomized Fischer rats (Charles River, Raleigh, NC) were individually housed in standard cages with access to food and water *ad libitum*. Rats were maintained on a 12-hour light/dark cycle with lights on at 10:30 AM. Rats were handled and weighed daily for one week before experimental manipulations. Each study consisted of at least two cohorts. Experiments were conducted two weeks after ovariectomy, and 8–10 rats were in each group. All National Institutes of Health 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.

Hormone Replacement and Drug Administration

For single-hormone replacements, rats received subcutaneous injections of either estrogen (50 μg) at 48 hours or progesterone (500 μg) at 24 hours before cocaine or saline administration. For coadministration of hormones, rats received estrogen (10 μg or 50 μg, 48 hours) and progesterone (100 μg or 500 μg, 24 hours). To control for the times at which estrogen and progester-

one were injected, separate control groups received vehicle (sesame oil) 24 and 48 hours before exposure to cocaine. These doses fall within the range of doses used in previously published studies that aimed to determine interactions between gonadal hormones and cocaine.[11,15,16] The timing of progesterone administration was chosen on the basis of previous findings that showed maximal behavioral alteration when progesterone treatment was given 24 hours before cocaine administration.[14] Furthermore, the specific doses were based on a previously conducted dose-response study.[10] Cocaine solutions were prepared daily by dissolution in physiologic saline (.9%) and were injected intraperitoneally (15 mg/kg) in the home cage 30 minutes after lights were turned on.

Locomotor Activity and Statistical Analysis

Locomotor activity was recorded for each rat in its home cage for 30 minutes after saline or cocaine administration with a Photobeam Activity System from San Diego Instruments (San Diego, Calif), as previously described.[14] Locomotor counts represent the number of beam breaks recorded in each chamber. Total locomotor activity data are presented as means plus or minus standard error of the mean. To analyze locomotive activity, two-way analyses of variance were used 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 analyses of variance were performed on estrogen-, progesterone-, and estrogen+progesterone-treated groups, and comparisons were made with their respective controls. When significant interactions were obtained, Fisher least significant difference post hoc tests were used to assess differences between cocaine groups and their respective saline controls within each hormone group. For all analyses, $P < .05$ was considered to be significant.

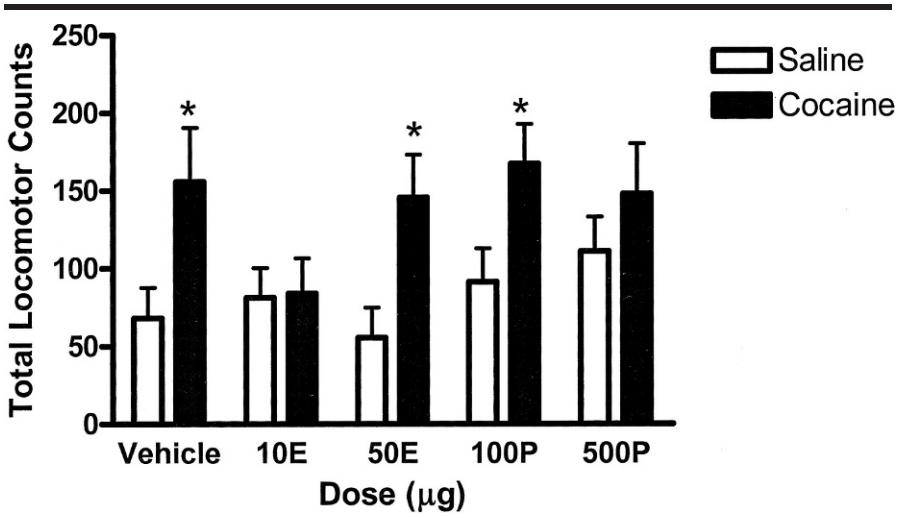

Figure 1. Dose effect of estrogen or progesterone administration on cocaine-induced ambulatory counts in ovariectomized female rats. Data are represented as cumulative ambulatory counts for the behavioral testing. *Denotes a significant difference ($P < .05$) between saline- and cocaine-treated rats. E = estrogen, P = progesterone.

RESULTS

Overall, cocaine increased total locomotor activity ($F[1,71] = 64.052$, $P < .001$; Figure 1 and $F[1,60] = 44.561$, $P < .001$; Figure 2). A significant interaction between hormone dose and drug treatment was observed in this group of rats ($F[4,71] = 5.325$, $P < .001$; Figure 1); administration of 10 μg estrogen or 500 μg progesterone decreased locomotor activity. When both hormones were administered, an interaction between drug and hormone was observed ($F[4,60] = 6.510$, $P < .001$; Figure 2): 10 μg estrogen + 100 μg progesterone, 10 μg estrogen + 500 μg progesterone, and 50 μg estrogen + 100 μg progesterone inhibited cocaine's effect.

DISCUSSION

Our group previously reported[5] that administration of either estrogen or progesterone alters cocaine responses in a dose-dependent manner. The present study extends those results by demonstrating that changes in the concentration ratio between estrogen and progesterone also affect locomotor responses to cocaine. Previous studies have had discrepant findings, reporting that coadministration of estrogen and progesterone has either no effect, inhibits, or stimulates cocaine-induced behavioral alterations and rewarding effects.[8,11,13,16] However, all of those studies tested only one dose of estrogen and progesterone. Our observations in the present study suggest that the conflicting results of those previous studies may have resulted from the different doses used.

Our results suggest that estrogen and progesterone interact differentially, not only temporally as previously shown, but also according to their concentrations, and that various ratios can either enhance or inhibit cocaine-induced behavioral responses. Therefore, the dynamic efficacy of estrogen and progesterone in altering cocaine behavioral responses may be physiologically relevant. For example, because progesterone and estrogen serum levels are constantly changing in females (humans and rats), this endocrinologic profile may ultimately affect a female's behavioral and subjective responses to cocaine. This

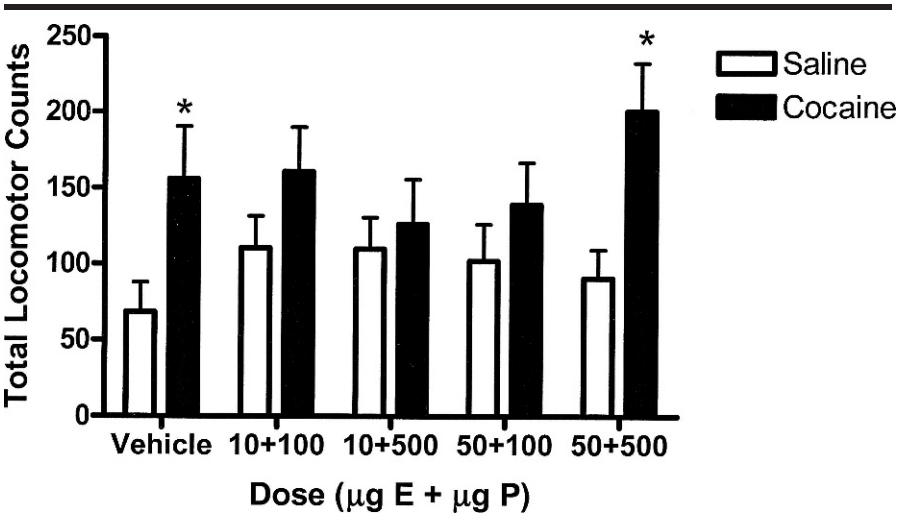

Figure 2. Dose effect of estrogen plus progesterone coadministration on cocaine-induced ambulatory counts in ovariectomized female rats. Data are represented as cumulative ambulatory counts for the behavioral testing. *Denotes a significant difference ($P < .05$) between saline-treated and correspondent cocaine-treated rats. E = estrogen, P = progesterone.

constant change may, in part, explain the previously reported estrous cycle-mediated responses to cocaine. Thus, women at different stages of the menstrual cycle may use different doses of cocaine to achieve greater subjective effects of the drug, depending on the concentration of progesterone and estrogen in their serum or how long ago higher serum levels occurred. Moreover, the development of tolerance and sensitization in females may be also be affected by the ratio of estrogen to progesterone. This study further illustrates how the complicated endocrinologic profile of females affects outcomes in addictive disorders.

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