Influence of Ovarian Hormones and Estrous Cycle on the Behavioral Response to Cocaine in Female Rats

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ABSTRACT

Both humans and experimental animals demonstrate gender differences in response to cocaine. However, the mechanisms underlying these differences remain unclear. The purpose of the present study was to determine whether ovarian steroid hormones play a role in the locomotor response to cocaine in rats. Initial assessments of locomotor activity measured using photobeam monitors verified the robust gender difference in response to cocaine in our experimental paradigm. Subsequently, cocaine (5.0, 7.5, and 10.0 mg/kg) was shown to increase total horizontal activity in a dose-dependent manner in independent groups of intact females; the 5.0 mg/kg dose was selected for use in additional studies to determine the effect of estrogen (E) and progesterone (P) on the response to cocaine. Mature female rats were ovariectomized (OVX) or OVX and implanted with hormone-filled (E or P) Silastic capsules. Three to 4 weeks later, automated and observational measures of behavior were recorded after the administration of 5 mg/kg cocaine. Hormone replacement with E or E + P (but not P alone) resulted in greater cocaine-evoked hyperactivity than was observed in OVX animals. On measurement in normally cycling rats, hyperactivity induced by 5 mg/kg cocaine was greater during proestrus and estrus than during diestrus 2. The results of this series of experiments demonstrate that E significantly influences the responsiveness of female rats to cocaine. The enhanced response to cocaine was demonstrated in the presence of pharmacologically administered E as well as correlated with the normal estrous cycle.

Gender differences in the response to cocaine have been demonstrated in both humans and experimental animals. The human literature, although limited in scope, contains reports that women cocaine users demonstrate different patterns of abuse than men (Griffin et al., 1989). In addition, the self-reported “nervous” response elicited by intranasal cocaine is greater and the duration of the “high” is longer in women than in men (Kosten et al., 1996).

Experimental animal models provide more specific information concerning gender differences in response to cocaine. In rats, females are more sensitive than males to the locomotor stimulant effects of cocaine (Glick et al., 1983; Van Haaren and Meyer, 1991; Bowman and Kuhn, 1996). In drug discrimination studies, acquisition of a cocaine-saline discrimination was similar in intact females and males and the respective dose-effect curves were similar, but the duration of the effect of cocaine was shorter in female rats (Craft and Stratmann, 1996). Gender has also been shown to affect cocaine self-administration, with the estrous cycle influencing the response in female rats (Roberts et al., 1989).

Gender differences in cocaine metabolism could underlie gender differences in cocaine responsiveness. However, a recent publication (Bowman et al., 1999) indicates that this is highly unlikely. This group injected male and female rats with 15 mg/kg cocaine i.p. and measured brain and plasma levels of cocaine and two of its major metabolites over the next 90 min. No gender differences in brain or plasma levels of cocaine were observed over the course of the experiment, whereas plasma levels of benzoylecgonine (a biologically active metabolite of cocaine) were lower in female than in male rats. Thus, as thoroughly discussed by Bowman et al. (1999), gender differences in metabolism do not appear to account for the enhanced sensitivity of female rats to cocaine.

There are permanent differences between male and female brains that are initiated by sex hormone exposure during specific developmental periods. In addition, on a day-to-day basis, sex hormones play a dynamic, modulatory role in many neuronal processes such as those involved in sexual behavior and reproduction. It is our working hypothesis that gender differences in the response to cocaine are also due to dynamic effects of ovarian steroids, acting via regulation of the dopamine (DA) and serotonin (5-HT) substrates involved in the

ABBREVIATIONS: DA, dopamine; 5-HT, serotonin (5-hydroxytryptamine); E, estrogen; P, progesterone; OVX, ovariectomy.
central actions of cocaine (e.g., Callahan and Cunningham, 1997; Callahan et al., 1997; McMahon and Cunningham, 1999). This hypothesis is consistent with the study cited earlier suggesting estrous cycle effects on the response to cocaine as well as the report that gender differences in response to cocaine in rats arise at puberty as adult levels of sex hormones are established (Bowman and Kuhn, 1996).

The present study was designed specifically to test the hypothesis that ovarian hormones affect the behavioral sensitivity of female rats to cocaine. To this end, the locomotor activity and stereotypic effects of cocaine were assessed in intact, ovariectomized (OVX), and hormone-replaced OVX female rats.

Materials and Methods

Animals

Adult female (200–250 g) and male (350–400 g) age-matched Sprague-Dawley (virus antibody-free) rats were obtained from Harlan (Houston, TX), housed three or four to a cage with food and water available ad libitum, and maintained at a constant temperature (21–23°C) and humidity (45–50%) with lights on 7:00 AM to 7:00 PM except where otherwise noted. All experiments were carried out in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

OVX and Hormone Implant Surgery

Female rats were anesthetized with a cocktail composed of 43 mg/kg ketamine, 8.6 mg/kg xylazine, and 1.5 mg/kg acepromazine administered i.m. in 0.9% NaCl before surgical bilateral ovariectomy through a dorsal incision and intrascapular placement of hormone implants. Hormones were administered by way of Silastic (polydimethylsiloxane) implants (Bridges, 1984). Briefly, Silastic tubing (i.d., 0.078 inches; o.d., 0.125 inches; Allied Biomedical, Paso Robles, CA) was packed with crystalline hormone. Plugs were made using short segments of wooden applicator sticks, and the implants were sealed into place. Experiments were conducted 3 to 4 weeks after surgery and implant placement.

Behavior Measurement

Locomotor activity was monitored and quantified with an open field activity system (San Diego Instruments, San Diego, CA). All animals were habituated to the activity chambers for 3 h/day for 2 days before the test day (except where otherwise noted). Each activity monitor, housed within a sound- and light-attenuating enclosure, consisted of a 40 × 40 × 40-cm clear Plexiglas box within a 4 × 4 matrix of photobeams adjusted to 5 cm above the cage floor. Each monitor was equipped with another horizontal row of 16 photobeams that was located 11 cm above the 4 × 4-photobeam matrix to measure vertical activity. The control software counted and stored total horizontal as well as vertical beam interruptions in 5-min bins. A video camera (low-light, adjustable aperture) and video monitor provided the observer with the ability to score animals for the presence of particular behaviors.

A quantitative measure of expression of rodent behaviors was recorded during the automated measurement of activity using a modification (McMahon and Cunningham, 1999) of the technique developed by Kelley (1998). At 5, 15, 30, 60, 90, and 120 min after the cocaine injection, each rat was observed for 1 min by an observer who was blind to the experimental conditions.

Experimental Design

Experiment 1: Gender Difference in Response to Cocaine Administration. Using independent treatment groups, the locomotor response to an i.p. injection of saline (1 ml/kg) or cocaine (10 or 15 mg/kg) was recorded in 20 male and 22 female rats (n = 6–8 rats/group). Animals were habituated to the test chamber as described earlier. On the day of each experiment, animals were habituated for 1 h and then saline or cocaine was administered and activity was monitored for 60 min immediately after the injection.

Experiment 2: Cocaine Dose-Response in Female Rats. To establish an optimal dose of cocaine to use in future studies of female rats, the dose-response relationship for cocaine was established using independent groups of naive, intact female rats. Habituated, intact females (n = 48) were divided into five dose groups of 8 to 12 rats/group. On the day of testing, rats were placed in the activity chamber and locomotor activity was monitored for 60 min of habituation. Subsequently, each rat received one challenge injection of saline (1 ml/kg i.p.) or cocaine (2.5, 5.0, 7.5, or 10 mg/kg i.p.), and activity was monitored for an additional 120 min.

Experiment 3: Effects of E and P on Response to Cocaine in OVX Rats. The intact female rats previously challenged with a single dose of saline or cocaine (experiment 2) were anesthetized 6 weeks later and OVX or OVX and implanted with E, P, or E + P as described earlier (n = 12/group; randomized). Three to four weeks after OVX and hormone implantation, activity was measured during a 60-min rehabilitation to the activity monitors. Immediately after rehabilitation, half of each treatment group was administered saline (n = 6) or cocaine (5 mg/kg; n = 6), and locomotor activity was monitored for 120 min with concurrent behavioral scoring.

Experiment 4: Estrous Cycle Influence on the Response to Cocaine. Intact cycling female rats were housed as described earlier with a controlled light/dark cycle (lights on 6:00 AM to 8:00 PM). Estrous cycles were monitored cytotologically by vaginal lavage in a group of 24 naive intact female rats for 14 days before the start of the experiment. Vaginal samples were taken by flushing 60 to 75 μl of methylene blue (0.1% in water) in and out of the vagina using a micropipette and then placing a drop of exudate on a slide. The resulting cytological displays of exfoliated cells showed histologic variations that indicated the stage of the estrous cycle. Vaginal cytology was evaluated under light microscopy to determine the stages of the estrous cycle based on the predominant cell type (Waynforth and Flecknell, 1992). The experiment was carried out without prospective regard for the day of the estrous cycle.

Vaginal lavage was performed before placement in the chambers each day. On the first experimental day, rats were habituated to the activity chamber for 3 h. On the second day, after 60 min of habituation, rats received a saline injection (1 ml/kg i.p.), and activity was monitored for 120 min. On the third day, after 60 min of habituation, rats received a cocaine challenge (5 mg/kg i.p.), followed by 120 min of automated activity monitoring and behavioral observations. The 1st h of habituation was recorded each day. Vaginal samples were also taken again in the afternoon of the cocaine challenge and the next morning to confirm the stage of cycle on the test day. After locomotor activity data were obtained, the data for individual rats were grouped according to the day of the estrous cycle determined in the morning immediately before measurement of activity.

Drugs

Cocaine hydrochloride (National Institute on Drug Abuse, Rockville, MD) was dissolved in physiological saline (0.9% NaCl) and administered i.p. such that a volume of 1 ml/kg delivered the desired dose. 17β-Estradiol (Sigma Chemical Co., St. Louis, MO) and progesterone (Sigma Chemical Co.) were administered in crystalline
form sealed into Silastic tubing as described earlier (4 mm and 40 mm, respectively).

**Statistical Analysis**

Data collected in automated activity monitors for the entire 60-min (experiment 1) or 120-min (experiments 2–4) session are presented as mean total horizontal or vertical activity counts for the session (±S.E.). A one-way ANOVA was used to detect the effects of dose on locomotion in intact female rats (experiment 2). A two-way ANOVA was used to assess the effects of treatment (gender or hormone), dose, and treatment × dose interactions (experiments 1 and 3). For experiment 4, separate one-way ANOVAs were used for each test (habituation, saline, or cocaine) because rats were categorized into different groups on each test day due to fluctuations in the estrous cycle. Individual mean values were compared using Dunn’s (Bonferroni’s t) planned comparisons procedure (experiments 1 and 2) or Duncan’s multiple-range test (experiments 3 and 4). All statistical analyses were conducted with an experiment-wise error rate (α) of 0.05 (SAS for Windows, Version 6.12).

**Results**

**Experiment 1: Gender Difference in Response to Cocaine Administration.** This experiment was carried out to determine whether our paradigm for measuring locomotor activity would reveal gender differences in the hyperactivity evoked by cocaine. Thus, we assessed the locomotor response to cocaine administration at two doses in independent groups of male and female rats (Fig. 1). A main effect of dose ($F_{2,36} = 25.17, P < .001$), gender ($F_{1,36} = 29.85, P < .001$), and gender × dose interaction ($F_{2,36} = 10.31, P < .001$) was observed for total horizontal activity. Female rats exhibited greater horizontal activity than males after either 10 or 15 mg/kg cocaine ($P < .05$). Horizontal activity observed after a saline injection did not significantly differ between male and female rats.

**Experiment 2: Cocaine Dose-Response in Female Rats.** Because of the dramatic response exhibited by female rats in comparison with males in experiment 1, it was necessary to optimize the dose of cocaine in female rats for use in further experiments. A dose-response relationship was established using independent groups of female rats tested after injections of 0, 2.5, 5.0, 7.5, and 10 mg/kg cocaine; Fig. 2A illustrates the time course of activation evoked by cocaine. A main effect of dose was observed for total horizontal activity ($F_{4,43} = 12.36, P < .001$; Fig. 2B); planned comparisons indicated that doses of 5.0, 7.5, and 10 mg/kg significantly increased activity above saline levels ($P < .05$; Fig. 2B). Previous experiments have demonstrated that male rats generally show very little hyperactivity at 5.0 mg/kg i.p. (M. Bankson and K. Cunningham, unpublished results; Antoniou and Kafetzopoulos, 1996). Because a dose that stimulates a submaximal but significant response is ideal for studying modulatory effects of hormones on cocaine-induced hyperactivity, the 5.0-mg/kg dose of cocaine was selected for subsequent studies of the response to cocaine in female rats ovariectomized and/or replaced with E and/or P.

**Experiment 3: Effects of E and P on the Response to Cocaine in O VX Rats.** To observe the influence of the ovarian hormones E and P on cocaine-induced behaviors, saline or cocaine (5 mg/kg) was administered to OVX and hormone-replaced OVX female rats. The data in Fig. 3 show that animals in the E-treated (OVX + E and OVX + EP)
groups exhibited more horizontal locomotor activity in response to cocaine than did OVX or OVX + P animals. Analysis of total horizontal activity during the cocaine challenge indicated a main effect of hormone ($F_{3,40} = 5.66, P < .001$) and drug ($F_{1,40} = 30.83, P < .001$), but no hormone × drug interaction ($F_{3,40} = 2.51, P = .072$). Post-hoc comparisons revealed that when treated with E alone or E in combination with P, OVX rats exhibited a significant enhancement of cocaine-evoked horizontal activity in comparison to the hormone-free OVX group ($P < .05$).

The data shown in Fig. 4 demonstrate that hormone treatment also affected the vertical activity in response to 5 mg/kg cocaine. Analysis of the vertical activity data demonstrated a main effect of hormone ($F_{3,40} = 5.80, P = .002$) and drug ($F_{1,40} = 18.13, P < .001$) as well as a hormone × drug interaction ($F_{3,40} = 3.20, P = .034$). Again, post hoc comparisons revealed that when treated with E alone or E + P, OVX rats showed a significant enhancement of cocaine-evoked vertical activity in comparison with the hormone-free OVX group ($P < .05$; Fig. 4).

Hormone treatments also affected locomotor activity during habituation and in response to saline injection (Table 1). During rehabilitation (see Materials and Methods), a main effect of hormone was revealed for both horizontal ($F_{3,44} = 3.29, P = .029$) and vertical ($F_{3,44} = 4.17, P = .011$) activity with post hoc comparisons revealing a significant effect of E on horizontal activity and a significant effect of both E and P on vertical activity. Furthermore, in response to the saline injection, animals in all three hormone treatment groups exhibited significantly greater horizontal activity than did OVX rats, but differences in vertical activity between these groups did not achieve statistical significance.

Other behavioral measures, as quantified using observational time sampling, substantiated the observation that cocaine-evoked behaviors were affected by hormone treatment. Observational scores indicated that overall activity was
lower in OVX than hormone-treated animals (data not shown). There was no indication that expression of stereotypical behaviors in response to cocaine correlated with reductions in locomotor activity.

Experiment 4: Estrous Cycle Influence on the Response to Cocaine. To determine whether the effect of the ovarian hormones on cocaine-induced behaviors is manifest in the natural state of an intact cycling female, the estrous cycle was monitored in intact rats before and during the experimental period. The data in Fig. 5 demonstrate that in response to cocaine, there was a main effect of estrous stage on horizontal activity ($F_{3,20} = 5.20, P = .008$). Post hoc tests indicated that horizontal activity of rats in proestrus and estrus was significantly elevated over that of rats in diestrus 2 ($P < .05$).

The data in Fig. 6 demonstrate a main effect of the estrous cycle on cocaine-evoked vertical activity ($F_{3,20} = 3.93, P = .024$). Planned comparisons show that increases in vertical activity in response to cocaine were significantly enhanced during proestrus when compared with all other stages of the estrous cycle ($P < .05$).

During habituation, and after the saline challenge, no differences in horizontal and vertical activity between cycle stages were observed (Table 2).

Although some variability in behaviors over the estrous cycle was seen during observational time sampling of behavior, no significant differences between cycle stages were observed, and there was no indication that cocaine-induced stereotyped behaviors were interfering with locomotor activity (data not shown).

Discussion

This study demonstrates that estrogen enhances the response to cocaine in OVX female rats. In addition, based on the finding that hyperactivity evoked by cocaine injection varied across the estrous cycle, the estrogen effect appears to be dynamic and to occur at normal, physiological E concentrations. These findings indicate that the impressive sensitivity of intact female rats to the locomotor stimulant effects of cocaine is due at least in part to gender-based differences in sex hormones, particularly E.

Open field activity in photobeam monitors proved to be a robust method to detect gender differences in the behavioral response to cocaine. Based on a dose-response curve generated in intact female rats, we carried out the subsequent experiments using 5 mg/kg cocaine. This dose, although not generally effective in males (M. Bankson and K. Cunningham, unpublished results; Antoniou and Kafetzopoulos, 1996), provided a clear stimulation of locomotor activity in females.

To address the hypothesis that ovarian hormones are responsible for the enhanced response to cocaine in females, our approach was to establish chronic, steady-state levels of E, P, or E + P in OVX female rats using hormone-filled Silastic implants. In this experiment, there was no attempt to mimic any natural endocrine state, but rather, the goal was to determine whether the presence or absence of circulating E and/or P would modulate the behavioral response to...
caine. The ability of steroid-filled Silastic tubing to establish and maintain constant blood levels of E or P has been well described (Bridges, 1984). The blood level of hormone achieved is directly proportional to the length of the Silastic implant. We (Hope et al., 1992) and others (Bridges, 1984) have previously shown that the 4- and 40-mm implants used here for E and P, respectively, establish blood hormone levels roughly equivalent to the peak levels of these hormones during the estrous cycle in the rat (Smith et al., 1975). Again, it should be emphasized that although the serum concentrations of hormones established in these animals are within the physiological range, a normal rat is not exposed continuously to these hormone levels for more than 1 day at a time except during pregnancy (Smith et al., 1975). In the present experiments, these levels were maintained at a steady state for 3 to 4 weeks.

Animals maintained with E implants demonstrated a significantly enhanced response to cocaine compared with OVX animals. The enhanced responsiveness was demonstrated by increased horizontal and vertical activity. The data presented here as well as other data emerging from our laboratory (not shown) suggest that vertical activity in response to cocaine is particularly robust in E-treated female rats. Here, we found a statistically significant interaction between cocaine and hormone treatment for vertical activity, although horizontal activity revealed significant effects of cocaine and hormone but not a significant interaction. These findings provide strong support for the concept that circulating levels of E play an important modulating role in the hyperactivity evoked by cocaine.

Animals treated with P alone did not exhibit increased locomotor activity in response to cocaine. Interestingly, when animals received both E and P, locomotor activity was increased compared with OVX animals, but the addition of P to the E treatment appeared to slightly attenuate the E effect. The present experiments do not provide us with any explanation for this effect of P, but as discussed later, both E and P can function to regulate gene transcription. Thus, we speculate that the net modulation by E of 5-HT and DA substrates important in the behavioral response to cocaine might be differentially regulated in the presence or absence of P.

In the normal female rat, E and P levels fluctuate over a 4- to 5-day estrous cycle, with both hormones reaching their maximal levels during proestrus (Smith et al., 1975). Both E and P decline during estrus to reach their lowest levels during diestrus 2 and then begin to increase again for the next cycle. Thus, hormone levels in normally cycling female rats fluctuate considerably over successive 4- to 5-day cycles. Measurement of locomotor activity in response to cocaine in cycling females revealed that animals exhibited the greatest response during proestrus and estrus, when E and P levels are highest. It is interesting to note that the E + P replacement regimen (designed to provide hormone levels equivalent to an animal in proestrus) resulted in a response to cocaine quite similar to that found in normal cycling animals during proestrus and estrus. Furthermore, during normal cycling, the hyperactivity induced by cocaine was decreased significantly during diestrus-2 to approximately the same levels found in OVX animals.

Our findings that ovarian steroids, particularly E, enhance the response of female rats to cocaine are consistent with the existing body of literature concerning gender differences in response to psychostimulants. Both amphetamine-evoked hyperactivity and DA release vary with the estrous cycle as E and P levels change (Becker and Cha, 1989). Amphetamine-induced hyperactivity (Savageau and Beatty, 1981), rotational behavior and sensitization (Robinson et al., 1982a), and electrically stimulated rotational behavior (Robinson et al., 1982b) have all been shown to be greater in female than male rats. In female rats, OVX attenuated amphetamine-induced behavior (Camp et al., 1986) and DA release (Becker and Ramirez, 1981). Other recent investigations into the gender difference in the behavioral response to cocaine have also suggested that the gender difference may be hormonally based (Van Haaren and Meyer, 1991; Bowman and Kuhn, 1996; Craft and Stratmann, 1996).

Although the experiments presented here were designed to study cocaine-evoked behavior, we also recorded the activity of animals during the habituation paradigm and after saline (vehicle) injection. In these experiments, the spontaneous activity of well habituated animals did not differ between
intact male and female rats nor was any fluctuation in basal activity level evident across the estrous cycle. However, a hormonal influence on spontaneous activity was noted in hormone-treated O VX rats that consistently exhibited elevated levels of activity during habituation and after a saline injection in comparison with untreated O VX rats. Because hormone levels in our protocol approximate the peak levels of hormone seen at proestrus, these data are consistent with earlier studies that suggested E and P modulate spontaneous locomotor activity. Gender differences in spontaneous activity were recorded in the early 1900s by measuring wheel-running activity (Hitchcock, 1925). Another early study revealed that wheel-running activity varied over the estrous cycle exhibiting a peak of activity on the day of estrus (Wang, 1923). Female rats have also been shown to exhibit higher levels of open field activity than males (Slob et al., 1981). Further evidence that hormonal influence on activity levels can be mediated centrally comes from the demonstration that intrahypothalamic implants of E in O VX rats enhanced wheel-running behavior (Colvin and Sawyer, 1969).

An attractive explanation for our observation that E enhances the response to cocaine is that E modulates the neural substrates through which cocaine acts. There are currently two known receptors for estrogen, ERα and ERβ (Kuiper et al., 1996); both are found widely distributed in the brain (Hirata et al., 1992; Shughru et al., 1997), and both are known to function as transcription factors. Thus, one possible mechanism underlying E effects on the cocaine-evoked hyperactivity is that E may regulate the expression of one or more of the receptors and/or reuptake transporters through which cocaine exerts its effects. For example, cocaine binds to the reuptake transporters for DA, 5-HT, and nor epinephrine and inhibits the reuptake of these neurotransmitters (Koe, 1976). Potentiation of mesocorticolimbic DA neurotransmission has been implicated as the mechanism by which cocaine mediates many of its behavioral effects (Kalivas and Nemeroff, 1988; McBride et al., 1999), and more recent evidence supports a modulatory role for 5-HT (Callahan and Cunningham, 1997; McMahon and Cunningham, 1999). Bethea et al. (1998) have recently reviewed the literature concerning E regulation of 5-HT substrates, and there also are examples in the literature of E regulation of DA substrates (e.g., Di Paolo et al., 1982; Morissette and Di Paolo, 1993). Unfortunately, the data currently available regarding E regulation of expression of 5-HT and DA substrates have been collected from a wide variety of hormone treatment models, few of the effects have been correlated with functional activity of the receptor or transporter, and none of the effects have been clearly associated with any behavioral change in a cocainetreated animal. However, the data that are currently available do support the hypothesis that E has the capability of regulating the expression of transporters and receptors in various brain areas.

In addition to its ability to regulate gene transcription, evidence has accumulated to demonstrate that E also acts at the membrane in a variety of cell types, including neurons, via activation of a variety of second-messenger pathways and ion channels (Watson et al., 1998; Watson and Gametchu, 1999). Thus, it is interesting to speculate that E modulation of cocaine-evoked hyperactivity may involve some of these membrane-initiated pathways as well. For example, E has been shown to enhance DA release in the striatum and in striatal preparations in vitro (Becker and Cha, 1989; Becker, 1990), as well as to modulate DA receptor-mediated effects on adenylylcyclase in cultured striatal neurons (Maus et al., 1989).

In conclusion, we have presented data supporting the concept that E plays a major role in the gender differences observed in response to cocaine. We suggest that the mechanisms underlying these E effects may involve a combination of E regulation of expression of neurotransmitter receptors and uptake transporters as well as direct modulation of neuronal function via E interactions with receptors and/or reuptake transporters at the plasma membrane. Currently, we do not have sufficient information regarding the specific effects of E on these processes to formulate a complete model of the role of E in regulating the mesolimbic pathways involved. However, increasing our understanding of these mechanisms should not only reveal the mechanisms underlying gender differences in the response to abused stimulants but also enhance our understanding of other problems involving similar neurocircuity, such as depression and schizophrenia.

References
Callahan PM, De la Garza R and Cunningham KA (1997) Ovarian hormone influence on cocaine behaviors 885

### TABLE 2
Baseline activity counts during habituation (60 min) and after an injection of 1 ml/kg saline, i.p. (120 min) in cycling female rats

<table>
<thead>
<tr>
<th></th>
<th>Total Horizontal Activity</th>
<th>Total Vertical Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Habitation</td>
<td>Saline</td>
</tr>
<tr>
<td>Diestrus 1</td>
<td>2599.0 ± 147.8</td>
<td>873.3 ± 137.6</td>
</tr>
<tr>
<td>Diestrus 2</td>
<td>2442.8 ± 193.0</td>
<td>984.6 ± 132.4</td>
</tr>
<tr>
<td>Proestrus</td>
<td>2148.8 ± 200.5</td>
<td>995.8 ± 142.8</td>
</tr>
<tr>
<td>Estrus</td>
<td>1976.4 ± 191.7</td>
<td>884.3 ± 185.2</td>
</tr>
</tbody>
</table>

Values are mean ± S.E.


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