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Amphetamine Sensitization in Reproductively Experienced Female Rats

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Abstract

Recent studies have supported the hypothesis that pregnancy and parturition are associated with altered sensitivity of brain dopamine systems. An increased behavioral sensitivity to a direct-acting D1/D2 receptor agonist (apomorphine) has also been observed several weeks after lactation, suggesting that these adaptations are long-lasting. To further characterize this phenomenon, the effects of reproductive experience on behavioral sensitization to an indirect-acting dopamine agonist (amphetamine) in female rats were studied. In two separate experiments, nulliparous and primiparous (12–16 weeks post-weaning) female rats were pretreated with amphetamine (1.0 or 5.0 mg/kg) or vehicle (saline) once daily for 5 consecutive days. After 10 days of withdrawal, all animals were challenged with a low dose of amphetamine (25% of pretreatment dose). Locomotor activity was measured following each drug or vehicle administration. Locomotor sensitization to amphetamine challenge was observed in all animals pretreated with 1 mg/kg, regardless of reproductive experience. In contrast, primiparous animals pretreated with 5 mg/kg amphetamine displayed a significantly larger locomotor response to the challenge compared to nulliparous controls. The findings indicate enhanced behavioral sensitization to amphetamine in reproductively-experienced rats, and confirm previous reports of lasting adaptations of dopamine systems following pregnancy and lactation.

Keywords

amphetamine; sensitization; postpartum; puerperal; reproductive experience; dopamine

INTRODUCTION

Postpartum (puerperal) psychosis is a significant psychiatric condition that develops within 6 weeks of parturition with an incidence of 0.1–0.5% [29]. The condition is often characterized by a combination of symptoms, including mania (predominantly), delirium, depression, catatonia, hallucinations, and delusions [3, 19]. Though the etiology is not fully understood, the precipitous postpartum decline in circulating estrogen is believed to contribute to the onset of symptoms [1, 2, 3, 13, 21, 32]. Accordingly, 17-beta estradiol has been studied as a potential treatment for this condition [2]. While this approach has shown

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some promise, more comprehensive clinical studies are needed to determine the efficacy hormone replacement therapy.

In addition to estrogen withdrawal, symptom onset in puerperal psychosis may involve altered forebrain dopamine (DA) functioning [34, 35]. For example, Wieck et al. [35] found increased sensitivity to a direct-acting DA D1/D2 receptor agonist (apomorphine) in postpartum women at risk for puerperal psychosis. Consistent with this finding, puerperal psychosis is responsive to typical and atypical antipsychotic treatment [3, 31]. Moreover, recent animal studies have revealed alterations in DA function in postpartum [9] and estrogen-withdrawn [7] female rats. Together, the data suggest that DA dysfunction may play an important etiological role in puerperal psychosis.

Several studies and anecdotal evidence indicate that, while the majority of women with puerperal psychosis respond to treatment, relapse during subsequent pregnancies is common (>50%). Moreover, the severity of symptoms often increases with each episode [3, 26, 27, 31]. This pattern is suggestive of a sensitization process, perhaps similar to the “kindling” phenomenon associated with cycle acceleration in bipolar disorder [25]. Interestingly, sensitization of DA systems is believed to underlie the development of psychostimulant psychosis in humans following repeated exposure indirect-acting DA agonists such as cocaine and amphetamine (AMPH). Psychostimulant-induced psychosis resembles the positive symptoms of schizophrenia, and the phenomenon has been modeled extensively in rodents [12]. Thus, given the evidence for DAergic involvement in puerperal psychosis, it is conceivable that a DA-mediated sensitization triggers symptom recurrence in subsequent pregnancies, and that this process may be studied in laboratory animals.

Previous reports have described parity-induced alterations in the activity of forebrain [11, 14, 15] and hypothalamic [4, 10, 11] DA systems in the female rat. Studies conducted in our laboratory have further indicated that multiparity also alters forebrain DA function [5]. Specifically, the stereotypic effects of apomorphine are markedly augmented in both primiparous and multiparous female rats at 3 weeks post-weaning, compared to nulliparous controls. Multiparous animals were also found to be more sensitive to the disruptive effects of apomorphine on prepulse inhibition. These effects of reproductive experience were accompanied by increased striatal and hypothalamic DAergic activity [5]. Together, the findings suggest that a normal consequence of parity is the induction of a long-lasting DAergic sensitivity. Such neuroadaptations may underlie vulnerability to postpartum psychiatric diseases such as puerperal psychosis. Thus, the present study was designed to further characterize DAergic sensitivity following reproductive experience. Based on the data cited above, it was predicted that behavioral sensitization to AMPH [12] would be augmented in reproductively-experienced female rats.

MATERIALS AND METHODS

Experimental Animals

For this work, experimental animals were adult female Sprague-Dawley rats generated in our breeding colony and group-housed under standard conditions (plastic cages 40 × 20 × 18 cm; 14:10 h light:dark cycle (lights on at 700 h); 21–24°C colony temperature; 40–60% humidity; *ad libitum* food and water). To generate primiparous animals, females were mated at 12 weeks of age with adult male Sprague-Dawley rats (Charles River Breeding Laboratories, Kingston, NY). Births were monitored daily, and litters were culled to 10 pups. Primiparous females cared for litters until pups reached 21 days of age. Experimental treatments began at 12–16 weeks post-weaning. Age-matched nulliparous female rats were used as controls in all experiments. All procedures were approved by the Institutional

Animals Care and Use Committee of Tufts University, and conducted in accordance with the National Research Council (NRC) Guide for the Care and Use of Laboratory Animals.

Experimental Design and Procedures

Two experiments were conducted in the present study to determine the effect of reproductive experience on behavioral sensitization to AMPH [12]. For Experiment I, primiparous and age-matched nulliparous female rats were pretreated with a low dose (1 mg/kg, i.p.) of AMPH (d-amphetamine sulfate, Sigma, St. Louis, MO) or its saline vehicle (0.9% NaCl, 1 ml/kg) once daily for 5 consecutive days. Following a 10-day withdrawal, all animals were challenged with a low, threshold dose of AMPH (0.25 mg/kg, i.p.). For Experiment II, the procedure was identical to that used for Experiment I, except that a high dose of AMPH (5 mg/kg or saline vehicle) was used for pretreatment. A challenge of 1.25 mg/kg AMPH was administered after 10 days of withdrawal, with the dose chosen to maintain the same pretreatment:challenge ratio as used in Experiment I. For both experiments, animals were placed individually into standard housing cages for 120 min following each pretreatment and AMPH challenge (all treatments between 0800–1400 hr). Thus, the contexts for sensitization development and expression were identical. Locomotor activity was measured for 120 min following each daily treatment and challenge using PC-interfaced horizontal photobeam frames (SmartFrame® cage rack system, Hamilton/Kinder, Poway, CA) which continuously tracked individual animal movement within the standard housing cage. Raw activity data (photobeam breaks) were collected in both 30 min intervals and a single 120 min interval using MotorMonitor® software (Hamilton/Kinder). Data were subjected to Two-way ANOVA (variables = Reproductive Experience and Pretreatment) or Three-way Repeated Measures ANOVA (between subject variables = Reproductive Experience and Pretreatment; within subject variable = Time in days or min). Post-hoc analyses were conducted using the Tukey Test. Statistical results are detailed in the figure captions.

RESULTS

Experiment I

Table 1 depicts the locomotor responses to low-dose AMPH (1 mg/kg) or saline on each pretreatment day. Three-way Repeated Measures ANOVA revealed a main effect of Pretreatment condition [$F(1, 27) = 99.917$, $P < 0.0001$]. However, no effects of Reproductive Experience, Time, or any interactions were found (all P 's > 0.05). Post-hoc analysis indicated the Pretreatment effect was due to significantly increased locomotor activity in AMPH-pretreated groups versus saline controls, regardless of Reproductive Experience and Time of testing. Thus, AMPH produced a robust motor response following each daily administration, but did not elicit behavioral sensitization *per se* during the pretreatment phase.

Following a 10-day withdrawal, a 0.25 mg/kg AMPH challenge produced marginally elevated locomotor responses in all low-dose AMPH-pretreated animals, regardless of reproductive status (Figure 1, Upper Panel). While this is suggestive of AMPH sensitization, a Three-way Repeated Measures ANOVA did not reveal a significant Time X Pretreatment interaction. However, Two-way ANOVA conducted on total photobeam breaks (collapsed across Time) revealed a statistically significant effect of Pretreatment (Figure 1, Lower Panel). Post-hoc analysis indicated that this effect was due to a significantly increased response to AMPH challenge in animals pretreated with AMPH compared to those treated with saline. Nevertheless, there was no difference in the magnitude of AMPH sensitization between primiparous and nulliparous animals.

Experiment II

Locomotor responses to high-dose AMPH (5 mg/kg) or saline on pretreatment days 1 and 5 are depicted in Table 1. Three-way Repeated Measures ANOVA revealed a main effect of Pretreatment condition [$F(1, 28) = 12.47$, $P < 0.001$]. However, as in Experiment I, no effects of Reproductive Experience, Time, or any interactions were observed (all P 's > 0.05). Again, post-hoc analysis indicated that the Pretreatment effect was due to significantly increased locomotor activity in AMPH-pretreated groups versus saline controls, regardless of reproductive status or day of testing. Thus, high-dose AMPH induced increased motor activity following each daily administration, but the expression of behavioral sensitization during this pretreatment phase was not observed. Of note, when collapsed across the 5 pretreatment days, the overall magnitude of high-dose AMPH-induced activity (158% of saline controls) was not as large as that produced by low-dose AMPH treatment (253% of saline controls). While not quantified in the present study, this difference was likely due to a reduction in overall locomotion resulting from the emergence of focused stereotypy. Indeed, intense (stationary) sniffing and grooming were noted on casual observation of all animals treated with high-dose AMPH during the pretreatment phase.

Following a 10-day withdrawal from high-dose AMPH pretreatment (5 mg/kg), primiparous animals showed enhanced locomotor responses to a 1.25 mg/kg challenge (Figure 2, Upper Panel). Indeed, Three-way Repeated Measures ANOVA revealed a significant Time X Reproductive Experience X Pretreatment interaction. Post-hoc analysis indicated that this interaction was largely due to persistent increase in locomotor activity in AMPH-pretreated primiparous animals compared to all other groups. Of note, post-hoc analysis also revealed a significant Reproductive Experience effect in saline-pretreated animals during the initial testing period (30 min). Subsequent Two-way ANOVA conducted on total photobeam breaks (collapsed across Time) also revealed a statistically significant effect of Reproductive Experience (Figure 2, Lower Panel). Post-hoc analysis indicated that this effect was due to an overall increase in AMPH-induced activity in primiparous animals (regardless of pretreatment condition). However, the effect appears to be driven by increased sensitivity to the challenge in AMPH-pretreated primiparous animals compared to AMPH-pretreated nulliparous animals ($P = 0.056$).

DISCUSSION

This study was undertaken to test the hypothesis that reproductive experience is associated with augmented behavioral sensitization to AMPH. We now report that repeated treatment with high-dose AMPH facilitates the development of sensitization in primiparous female rats at 12–16 weeks post-weaning. These findings are consistent with previous reports of increased sensitivity to DA agonist treatment in parous women [35] and laboratory animals [5, 9, 10, 11, 15].

The behavioral manifestation of psychostimulant (e.g. cocaine, AMPH) sensitization in humans includes marked delusions and hallucinations which are often indistinguishable from those observed in idiopathic psychosis [12, 17, 28]. Psychostimulant sensitization can be induced in laboratory rodents via intermittent exposure to behaviorally-activating doses, followed by a withdrawal period of days to weeks. Upon subsequent psychostimulant challenge with a low, sub-threshold dose, animals exhibit an augmented behavioral response (i.e. behavioral sensitization) compared to animals receiving the drug for the first time. These effects are associated with increased neurotransmission and receptor sensitivity in forebrain DA systems, including mesolimbic and mesocortical pathways [16]. Thus, given the purported role of DA in schizophrenia, rodent psychostimulant sensitization has been used extensively to study the neural underpinnings of psychotic illness [12, 28].

In the present work, we employed the psychostimulant sensitization model to study the effect of reproductive experience on DAergic sensitivity. Based on the literature indicating that parity enhances DAergic function in rodents [5, 8, 9, 11, 15], it was hypothesized that repeated AMPH administration would lead to more rapid development of locomotor sensitization during either the pretreatment period and/or upon drug challenge following a withdrawal period. In Experiment I, we tested this hypothesis using a 5-day, low-dose (1 mg/kg) AMPH pretreatment regimen. On each of the 5 pretreatment days, AMPH produced marked locomotion. The magnitude of activation was similar in both primiparous and nulliparous animals, indicating no reproductive experience effect on AMPH-induced behavior. Likewise, there was no evidence of behavioral sensitization during this phase of the experiment for either reproductive experience group. It is frequently reported that the *expression* of psychostimulant sensitization does not emerge during the pretreatment phase. Rather, sensitization is often revealed after a period of withdrawal and subsequent challenge with a smaller dose of the sensitizing agent [12, 28]. Indeed, after 10 days of withdrawal, animals in the present study showed a sensitized behavioral response to a challenge of 0.25 mg/kg (25% of the pretreatment dose) compared to animals receiving the drug for the first time. This sensitization, however, was observed in both primiparous and nulliparous animals in Experiment I, a result which does not support the hypotheses of augmented AMPH sensitization in reproductively-experience animals.

Experiment II employed a design that was identical to that used in Experiment I, but with higher pretreatment and challenge doses of AMPH (5 and 1.25 mg/kg, respectively). During pretreatment with this higher dose of AMPH [12], behavioral activation manifested as intense (focused) stereotypy, a profile indicative of a striatal hyperdopaminergic state. In this regard, there was neither an effect of reproductive experience, nor evidence for the development of behavioral sensitization during the pretreatment regimen. However, after 10 days of withdrawal, primiparous animals pretreated with high-dose AMPH showed a sensitized behavioral response to AMPH challenge when compared to all other groups. Of note, primiparous animals that were pretreated with saline also exhibited a trend toward increased response to AMPH challenge compared to their nulliparous counterparts. The reason for this is unclear, but may reflect the development of stress-induced sensitization during the pretreatment phase, and its cross-sensitization to AMPH challenge [17, 23]. Overall, the findings of Experiment II support the hypothesis that reproductively-experienced animals exhibit increased sensitivity to the behavioral-sensitizing effect of high-dose AMPH treatment.

Sensitization to psychostimulants in animal models is highly regimen-dependent. There is now an extensive literature describing numerous treatment protocols that produce varying degrees of sensitization [12]. In the present study, we observed modest sensitization in animals pretreated with low (1 mg/kg) and high (5 mg/kg) AMPH for 5 consecutive days, followed by a 10 day withdrawal and subsequent AMPH challenge. The rationale for the protocol used herein was based on the hypothesis that behavioral sensitization would be markedly augmented in primiparous animals. Hence, the regimen chosen was designed to induce only mild sensitization in control animals, thus avoiding ceiling effects. Indeed, using the 5 mg/kg daily pretreatment regimen (Experiment II), we found the degree of sensitization to AMPH challenge in primiparous animals to be approximately 132% of nulliparous controls. Thus, it may be concluded that the sensitizing regimen used in the present study was appropriate for the detection of differential AMPH sensitization in nulliparous and primiparous female rats.

The present study supports previous data indicating increased DAergic function in reproductively-experienced female rats [4, 5, 8, 9, 11, 15]. Specifically, we now report that primiparous animals exposed to a sensitizing regimen of AMPH at 12–16 weeks post-

weaning exhibit a greater sensitivity to AMPH challenge compared to nulliparous animals. The magnitude of this effect is strikingly similar to that reported by Hucke et al. [15], who studied the effects of repeated AMPH in primiparous female rats at 2 weeks post-weaning. Their data revealed that 7 daily treatments of AMPH followed by a 3 day withdrawal produced an increased motor response to AMPH challenge (0.5 mg/kg) in primiparous animals versus nulliparous controls. Thus, the present study confirms the findings of Hucke et al. [15], and indicates that this response persists for several months after weaning. In terms of behavioral significance, it may be speculated that a persistent enhancement of DA function in parous animals underlies maternal motivation and associated behaviors [6, 18, 20, 24, 33]. While these adaptations may contribute to the increase in maternal care associated with experience [22, 30], a better understanding of their relevance requires further study. Nevertheless, the finding of lasting, differential AMPH sensitization in primiparous animals is compelling, given the purported validity of rodent psychostimulant sensitization as a model of human psychotic illness [12, 17, 28]. Accordingly, the results provide additional insights into the phenomenon of DAergic sensitivity in reproductively-experienced females, and provide a model with which to study the vulnerability to postpartum psychiatric disturbances such as puerperal psychosis.

CONCLUSIONS

In conclusion, the present findings suggest that an enhancement of behavioral sensitization to amphetamine results from reproductive experience in female rats. These results may contribute to the development of a novel model with which to study lasting adaptations of brain DA systems following pregnancy and lactation.

Acknowledgments

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Highlights

- Effects of reproductive experience on amphetamine sensitization were tested.
- Animals were primiparous and age-matched nulliparous female rats.
- Animals were treated with amphetamine (1 or 5 mg/kg) or saline for 5 consecutive days.
- All animals were challenged with low-dose amphetamine after 10 days of withdrawal.
- High-dose amphetamine treatment increased response to challenge in primiparous rats.
- Increased amphetamine sensitization may be a consequence of reproductive experience.

Figure 1.

Low-dose AMPH sensitization in primiparous rats. Reproductively experienced female rats were treated for 5 consecutive days with 1 mg/kg AMPH or its saline vehicle (0.9% NaCl, 1 ml/kg, i.p.). Following a 10-day withdrawal, all animals were challenged with 0.25 mg/kg AMPH and locomotor activity was tested for 120 min. Data are mean photobeam breaks ($\pm$ SEM) for groups of 8 animals. Upper Panel (30 min intervals): Three-Way Repeated Measures ANOVA – Time [$F(3, 84)=117$, $P<0.001$], Time X Reproductive Experience [$F(3, 84)=0.907$, $P<0.401$], Time X Pretreatment [$F(3, 84)=2.26$, $P<0.087$], Time X Reproductive Experience X Pretreatment [$F(3, 84)=0.195$, $P<0.9$]. Lower Panel (collapsed across 2 hours): Two-Way ANOVA – Reproductive Experience [$F(1, 28)=0.689$, $P<0.413$], Pretreatment [$F(1, 28)=7.5$, $P<0.01$], Reproductive Experience X Pretreatment [$F(1, 28)=0.28$, $P<0.87$]. Tukey: * $P<0.05$ = AMPH vs. saline, collapsed across Reproductive Experience.

Figure 2.

High-dose AMPH sensitization in primiparous rats. Reproductively experienced female rats were treated for 5 consecutive days with 5 mg/kg AMPH or its saline vehicle (0.9% NaCl, 1 ml/kg, i.p.). Following a 10-day withdrawal, all animals were challenged with 1.25 mg/kg AMPH and locomotor activity was tested for 120 min. Data are mean photobeam breaks ($\pm$ SEM) for groups of 8 animals. Upper Panel (30 min intervals): Three-Way Repeated Measures ANOVA – Time [$F(3, 84)=15.13$, $P<0.001$], Time X Reproductive Experience [$F(3, 84)=0.571$, $P<0.636$], Time X Pretreatment [$F(3, 84)=0.343$, $P<0.794$], Time X Reproductive Experience X Pretreatment [$F(3, 84)=4.13$, $P<0.009$]. Lower Panel (collapsed across 2 hours): Two-Way ANOVA – Reproductive Experience [$F(1, 28)=4.11$, $P\leq 0.05$], Pretreatment [$F(1, 28)=3.0$, $P<0.094$], Reproductive Experience X Pretreatment [$F(1,$

28)=0.622, $P<0.437$]. Tukey: $^{\dagger}P<0.05$ = primiparous saline vs. nulliparous saline. $*P<0.05$ = primiparous AMPH vs. all groups. $**P<0.05$ = primiparous vs. nulliparous, collapsed across Pretreatment condition.

Table 1Locomotor Activity Across Pretreatment Days (mean photobeam breaks $\pm$ SEM)

Experiment	Drug Pretreatment	Reproductive Experience	n	Day 1	Day 2	Day 3	Day 4	Day 5
Exp. I	Saline	Nulliparous	8	3406 $\pm$ 280	3160 $\pm$ 178	3751 $\pm$ 337	4474 $\pm$ 856	4709 $\pm$ 932
		Primiparous	8	3109 $\pm$ 295	4221 $\pm$ 903	3695 $\pm$ 454	3538 $\pm$ 442	3554 $\pm$ 446
	AMPH 1 mg/kg	Nulliparous	8	9248 $\pm$ 720	9289 $\pm$ 733	10147 $\pm$ 897	9570 $\pm$ 1109	9124 $\pm$ 967
		Primiparous	8	9300 $\pm$ 468	9467 $\pm$ 798	9999 $\pm$ 1103	9836 $\pm$ 807	9209 $\pm$ 714
Exp. II	Saline	Nulliparous	8	3188 $\pm$ 345	2809 $\pm$ 322	3000 $\pm$ 356	2549 $\pm$ 287	2408 $\pm$ 309
		Primiparous	8	3476 $\pm$ 359	3238 $\pm$ 279	2810 $\pm$ 206	2750 $\pm$ 209	3005 $\pm$ 128
	AMPH 5 mg/kg	Nulliparous	8	5605 $\pm$ 936	4345 $\pm$ 966	3424 $\pm$ 512	3510 $\pm$ 781	4035 $\pm$ 464
		Primiparous	S	5168 $\pm$ 1006	5204 $\pm$ 1052	4897 $\pm$ 633	4808 $\pm$ 973	5326 $\pm$ 1355