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Reproductive experience modulates dopamine-related behavioral responses

Erica E.T.S. Hucke[a], Pablo E. Cruz-Casallas[b], Lúcia H. Sider[a], Luciano F. Felicio[a,*]

[a]*Departamento de Patologia, Faculdade de Medicina Veterinária, Universidade de São Paulo, Av. Prof. Orlando Marques Paiva, 87, Cidade Universitária, CEP 05508-970 São Paulo, Brazil*

[b]*Escuela de Medicina Veterinaria, Universidad de Los Llanos, Villavicencio, Meta, Colombia*

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Abstract

Reproductive experience (RE), i.e., mating, pregnancy, parturition and lactation, has long-term physiological effects. It reduces the basal levels of circulating prolactin in parous women, decreases the intensity of nocturnal and diurnal prolactin surges in multigravid rats during early pregnancy, as well as the hormonal and neurochemical responses to the dopamine receptor antagonists metoclopramide and haloperidol. In the present study, we evaluated the possible influences of RE on some dopaminergic-related behaviors: (1) acute responses to a new environment represented by an open-field arena plus injection stress; (2) modulation of behavior after a short-term withdrawal subsequent to 7 days amphetamine (AMPH) pretreatment; (3) stereotypy elicited by AMPH and apomorphine (APO); and (4) APO-induced hypothermia. In the 3-min open-field test, there was a decrease in locomotor activity as a function of RE. Behavioral depression was mild and AMPH pretreatment revealed RE alterations. APO-induced stereotyped behavior was slightly more intense in primiparous animals, although no significant differences were found in AMPH-induced stereotyped behavior. No differences were observed between intact and ovariectomized primiparous and nulliparous animals in APO-induced hypothermia. Our data suggest that RE modifies some DA-related behavioral responses. The physiological relevance of the phenomenon is discussed.

Keywords: Parity; Motor activity; Hypothermia; Stereotypy; Dopamine

1. Introduction

Reproductive experience (RE) is a very important event in a female's life. In experimental animals, it can be described as a rich social and hormonal experience, starting with male interaction and mating, then pregnancy and delivery and at last, lactation, pup relationship and weaning. This paper addresses this whole experience as a possible driving force behind brain modifications. Pregnancy and lactation have shown long-term endocrine and behavioral effects. Both metabolism and serum concentrations of estrogens (Cole et al., 1976; Musey et al., 1987a; Tricho-poulus et al., 1980), prolactin (PRL) and cortisol are modulated by RE (Musey et al., 1987b; Vleugels et al., 1986; Wang et al., 1988; Zuppa et al., 1988). In addition, RE induces a long-lasting facilitation of maternal behavior (Cohen and Bridges, 1981; Kinsley and Bridges, 1988; Mann and Bridges, 1992; Mann et al., 1989). Parity reduces circulating basal PRL levels in women (Musey et al., 1987b) and rats (Mann et al., 1989). The decrease in plasma PRL levels after an RE may be related to the decreased incidence of breast cancer in parous women (Musey et al., 1987a,b; Wang et al., 1988; Zuppa et al., 1988). The reduced circulating levels of PRL in parous women as well as in rats could be a consequence of changes in the dopaminergic regulation of PRL secretion (Bridges et al., 1993, 1997; Mohankumar et al., 1997). Inhibition of PRL release depends on pituitary dopamine (DA) receptor activation (Ben-Jonathan et al., 1979; Bjorklund et al., 1974; Mohankumar et al., 1997), which is a consequence of tubero-infundibular dopaminergic neuron activity (Ben-Jonathan et al., 1979; Bjorklund et al., 1974; Mohankumar et al., 1997; Zabavnik et al., 1993). It has been already reported that during lactation there is an increase in D_2 receptor mRNA within the anterior pituitary (Zabavnik et

* Corresponding author. Tel.: +55-11-3818-7934; fax: +55-11-3818-7829.

E-mail address: lfelicio@usp.br (L.F. Felicio).

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al., 1993) that may be a consequence of decreased tyrosine hydroxylase activity during this period (Escalada et al., 1996). As the author suggests (Bridges et al., 1997), these changes, if long-lasting, can be responsible for decreased effectiveness of D_2 antagonists in stimulating PRL in experienced females (Bridges et al., 1997; Hucke et al., 1998). This can also be a consequence of modifications of endogenous dopaminergic activity/tone (Bridges et al., 1997; Hucke et al., 1998). Previous data have suggested that dopaminergic systems may be influenced by parity as well. During pregnancy, nocturnal and diurnal PRL surges are less intense in multigravid than in primigravid female rats (Bridges et al., 1993) and suckling-induced PRL release occurs later and with less intensity in multiparous animals compared to primiparous lactating animals (Mann and Bridges, 1992; Mann et al., 1989). Responses to the DA antagonist metoclopramide are also decreased in parous women (De Los Monteros et al., 1991). Other studies have shown that the haloperidol-induced increase in striatal dopaminergic terminals activity is less intense both in pregnant (Felicio et al., 1996) and in cycling (Hucke et al., 1998) experienced rats as compared to primigravid and virgin rats respectively. Thus, a series of facts relate DA and RE and there are few studies on the possible influences of RE on motor activity and on dopaminergic striatal and hypothalamic sensitivity (Byrnes and Bridges, 1999; Felicio et al., 1996; Hucke et al., 1998, 1999).

Dopaminergic transmission was addressed through its relationship to motor functions (Coté and Crutcher, 1991; Felicio et al., 1987, 1989; Ghez and Gordon, 1995; Mason, 1984; Palermo-Neto, 1984; Role and Kelly, 1991). Classical dopaminergic-related behaviors such as APO- and AMPH-induced stereotypy and open-field activity were studied in nulliparous and primiparous females (Coté and Crutcher, 1991; Felicio et al., 1987, 1989; Ghez and Gordon, 1995; Mason, 1984; Palermo-Neto, 1984; Role and Kelly, 1991) to evaluate the possible influences of RE on motor activity in rats. Since DA is widely related to drug abuse, open-field observations were also performed to look at the possible influences of RE on the behavioral syndrome elicited by short-term AMPH withdrawal (Paulson and Robinson, 1996; Paulson et al., 1991). In addition, hypothalamic DA receptor sensitivity was indirectly addressed using apomorphine's (APO) ability to induce hypothermia (Onaivi, 1997; Vanzeler et al., 1990) by stimulating hypothalamic DA receptors (Onaivi, 1997; Vanzeler et al., 1990).

2. Method

2.1. Subjects

Age-matched female Wistar rats from our colony, 90 days old at the beginning of the experiments, were randomly housed in polypropylene cages in groups of five animals per cage under a 12/12 h light–dark cycle (lights on at 0600 h). Food and water were available ad libitum throughout the experiment. The animals used in this study were maintained in accordance with the guidelines of the Committee on Care and Use of Laboratory Animal Resources, National Research Council (USA). A group of 146 females from the original set was mated and allowed to give birth (litters were culled to six pups), raise their litters to weaning (21 days) and rest for 15 more days. This is the primiparous group and throughout this period, the nulliparous females were kept waiting so that the experimental groups would be age-matched. Females were tested in proestrus to avoid the influences of the estrous cycle on behavior. Behavioral tests were performed at least 4 h after vaginal smear procedures. Proestrus was chosen because it is an estrogenic phase when the females are more active. Estrogens are able to increase DA receptor density (Joseph et al., 1989) and regulate neural activity and plasticity (Keefe et al., 1991; McEwen, 1988, 1991; McEwen et al., 1991). In Experiment 4, females were ovariectomized (ovex) under pentobarbital anesthesia. After surgery, the animals were allowed to recover for 7 days before any experimental procedure.

2.2. Drugs

A freshly prepared aqueous solution of APO hydrochloride (Sandoz) was administered subcutaneously in a volume of 1.0 ml/kg body weight. The same preparation was used for amphetamine sulphate DL (AMPH; Sigma), which was injected intraperitoneally.

2.3. Experiment 1: open-field behavior of intact nulliparous and primiparous female rats

Locomotor activity in the open-field was measured as described elsewhere (Broadhurst, 1960; Felicio et al., 1989; Palermo-Neto, 1984) in a circular arena for adult animals measuring 80 cm in diameter and 30 cm in height. Hand-operated counters and stopwatches were employed to score locomotion frequency (number of floor units entered), rearing frequency (number of times the animal stood on its hind legs), immobility duration (total number of seconds without movement, freezing) and defecation (number of fecal boli left after each test). Each animal was tested in the open-field for 3 min. Two animal groups were tested: intact primiparous ($n = 11$) and age-matched nulliparous ($n = 12$) females injected with 1 ml/kg ip saline 10 min before each test. The open-field experimental room had the same light intensity as all other rooms in the animal facilities. The open-field arena was washed with 5% ethanol solution before each behavioral test to eliminate possible influences of odors left by previous subjects. To minimize circadian influences, the tests were performed between 1400 and 1700 h with nulliparous and primiparous animals intermixed. This experiment was designed to evaluate the possible influence of RE on acute responses to

a new environment represented by the open-field plus injection stress.

2.4. Experiment 2: effects of amphetamine treatment on motor activity of intact nulliparous and primiparous female rats

The motor activity of another set of nulliparous and primiparous females was measured in a circular arena for adult animals measuring 97 cm in diameter and 32.5 cm in height as recorded by a video camera attached to the ceiling. This camera was connected to a computer system that works with the software Etho Vision, Video Tracking, Motion Analysis and Behavior Recognition System, Version 1.80 (Noldus Information Technology, Wageningen, The Netherlands). Each animal was placed in the center of the arena and observed during a 20-min period. Parameters analyzed were total distance moved (cm), time spent in movement (s), mean velocity (cm/s) and rearing frequency. Rats from both groups were injected with 2.5 mg/kg AMPH for 7 consecutive days followed by a 3-day withdrawal period. AMPH stimulates DA release, inhibits its reuptake in the presynapses and can also affect the noradrenergic system. On the fourth day, independent of the estrous cycle phase (experimental design limits), animals received a 0.5 mg/kg AMPH injection 10 min before being placed in the center of the arena to start the behavioral test. This experiment was designed to study possible RE modulation on short-term behavioral (3 days) responses subsequent to 7 days AMPH pretreatment. AMPH doses for pretreament and challenge were chosen according to our previous laboratory data. Thus, our best choice of AMPH dose was 2.5 mg/kg, known to increase locomotor activity and to play a stimulant role during the 7-day period of pretreatment. The 3-day withdrawal period was chosen to observe possible changes in behavioral depression (Paulson et al., 1991) with a very low AMPH challenge (0.5 mg/kg). Many studies about AMPH withdrawal and behavioral depression or sensitization are available in the literature (Barr and Phillips, 1999; Caul et al., 1997; Chen et al., 1999; De Sousa et al., 1999; Fiorino and Phillips, 1999; Laudrup and Wallace, 1991; McEwen, 1988; Schindler et al., 1994; Wise and Munn, 1995). Paulson et al. (1991) showed that the phenomenon is time-dependent, i.e., there is a transient behavioral depression characterized by a spontaneous decrease in locomotor activity during the first week followed by a behavioral sensitization characterized by an increase in locomotor activity.

Control nulliparous and primiparous groups were treated with saline (1 ml/kg) for 7 days, being challenged with the same AMPH dose as done for the experimental group. The experimental arena room had the same light intensity as all other rooms in the animal facilities. The arena was washed with 5% ethanol solution before each behavioral test to eliminate possible influences of odors left by previous subjects. To minimize circadian influences, the tests were performed between 1400 and 1700 h with nulliparous and primiparous animals intermixed.

2.5. Experiment 3: APO-induced stereotyped behavior in intact nulliparous and primiparous female rats

Stereotypy was quantified in one set of females every 10 min (for 10 s) for 90 min immediately after APO (0.6 mg/kg) or AMPH (9 mg/kg) injection in another set of nulliparous and primiparous females. APO is a dopaminergic agonist that binds both D_1 and D_2 receptors. The method was proposed elsewhere (Setler et al., 1976; Standaert and Young, 1996; Tieppo et al., 1995, 1997, 2000; Troncone et al., 1988) and was modified for intact female rats in proestrus. Scores ranged from 0 (*asleep or still*) to 7 (*continuous gnawing on cage grids*) and were assigned to each animal at 10-min intervals for the presence of stereotyped sniffing, licking or gnawing of cage bars. Vaginal smears were performed every morning to detect the estrous cycle and females in proestrus were placed in behavioral cages about 3 to 4 h before observations. A blind observer recorded stereotypy. The tests were performed between 1400 and 1600 h to minimize circadian influences. The aim of this experiment was to determine possible influences of RE on stereotyped behavior.

2.6. Experiment 4: APO-induced hypothermia in ovariectomized and intact nulliparous and primiparous female rats

Rectal temperature was recorded 10, 20, 30, 60, 90 and 120 min after APO (1 mg/kg) injection. Before APO

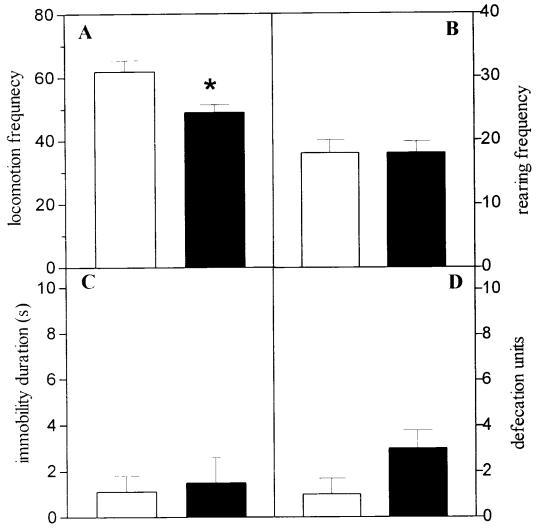

Fig. 1. Open-field behavioral observation of intact nulliparous (open bars) and primiparous (solid bars) female rats during a 3-min session. Nulliparous and primiparous rats were tested always in proestrus and injected with 1 ml/kg ip saline 10 min before each behavioral test (nulliparous = 12, primiparous = 11). (A) Locomotion frequency; (B) Rearing frequency; (C) Immobility duration in seconds; (D) Units of defecation. Means ± S.E.M. * indicates significant differences between primiparous and related nulliparous control group ($P < .05$; Student's t test).

injection, three consecutive measurements of body temperature were recorded every 5 min to determine the initial basal temperature. For measurements, a digital thermometer (Amarell Eletronic, Germany) was used, with a 5-cm long rectal probe 1 mm in diameter lubricated with petroleum jelly (Sidepal). Animals from both groups were randomly intermixed and all experimental procedures were performed between 0800 and 1200 h to minimize circadian influences. Intact females were tested in proestrus, and therefore, vaginal smears were taken before each experimental session to determine the phase of the estrous cycle. The aim of the experiment was to look at possible influences of RE on hypothalamic DA receptor sensitivity (Onaivi, 1997; Vanzeler et al., 1990, see also comments in the Introduction).

2.7. Statistical analysis

Locomotor and body temperature data were analyzed using parametric statistics, including student's t test, One-way, Two-way or Repeated Measures Analysis of Variance (ANOVA) followed by the Tukey–Kramer Multiple Comparisons Test. Stereotyped behavior data were analyzed using nonparametric statistics, including the Mann–Whitney U test, because these data only comprise an ordinal scale. All comparisons were based on two-tailed probabilities. The level of significance was set at $P<.05$.

3. Results

3.1. Experiment 1: open-field behavior of nulliparous and primiparous female rats

Locomotion decreased as a function of RE. There was a significant decrease in locomotion frequency in the primiparous group compared to the nulliparous control group ($P=.0092$; $t_6=2.868$; Student's t test). Rearing frequency, immobility duration and defecation were not significantly affected (Fig. 1).

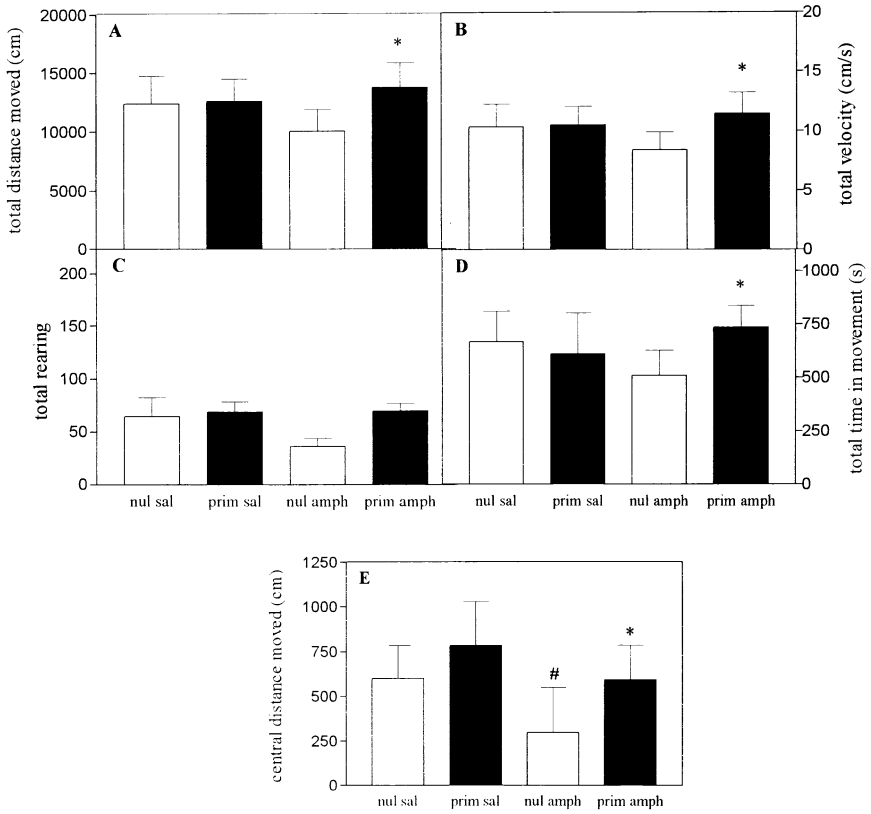

Fig. 2. Motor activity recorded by a video camera connected to a software system (Etho Vision, 1.80; Noldus Information Technology). Nulliparous and primiparous females were observed during a period of 20 min. Animals from both groups were treated with 2.5 mg/kg AMPH or 1 ml/kg saline for 7 consecutive days, with a 3-day withdrawal period and on the fourth withdrawal day, rats were injected with 0.5 mg/kg AMPH 10 min before the behavioral test. Four experimental groups were tested: nulliparous and primiparous rats injected with saline (7 days) + AMPH on the test day (nul sal = 9; prim sal = 9); nulliparous and primiparous rats injected with AMPH (7 days) + AMPH on the test day (nul amph = 9; prim amph = 9). (A) Distance moved (cm); (B) Mean velocity (cm/s); (C) Rearing frequency; (D) Time spent in movement (s); (E) Distance moved in the central area of the arena (cm). Means ± S.E.M. # indicates a significant difference from nulliparous saline-pretreated females; * indicates a significant difference from nulliparous AMPH-pretreated females ($P<.05$; ANOVA followed by the Tukey–Kramer test).

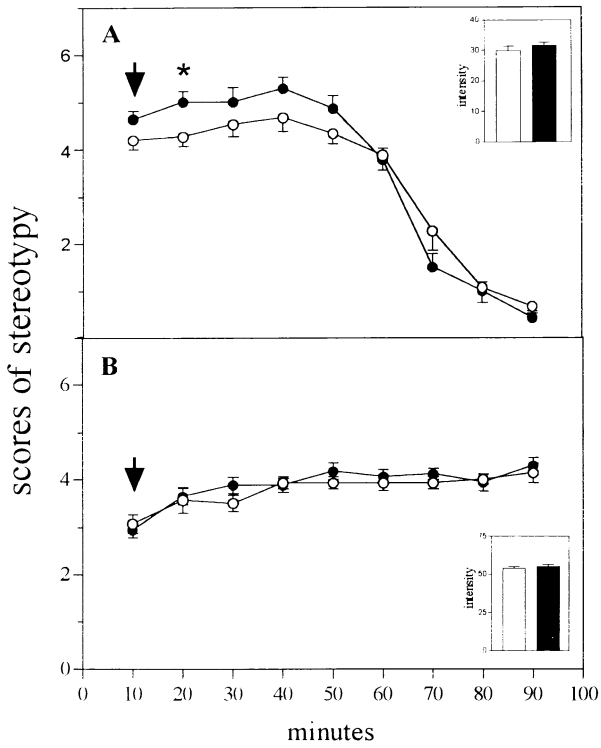

Fig. 3. Effects of reproductive experience on apomorphine-induced (APO; 0.6 mg/kg sc) and amphetamine-induced (AMPH; 9 mg/kg ip) stereotyped behavior scored every 10 min during a 90-min session, respectively. Arrows indicate the time of drug injection. Inset figures show respective stereotypy intensity (total sum of scores). (A) APO-treated nulliparous rats ($n=15$; open circles and bars) and primiparous rats ($n=15$; solid circles and bars). (B) AMPH-treated nulliparous rats ($n=14$; open circles and bars) and primiparous rats ($n=17$; solid circles and bars). Means ± S.E.M. *$P=.04$ (Mann–Whitney's U test).

3.2. Experiment 2: effects of amphetamine treatment on motor activity in nulliparous and primiparous female rats

The results show differences between nulliparous and primiparous females after AMPH pretreatment (Fig. 2). Since two-way ANOVA showed no significant interaction between the factors analyzed, i.e., reproductive status and drug treatment, data were evaluated by one-way ANOVAs. There were significant differences between nulliparous and primiparous females pretreated with AMPH. Primiparous females showed an increase in total velocity ($P=.006$; $F_{3,32}=5.066$; ANOVA), total distance moved ($P=.006$; $F_{3,32}=5.069$; ANOVA) and total time spent in movement ($P=.0162$; $F_{3,32}=3.979$; ANOVA) compared to nulliparous females. The same difference was observed in total distance moved in the central area of the arena, i.e., AMPH pretreatment revealed that primiparous females showed an increased central distance moved ($P=.006$; $F_{3,32}=7.465$; ANOVA) compared to nulliparous females. Also, nulliparous females pretreated with AMPH showed a decrease in the central distance moved compared to the nulliparous control group pretreated with saline ($P=.0006$; $F_{3,32}=7.465$; ANOVA). This can be a consequence of increased anxiety or fear elicited by AMPH pretreatment in the nulliparous group.

3.3. Experiment 3: APO-induced stereotyped behavior of nulliparous and primiparous female rats

The scores assigned to nulliparous and primiparous females after APO injection demonstrated a slight difference between nulliparous and primiparous females. Only at 20 min of score assignment did we observe significantly higher stereotypy in primiparous compared to nulliparous females ($P=.04$; $U=161.5$; Mann–Whitney test; Fig. 3). However, the intensity of stereotyped behavior, sum of scores, observed over a period of 90 min, did not differ significantly between nulliparous and primiparous animals. AMPH-induced stereotyped behavior did not differ significantly between nulliparous and primiparous females.

3.4. Experiment 4: APO-induced hypothermia in ovariectomized and intact nulliparous and primiparous female rats

Body temperature did not differ significantly between intact and ovex nulliparous and primiparous females ($P>.05$; Repeated Measures ANOVA; Fig. 4).

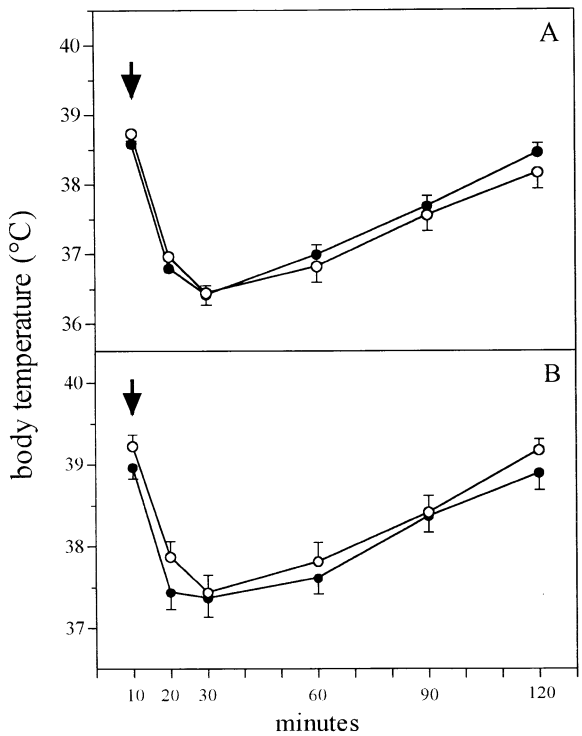

Fig. 4. Body temperature measured 10, 20, 30, 60, 90 and 120 min after the injection of 1 mg/kg sc APO in nulliparous (open circles) and primiparous (solid circles) female rats. Arrows indicate the moment of drug injection. (A) Intact females in proestrus (nulliparous = 11; primiparous = 10); (B) Ovariectomized females (nulliparous = 13; primiparous = 11). Means ± S.E.M.

4. Discussion

The present results show that RE modulates some DA-related behavioral responses. Both 3 and 20 min motor activity, and APO-induced stereotypy showed some differences between primiparous and nulliparous rats. DA has been widely related to motor activity (Coté and Crutcher, 1991; Felicio et al., 1989; Ghez and Gordon, 1995; McEwen et al., 1991; Palermo-Neto, 1984). RE-induced changes in behavioral responses may reflect some RE influence on dopaminergic neurotransmission (Bridges et al., 1993; Felicio et al., 1996; Hucke et al., 1998). The main central DA pathways are the mesocortical, nigrostriatal, mesolimbic and tuberoinfundibular pathways (Ungerstedt, 1971). The behavioral results presented here may reflect alterations in one or all of these pathways. However, since the nigrostriatal system is the one more related to motor function (Mason, 1984), it is the first to be chosen.

Motherhood influences behavioral responses to aversive stimuli in rodents (Kinsley et al., 1999; Silva et al., 1997). Other authors have reported parity-induced decreases in anxiety as well as improvement in learning (Kinsley et al., 1999). Our data showed a decrease in locomotion in experienced animals in the 3-min session, an acute response. This may have been due to an RE-induced decrease in response to stress and novelty. Decreased locomotion frequency is accompanied by a trend to increasing defecation, although this effect failed to achieve statistical significance. This could be suggestive of an increase in fear or anxiety and the consequence would have been a decrease in locomotion. Furthermore, in the 20-min session (Experiment 2), differences were observed only between AMPH-pretreated primiparous and AMPH-pretreated nulliparous females but not in saline-pretreated control animals. AMPH pretreatment revealed RE-induced changes on behavioral responses. The decreased distance moved by the nulliparous group particularly in the central area of the arena after AMPH pretreatment may have been due to an RE-sensitive increase in fear or anxiety responses elicited by pretreatment with the stimulant. In addition, AMPH pretreatment may have reversed the anxiety or fear suggested to have occurred in the primiparous group in the 3-min session.

It was observed that AMPH-pretreated primiparous females moved significantly longer distances in total area of the arena, and displayed more velocity and time in movement than nulliparous animals. AMPH pretreatment revealed RE-induced differences in motor activity. Though the expression of behavioral depression (Paulson and Robinson, 1996; Paulson et al., 1991) was mild, i.e., statistically significant only for the central distance moved by the nulliparous group, the AMPH challenge revealed an important RE-induced change in a dopaminergic response. Since AMPH challenge after a short period of withdrawal does not modify DA concentration responses (Paulson et al., 1991; Paulson and Robinson, 1996), this different response pattern may have been due to RE-induced differences in compensatory mechanisms of dopaminergic synapses in response to AMPH pretreatment.

It is well known that dopaminergic overstimulation leads to stereotyped behavior in different species (Tieppo et al., 1995, 1997, 2000; Troncone et al., 1988). This behavior can be induced by the DA receptor (D_1/D_2) agonist APO (Ljunberg and Ungerstedt, 1977, 1978) or by the DA-releasing agent AMPH (Robbins, 1978; Tieppo et al., 2000). The effects are dose-dependent in both cases (Clark et al., 1991; Felicio et al., 1989; Kihara et al., 1993; Mueller et al., 1990). The main components of stereotypy differ both in qualitative and quantitative terms depending on the drug used to elicit the phenomenon (Fray et al., 1980; Tieppo et al., 2000). This was also observed in the stereotypy studies reported here. AMPH-induced stereotyped behavior showed no significant differences between virgin and experienced females, a fact possibly suggesting that presynaptic mechanisms involving acute DA release stimulation and reuptake block might not be altered by RE. On the other hand, APO-induced stereotypy, although only significant at one point, showed a trend to greater intensity up to 60 min in primiparous females compared to nulliparous animals. This difference may have been due to an RE-induced increase in sensitivity to a direct stimulation of the DA receptors by this agonist, suggesting an RE-induced modification of postsynaptic striatal mechanisms. Increases in APO-induced stereotypy as a function of RE were observed by other authors (Byrnes and Bridges, 1999).

APO-induced hypothermia is due to the stimulation of DA receptors in the hypothalamus (Paulson et al., 1991; Vanzeler et al., 1990). Our results showed no differences between groups. An intact hypothalamic–pituitary–gonadal axis is important for behavioral expression and steroid hormone mediation of neural plasticity (McEwen, 1988, 1991; McEwen et al., 1991). In addition, the ovariectomy-induced influence on hypothalamic DA concentrations may be modulated by RE (Hucke et al., 1999). The present data did not show significant changes in body temperature between ovex and intact females after APO injection. These results suggest that RE does not influence hypothalamic sensitivity to dopaminergic stimulation and ovariectomy does not help to reveal any differences. Alternatively, APO-induced hypothermia may not be a sensitive enough approach to reveal RE-induced changes in hypothalamic sensitivity to DA. Different dosages, challenges with different drugs or physiological states such as lactation may help to reveal RE-induced functional alterations in hypothalamic DA receptors. Also, these results are suggestive of different kinds of RE-induced regulation of dopaminergic function.

Taken together, our data show that parity influences dopaminergic-related behavioral responses, possibly by modulating dopaminergic function in different ways according to the brain region. This may be a relevant physiological phenomenon, although its significance still remains unknown. Would this be a way of optimizing system

homeostasis after a successful reproductive event? Alternatively, would it reveal different kinds of behavioral responses after a rich previous behavioral experience? Is the whole RE important for the expression of this phenomenon? Authors have suggested that changes occurring during lactation are crucial for brain modifications (Kinsley et al., 1999; Kolb et al., 1998; Lee et al., 1999a,b). Maternal behavior and pup care plus hormonal changes can contribute to these changes (Kinsley et al., 1999; Kolb et al., 1998; Lee et al., 1999a,b). Finally, our data add information about changes in brain functions due to previous reproductive history. Also, these results may have implications for drug abuse during, or following, reproductive periods and reproductive senescence.

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