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Increased sensitivity of dopamine systems following reproductive experience in rats

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Abstract

Several studies have suggested that alterations in forebrain dopamine activity during the postpartum period may result in the onset of postpartum psychosis in women [J. Psychosom. Obstet. Gynecol. 19 (1998) 104; Prog. Neuro-Psychopharmacol. Biol. Psychiatry 17 (1993) 571; J. Clin. Psychiatry 51 (1990) 365.]. The present study investigated whether increased dopamine activity in these forebrain regions is a normal consequence of reproductive experience in rodents. Both intact and ovariectomized parous and nulliparous females were tested for their responses to the dopamine agonist apomorphine using two behavioral measures, prepulse inhibition (PPI) and oral stereotypy. In addition, dopamine and DOPAC levels were measured in tissue from the striatum and nucleus accumbens together with circulating plasma prolactin levels. The results of the behavioral studies demonstrate an increased response to apomorphine in parous females. Parous subjects also had increased levels of dopamine and DOPAC in striatal tissue and lower levels of circulating prolactin. Ovariectomy in nulliparous females resulted in a potentiated response to apomorphine with regard to the disruption of PPI, as well as a significant decrease in the plasma prolactin levels, as compared with intact nulliparous females. These data suggest that increased dopamine activity in forebrain regions occurs as a consequence of parity, which persists for a minimum of several weeks postpartum. These findings support the hypothesis that increased dopamine sensitivity in forebrain dopamine regions may be one potential mechanism underlying the development of postpartum psychosis in women.

Keywords: Parity; Dopamine; Postpartum psychosis; PPI; Oral stereotypy; Prolactin; Apomorphine; Estrogen

1. Introduction

The postpartum period is a time of increased risk for the development of psychiatric disorders, a severe form being postpartum psychosis (Cookson, 1982; Kendell et al., 1987; Klompenhouwer and van Hulst, 1991; Musey et al., 1987; Nonacs and Cohen, 1998; Pedersen, 1999). Postpartum psychosis has an acute onset, usually occurring within 4 weeks after birth, and often in women with no prior mental illness (APA, 1994; Nonacs and Cohen, 1998; Rhode and Marneros, 1993). Characterized by symptoms including confusion and disorientation, psychomotor disturbances, depression, mania, hallucinations and delusions, this disorder, like other forms of psychosis, is usually treated with antipsychotic medication (Kendell et al., 1987; Klompenhouwer and van Hulst, 1991; Nonacs and Cohen, 1998). The majority of women respond to treatment, although relapse during subsequent pregnancies is common (>50%) and the severity of the disease during later births is often increased (APA, 1994; Pfuhlmann et al., 1999; Rhode and Marneros, 1993). While the onset of this disorder is clearly related to the biological consequences of pregnancy and parturition, the exact mechanism remains unknown. Analogous to other psychotic disorders, the underlying etiology of postpartum psychosis is thought to involve enhanced dopamine activity within the forebrain (Deuchar and Brockington, 1998; Kumar et al., 1993; Vinogradov and Csernansky, 1990; Wieck et al., 1991). One hypothesis proposed to explain the development of postpartum psychosis is that the elevated levels of estrogen during pregnancy, followed by a rapid decline in this hormone postpartum, cause an increase in the sensitivity or activity of brain dopamine systems, resulting in psychotic symptoms (Ahokas and Aito, 1999; Ahokas et al., 2000;

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Deuchar and Brockington, 1998; Kumar et al., 1993; Meakin et al., 1995; Vinogradov and Csernansky, 1990; Wieck et al., 1991).

Studies in animals have provided some support for the proposed effects of elevated levels of estrogens on forebrain dopamine receptors. For example, studies in female rats have shown that chronic estradiol treatment leads to increased density of striatal dopamine receptors (Di Paolo et al., 1981, 1982; Hruska, 1986; Hruska and Nowak, 1988; Levesque and Di Paolo, 1991). In addition, acute estradiol administration results in the potentiation of both dopamine release (Becker, 1990; Castner et al., 1993; Pedersen, 1999) and dopamine-mediated behaviors, including rotation and stereotypy (Becker, 1990; Diaz-Veliz et al., 1994; Di Paolo et al., 1981). These findings suggest that elevated levels of estradiol, such as those observed during pregnancy, may result in the up-regulation of dopamine release and receptor function in areas involved in psychosis. To date few studies have examined the potential alterations in forebrain dopamine function as a consequence of parity. The literature that does exist supports the hypothesis that there is an increase in dopamine activity associated with reproductive experience, although these animal studies focus on hypothalamic dopamine systems (Bridges et al., 1997; Felicio et al., 1997).

Many behavioral paradigms have been designed to study the sensitivity of forebrain dopamine systems. Of the behaviors studied in these paradigms, only a small number are both observed in psychotic patients and utilized as animal models of psychosis. We chose to examine the effects of parity on two such measures: prepulse inhibition (PPI) and stereotypy. PPI is the reduction in startle amplitude that is observed when a weak acoustic stimulus precedes (by approximately 100 ms) the presentation of a startle-eliciting stimulus (Graham, 1975; Swerdlow and Geyer, 1998). Often used to test the efficacy of antipsychotic drugs (Swerdlow and Geyer, 1998; Weike et al., 2000), PPI has been shown to be disrupted in both psychotic patients (Grillon et al., 1992) and rodents treated with dopamine agonists (Wan et al., 1994). In addition, studies in both women and rats have demonstrated that PPI is affected by ovarian hormones (Koch, 1998; Swerdlow et al., 1997). Stereotypy, which is characterized by repetitive behaviors, is also increased in schizophrenic patients and is reflective of increased dopamine activity (Pedro et al., 1994). Oral stereotypy represents a specific pattern of repetitive mouth movements including licking, mouthing, gnawing and biting, which typically emerge following the administration of drugs that either directly or indirectly stimulate striatal dopamine receptors (Conti et al., 1997; Yeghiayan et al., 1997). Moreover, drug-induced stereotypy is utilized as an animal model of the positive symptoms of psychosis (Samms-Dodd, 1999a,b).

The purpose of the present set of studies was to assess the effect of reproductive experience on forebrain dopamine systems using both behavioral and neurochemical methods. To examine potential changes in postsynaptic dopamine receptor activity we studied the effect of the direct dopamine agonist apomorphine on PPI and oral stereotypy in parous and nulliparous females. We also compared the responses of ovariectomized and intact females, to determine whether ovarian hormones, including estradiol, further impact dopamine receptor sensitivity. To examine possible alterations in dopamine content, we measured tissue levels of dopamine and its primary metabolite DOPAC within the striatum and nucleus accumbens, in intact parous and nulliparous females. Finally, as an indirect measure of hypothalamic dopamine activity (dopamine inhibits prolactin release), we examined plasma prolactin levels as a function of reproductive experience, as well as following ovariectomy. These studies were performed in females after they had weaned their litters to avoid the possible confounds that the hormonal changes of lactation would introduce. Given that in humans, postpartum psychosis increases in severity with subsequent pregnancies, it is probable that the effects of pregnancy on dopamine systems are long lasting. The results of these studies demonstrate an increased behavioral response to apomorphine following reproductive experience in both intact and ovariectomized subjects. Moreover, there is evidence of increased presynaptic activity in the nigrostriatal dopamine system, with both dopamine and DOPAC increased in parous females. Finally, prolactin levels in parous females were decreased, with levels similar to those observed following ovariectomy, indicating a parity-induced increase in the activity of the hypothalamic dopamine system as well. Overall, these findings support the hypothesis that one consequence of parity is a relatively persistent increase in dopamine activity in the hypothalamus as well as in brain regions involved in psychosis.

2. Materials and methods

2.1. Animals

Seventy female Sprague–Dawley rats (Crl:CD[SD]BR; 200–225 g) were purchased from Charles River Laboratories (Kingston, NY). The animals used in these experiments were maintained in accordance with the guidelines of the Committee of Care and Use of Laboratory Animal Resources, National Research Council. Subjects were housed in polypropylene cages ($45 \times 25 \times 20$ cm) with food and water available ad libitum in light (on 0500–1900 h)- and temperature (21–25°C)-controlled rooms.

2.2. Experimental design

2.2.1. Experiment 1

Forty-three age-matched females were generated to create four experimental groups; these included intact nulliparous ($n=10$), ovariectomized nulliparous ($n=11$), ovariectomized primiparous ($n=11$), and ovariectomized multiparous ($n=11$) females (See Table 1). All females were tested in four sessions; these included an initial

Table 1
Generation of age-matched reproductively experienced subjects

	Time in weeks							
Treatment	1	4	7	9	12	15	17	18
Multiparous	Mate	Birth	Wean	Mate	Birth	Wean	Ovx	Baseline testing
Primiparous				Mate	Birth	Wean	Ovx	Baseline testing
Nulliparous							Ovx	Baseline testing
Multiparous (intact)	Mate	Birth	Wean	Mate	Birth	Wean		Baseline testing
Nulliparous (intact)								Baseline testing

baseline testing session followed by three drug treatment sessions during which animals were treated with two doses of apomorphine (1 and 3 mg/kg) and vehicle (saline). Each subject received all three treatments in a counterbalanced order.

2.2.2. Experiment 2

Twenty-seven age-matched females were generated to create three experimental groups; these included intact nulliparous ($n = 11$), intact multiparous ($n = 8$), and ovariectomized nulliparous ($n = 8$) females. All females were tested in two sessions with an initial baseline testing session followed by a single-drug treatment session during which subjects were treated with apomorphine (1 mg/kg). One month following the completion of behavioral testing all subjects in Experiment 2 were rapidly decapitated for the collection of truck blood and brain tissue to allow for the subsequent analysis of plasma PRL and neurochemical analysis.

2.3. Drug treatment

Apomorphine hydrochloride (Sigma, St. Louis, MO) was dissolved in 0.9% NaCl (saline) immediately prior to administration. Apomorphine (1 or 3 mg/kg) or vehicle was administered via subcutaneous (sc) injection in a volume of 1 ml/kg body weight 5 min prior to behavioral testing. In experiments where animals received more than one drug dose, animals served as their own controls receiving saline and apomorphine (1 and 3 mg/kg) in a counterbalanced order with 4 days between each test session.

2.4. Behavioral testing

Given previous findings indicating alterations in PRL secretion between parous and nulliparous females, all behavioral testing was conducted between 0800 and 1200 h to correspond with a time of relatively stable PRL levels in the intact cycling animals. Prior to behavioral testing, all animals were acclimated to handling and to the testing environment.

2.4.1. Prepulse inhibition

Assessment of PPI was accomplished with an SR-Pilot startle chamber (San Diego Instruments, San Diego, CA). The chamber (inner dimensions: 17.5 cm × 12.5 cm × 19.5 cm) consisted of a speaker (diameter 11 cm) mounted on the top and a factory-calibrated piezoelectric sensing platform. Factory-set stimulus parameters were used for all experiments. These included continuous 65-dBA broad-band background noise and two trial types: *basic startle stimulus* of 40 mS, 115-dBA broad-band noise pulse, and a *prepulse stimulus* that consisted of a 40 mS, 85-dBA prepulse that preceded the basic startle stimulus by 100 mS. These two stimulus trial types are referred to as pulse and prepulse trials, respectively. All behavioral responses to stimuli were recorded in arbitrary startle units. For each testing session, animals received a total of 42 stimuli presented in pseudorandom order with a 15-s interstimulus interval. The percent of PPI expressed within each test session was calculated as follows: [100 − (mean prepulse response/mean pulse response) × 100)].

2.4.2. Oral stereotypy

During the course of a 15-min test period, oral stereotypy was measured at 5-min intervals for 30 s. Oral stereotypy, scored as either present or absent, included licking, mouthing, gnawing, and biting. Data are represented as the percent of females displaying oral stereotypies collapsed over the 15-min test period.

2.5. Neurochemical and endocrine analyses

2.5.1. Measurement of dopamine and DOPAC in tissue homogenates

On the day that tissue content was analyzed, frozen brains were mounted on a cryostat and 1 mg tissue punches were removed from the dorsolateral striatum and the shell region of the nucleus accumbens. Analysis of DOPAC and DA in tissue samples was accomplished with an isocratic HPLC system consisting of a Dynamax solvent delivery system (model SD-200; Rainin Instrument, Woburn, MA), which pumped mobile phase (NaH_2PO_4 75 mM; EDTA 100 mg/l; octyl sulfate 100 mg/l; 20% acetonitrile; pH 3.4) at a rate of 1.0 ml/min, and an ESA Coulochem model 5100A electrochemical detector (ESA, Bedford MA). Oxidation and reduction potentials were set at +0.34 and −0.04 V, respectively. All tissue was homogenized in mobile phase and centrifuged. Twenty-five microliters of supernatant was injected into a Rheodyne 7725i injector containing a 100-μl sample loop. DOPAC and DA were separated on a Rainin Microsorb-MV column (C18, 3 μm, 4.6 × 100 mm). The electrochemical detector was interfaced with a Macintosh 6100 computer, and peaks were integrated using Dynamax data analysis software. DA and DOPAC (picograms per milligram tissue) were determined based on comparison to an external standard curve.

2.5.2. Prolactin radioimmunoassay

Plasma concentrations of PRL were measured using the NIDDK rat PRL kit, which was supplied by the National Hormone Pituitary Program. This kit included reference preparation NIDDK-rPRL-RP-3 and anti-rat PRL S-9. All plasma samples were assayed in duplicate at volumes ranging from 1 to 50 μl. Assay sensitivity averaged 30–40 pg/tube; interassay and intraassay coefficients of variation were 5% and 9%, respectively.

2.6. Procedures

Following arrival, all females were allowed a 1-week habituation period prior to mating. Females were mated by placing two females with one resident male for a period of 1 week. On Day 1 postpartum all litters were culled to 10 pups. Females reared pups undisturbed until weaning at Day 21 postpartum. The sequence of mating utilized to generate age-matched primiparous and multiparous females is detailed in Table 1. Ovariectomies were performed under general anesthesia using Metofane (Mallinckrondt, Phillipsburg, NJ) 2 weeks after weaning of the first litter from primiparous females and the second litter from multiparous females. All animals were allowed a 1-week recovery following ovariectomy. Prior to drug testing, subjects were tested in the absence of any drug manipulation to determine whether reproductive experience alone could alter basal levels of PPI. Animals that were not ovariectomized began this baseline testing during diestrus, 3 weeks after weaning of their second litter. In all subjects, drug testing began 4 days after baselines were measured.

On each day of behavioral testing, subjects were removed from their home cage and placed in the PPI chamber for a 5-min habituation period. Animals were then injected with either saline or the direct DA agonist apomorphine (1 or 3 mg/kg, sc), and returned to the chamber. Five minutes later PPI testing commenced. Every 15 s either a pulse or a prepulse + pulse was presented in pseudorandom order for a total of 10 min. Startle amplitude was recorded following each stimulus presentation. The overall level of PPI was then determined for the entire 10-min session. The prepulse chamber had a clear front panel to allow for the simultaneous assessment of stereotypy during PPI testing.

For subjects in Experiment 2, 1 month following the completion of behavioral testing subjects were rapidly decapitated during the afternoon (1500 h) of diestrus and trunk blood was collected for analysis of plasma PRL. At this time brains were rapidly removed, frozen on dry ice, and stored at -80°C for subsequent neurochemical analysis.

2.7. Statistical analyses

PPI data were analyzed using a two-way repeated measures analysis of variance (ANOVA) with drug dose as the repeated factor and reproductive experience as the between-subjects factor. In experiments in which only one dose was used, data were also analyzed using a two-way repeated measures ANOVA, but with time (pretest vs. posttest) as the repeating factor and reproductive experience as the between-subjects factor. There were no significant differences in baseline levels of PPI among any of the groups. All PPI data were analyzed as raw PPI scores; however, the data are represented as the percent of change from baseline for ease of presentation. For data in which only a single dose of the drug was administered post hoc analysis was conducted using a paired Student's *t* test comparing baseline and drug effects. All other post hoc analyses were performed using Tukey's test. Dopamine and DOPAC data were analyzed using a Student's *t* test. Oral stereotypy data were analyzed using the Fisher exact probabilities test. Prolactin data were analyzed using a one-way ANOVA with Tukey's post hoc analyses.

3. Results

3.1. Experiment 1

3.1.1. Effect of ovariectomy on apomorphine-induced disruption of PPI in nulliparous females

Initial comparisons were made between age-matched, nulliparous ovariectomized and nonovariectomized (intact) females. A two-way repeated measures ANOVA revealed a significant main effect of drug [$F(2,38) = 3.83$, $P < .03$] and a trend toward an interaction between drug dose and reproductive status [$F(2,38) = 2.62$, $P < .08$]. Post hoc comparisons indicated that both doses of apomorphine decreased PPI in ovariectomized females ($P < .004$), but not in intact females ($P < .88$), as shown in Fig. 1. No significant differences in the acoustic startle response were observed between the two groups. These data indicate that removal of the ovaries in nulliparous females results in the disruption of PPI following administration of a DA agonist, an effect that is not observed in intact cycling females.

3.1.2. Effect of parity on apomorphine-induced disruption of PPI in ovariectomized females

To determine if reproductive experience would result in further alterations in the level of PPI, comparisons were made between age-matched nulliparous, primiparous, and multiparous females. All females were ovariectomized 1 week prior to collection of baseline PPI date. A two-way repeated measures ANOVA revealed a significant main effect of drug [$F(2,61) = 8.28$, $P < .001$] with no effect of reproductive experience and no interaction (see Fig. 2). To examine the nature of this drug effect, one-way ANOVAs were conducted for each level of reproductive experience. As described previously, there was a significant drug effect in nulliparous females [$F(2,20) = 7.25$, $P < .004$]

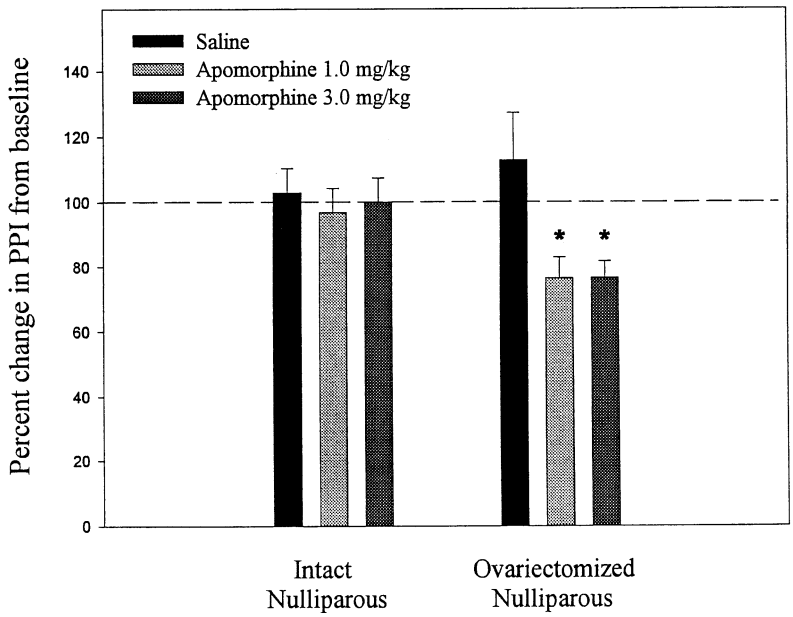

Fig. 1. The effects of apomorphine (1.0 and 3.0 mg/kg) on PPI in age-matched, intact and ovariectomized, nulliparous females. Results are presented as the mean (±S.E.M.) percent change in PPI from each subjects own baseline data ($n=10-11$). *$P<.05$ as compared with vehicle response.

with both doses decreasing PPI. A significant drug effect was also observed in primiparous females [$F(2,22)=3.83$, $P<.04$]; however, post hoc analysis revealed that only the 1.0-mg/kg dose of apomorphine significantly decreased the percent of PPI ($P<.04$). Finally, apomorphine also disrupted PPI in multiparous females [$F(2,20)=3.505$, $P<.05$). This effect was due to the ability of the highest dose of apomorphine to decrease PPI in these females ($P<.05$). Thus, parity neither reverses nor enhances the effect of ovariectomy on apomorphine-induced inhibition of PPI.

3.1.3. *Effect of parity on apomorphine-induced oral stereotypy in ovariectomized females*

In addition to measuring PPI, subjects were also monitored for the level of stereotypy induced by systemic apomorphine. These behaviors were measured during PPI testing. All animals exhibited stereotypic sniffing throughout the test period following administration of apomorphine. A significant effect of reproductive experience was observed with respect to the number of animals displaying oral stereotypies (including licking, mouthing and gnawing) during the 15-min test. Over 60% of females in both

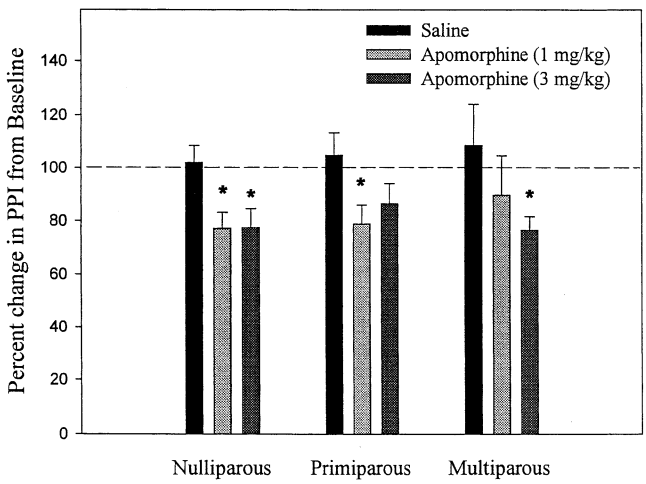

Fig. 2. The effects of apomorphine (1.0 and 3.0 mg/kg) on PPI in age-matched, ovariectomized females with varying amounts of reproductive experience. Results are presented as the mean (±S.E.M.) percent change in PPI from each subjects own baseline data ($n=11$ per group). *$P<.05$ as compared with vehicle response.

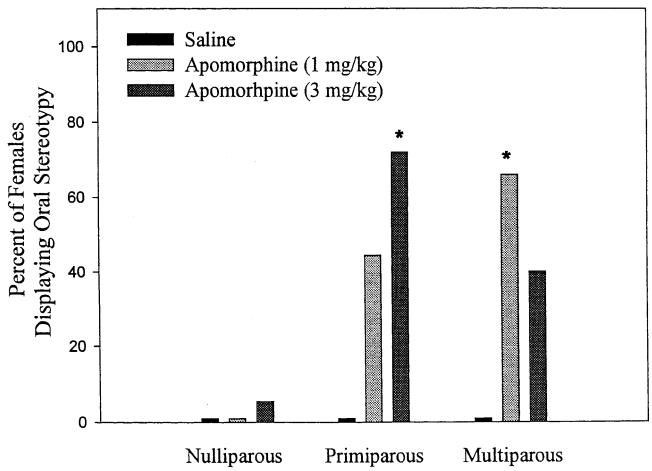

Fig. 3. The effects of apomorphine (1.0 and 3.0 mg/kg) on the induction of oral stereotypies in age-matched, ovariectomized females with varying amounts of reproductive experience. Results are presented as the percent of females within each treatment group displaying oral stereotypy over a 15-min test period ($n=5-6$). *$P<.05$ as compared with vehicle response.

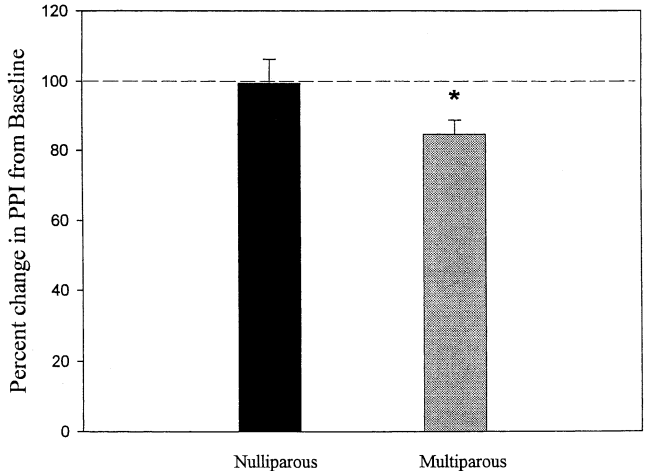

Fig. 4. The effects of apomorphine (1.0 mg/kg) on PPI in age-matched, intact nulliparous ($n=11$) and multiparous ($n=8$) females testing during diestrus. Results are presented as the mean (±S.E.M.) percent change in PPI from each subject's own baseline data. *$P<.05$ as compared with nulliparous females.

reproductively experienced groups displayed oral stereotypies following either dose of apomorphine, as illustrated in Fig. 3. The lack of an effect in the nulliparous females suggests that reproductively experienced females are more sensitive to the stereotypy-inducing effects of apomorphine.

3.1.4. Effect of parity on apomorphine-induced disruption of PPI in intact females

To determine whether reproductive experience results in altered PPI when ovarian hormones are still present, we examined the effects of apomorphine on the disruption of PPI in intact females. Two groups of age-matched females were generated, an intact nulliparous group and an intact multiparous group. All subjects were tested during diestrus, as the level of PPI is known to fluctuate over the estrous cycle (Koch, 1998). The effect of a single dose of apomorphine (1 mg/kg) was used and compared to the baseline level of PPI. A significant drug effect was observed [$F(1,17)=4.87$, $P<.04$]. Subsequent post hoc analysis indicated that there was a significant disruption in the level of PPI in the multiparous females [$t(8)=3.61$, $P<.009$], but not in the nulliparous females ($P<.65$), as shown in Fig. 4.

3.1.5. Effect of parity on apomorphine-induced oral stereotypy in intact females

Females were also tested for the level of stereotypy during PPI testing as described above. Similar to what was observed in the ovariectomized groups, a significant number of intact multiparous females displayed oral stereotypies following apomorphine ($P<.05$), while comparable behaviors were not observed in the intact nulliparous females, as seen in Fig. 5.

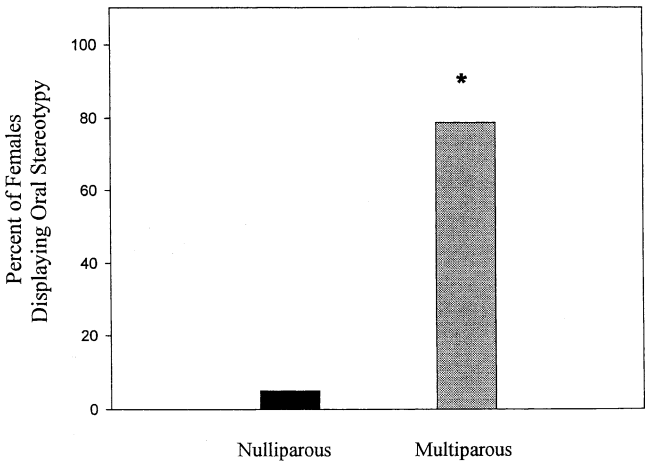

Fig. 5. The effects of apomorphine (1.0 mg/kg) on the induction of oral stereotypes in age-matched, intact nulliparous ($n=9$) and multiparous ($n=8$) females testing during diestrus. Results are presented as the percent of females within each treatment group displaying oral stereotypy over a 15-min test period. *$P<.05$ as compared with nulliparous females.

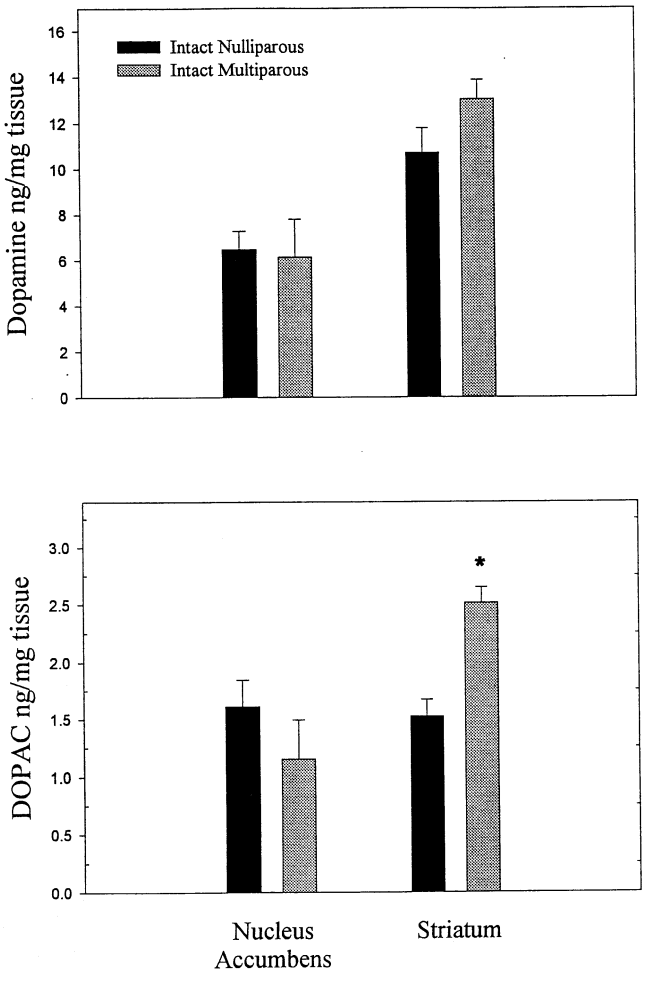

Fig. 6. The effects of parity on the level of dopamine and its primary metabolite DOPAC in tissue micropunches taken from the dorsolateral striatum and shell region of the nucleus accumbens. Results are presented as the mean (±S.E.M.) nanograms per milligram tissue. *$P<.05$ as compared to nulliparous females ($n=8-9$).

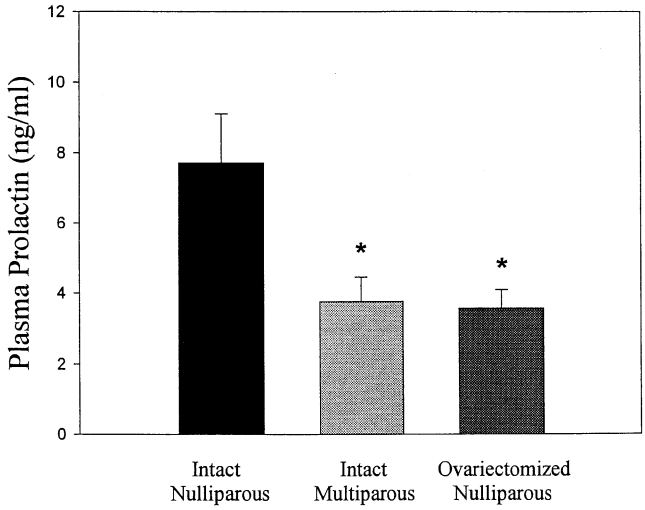

Fig. 7. The effects of parity and ovariectomy on circulating prolacting levels in age-matched, intact nulliparous ($n=10$), intact multiparous ($n=8$) and ovariectomized nulliparous ($n=8$) females. Results are presented as the mean (±S.E.M.) plasma prolactin (nanograms per milliliter). * $P<.05$ as compared to intact nulliparous females.

3.1.6. Effect of parity on forebrain dopamine in intact females

Both the striatum and the nucleus accumbens (shell region) from these two groups were analyzed for dopamine content. These data are shown in Fig. 6. No differences were observed between these two groups for either dopamine or its primary metabolite DOPAC within the nucleus accumbens. Within the striatum, however, there was a trend toward and increase in dopamine content in multiparous females ($P<.08$). A significant effect of reproductive experience was observed with regard to DOPAC content within the striatum [$t(8)=4.81$, $P<.001$], with multiparous females having increased content. A comparison of DOPAC-to-dopamine ratios revealed no significant differences between the groups.

3.1.7. Effect of parity on plasma prolactin levels

Decreased plasma PRL levels were found in both intact diestrous multiparous females and ovariectomized nulliparous females as compared to intact diestrous nulliparous females [$F(2,25)=5.42$, $P<.012$]. These data, shown in Fig. 7, are consistent with previous reports that demonstrate a reduction in circulating PRL in reproductively experienced females (Bridges et al., 1997). They also indicate that both parity and removal of the ovaries results in similar decreases in PRL levels, which likely result from an increase in dopamine activity within the tuberoinfundibular system.

4. Discussion

The present behavioral findings suggest that forebrain dopamine receptors are more sensitive in females that have experienced pregnancy and lactation, as compared to virgin females. Following systemic apomorphine, intact parous females were significantly more likely to engage in oral stereotypy and displayed a greater disruption of PPI, as compared to nulliparous controls. These same females also had increased levels of striatal DOPAC, and a trend towards increased striatal dopamine, again as compared to nulliparous females. Finally, plasma prolactin levels were reduced in parous females. Previous studies in rats have examined prolactin levels in ovariectomized parous females or in pregnant females (Bridges et al., 1997; Hafner et al., 1991). To our knowledge this is the first evidence of a persistent decrease in basal prolactin levels in cycling parous rats. Moreover, ovariectomized nulliparous females had prolactin levels comparable to those of intact multiparous females, suggesting that the removal of ovarian hormones can have consequences similar to the effects of parity. Decreases in circulating prolactin have also been demonstrated in parous women and are likely due to increased dopamine transmission within the arcuate nucleus (de los Monteros et al., 1991; Musey et al., 1987). Thus, it would appear that both dopamine receptor sensitivity as well as presynaptic dopamine activity are increased in forebrain and possibly hypothalamic regions following parity.

Parous females who were ovariectomized also demonstrated an apomorphine-induced disruption of PPI. However, similar effects were observed in ovariectomized nulliparous females. Increased behavioral responses to dopamine agonists following ovariectomy have been reported previously, with studies demonstrating increased locomotor behavior in ovariectomized females treated with apomorphine (Kazandjian et al., 1987). Thus, both parity and ovariectomy may have similar consequences with regard to their effects on dopamine systems that underlie the modulation of PPI. These similarities do not extend to all dopamine-mediated behaviors, as oral stereotypy was significantly enhanced by parity, but was not effected by ovariectomy. The similarity between parous and ovariectomized females, however, suggests that the long-term alterations in dopamine systems following parity may be due to pregnancy-induced alterations in ovarian hormone secretion or activity.

The onset of postpartum psychosis occurs soon after birth and while the cause of this disorder is unknown, the dramatic decrease in ovarian hormones that occurs postpartum is believed to play a role in the induction of this mental disorder (Ahokas and Aito, 1999; Ahokas et al., 2000; Cookson, 1982; Deuchar and Brockington, 1998). Based on the similarity to other psychotic disorders, including schizoaffective and bipolar disorder, as well as the favorable treatment response to dopamine antagonists, it has been suggested that one of the underlying mechanisms leading to postpartum psychosis may be dopamine hyperactivity in the forebrain (Kumar et al., 1993; Nonacs and Cohen, 1998). Moreover, the fact that a large percentage of

women who suffer postpartum psychosis on their first delivery relapse following subsequent pregnancies, and with more severe symptoms, suggests that changes in forebrain dopamine systems persist and may even increase with each pregnancy. The present work demonstrates that in rodents, parity results in both increased sensitivity to dopamine agonists, as well as increased dopamine activity in both hypothalamic and striatal dopamine systems. Thus, it may be that increased dopamine receptor sensitivity is a normal consequence of pregnancy and that these changes only negatively affect women with a preexisting susceptibility for dopamine-related mental illnesses.

The precise role of ovarian hormones in mediating this parity-induced increase in dopamine sensitivity is unclear. The majority of studies in both humans and rats have focused on the interaction between estrogens and dopamine. These findings indicate that estrogen may act like an "endogenous neuroleptic," masking any potential dopamine hyperactivity. Similar to what is observed following treatment with neuroleptics, chronic estrogen treatment has been shown to result in an up-regulation of dopamine receptors, as well as increased dopamine release (Becker, 1990; Di Paolo et al., 1981, 1982; Hruska, 1986; Hruska and Nowak, 1988). Similar alterations may occur during pregnancy, when estrogen levels remain elevated for a long period of time. During the postpartum period, the high levels of estrogen decline, while the dopamine system may still be in an up-regulated state. In susceptible females, this could result in the onset of psychotic symptoms, similar to what might be observed following the rapid withdrawal of neuroleptics. There are clinical findings that support this hypothesis. For example, females with preexisting psychiatric conditions, such as schizophrenia, are relatively symptom free during pregnancy, but are at high risk of relapse postpartum (Kazandjian et al., 1987). Moreover, estrogen supplements have shown some promise in the treatment of women with postpartum psychosis (Ahokas and Aito, 1999; Ahokas et al., 2000; Sichel et al., 1995).

The results of studies examining the impact of ovariectomy on dopamine function also suggest that ovarian hormones, particularly estrogens, may blunt the effects of dopamine. Following ovariectomy many dopamine-stimulated behaviors are enhanced (Diaz-Veliz et al., 1994; Kazandjian et al., 1987), suggesting an increase in dopaminergic activity. In humans, menopause is associated with alterations in dopamine systems as demonstrated by the postmenopausal onset of several psychotic disorders (Castle and Murray, 1993). The present results demonstrate an increase in sensitivity to apomorphine following ovariectomy with regard to PPI data. Indeed, ovariectomized nulliparous females were more similar to parous females with regard to dopamine sensitivity then they were to intact nulliparous females. Thus, it is possible that the decline in ovarian hormones that occurs postpartum can have consequences that are similar to those observed following ovariectomy.

In summary, the present studies demonstrate that in rodents parity results in increased dopamine receptor sensitivity and increased dopamine activity in both forebrain and potentially hypothalamic brain regions. In addition, ovariectomy also results in increased dopamine activity, although these results are more variable. Additional studies are needed to examine the time course of these changes postpartum to determine if they emerge soon after birth. The present work in rats supports the hypothesis that parity can induce changes in forebrain dopamine systems that may underlie postpartum psychosis in women.

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