



Dopaminergic activity mediates pups' over male preference of postpartum estrous rats

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ARTICLE INFO

Keywords:

Postpartum estrus
Pups-male preference
Maternal motivation
Sexual motivation
Dopaminergic system
Haloperidol

ABSTRACT

Pups have greater incentive value than males for rats during the postpartum estrus (PPE); a period when females are both maternally and sexually motivated. Mesolimbic dopaminergic system has been proposed as a general motivational circuit; however in the literature it has been more related to the control of the motivational aspects of maternal than sexual motivation of females. Therefore, we aimed to assess the effect of antagonizing dopaminergic neurotransmission of PPE females on their preference for pups over a male. To achieve this objective we tested PPE rats in a Y-maze with three-choice chambers (one containing eight pups, the other a male and the last one no stimulus) after the systemic administration of the dopaminergic antagonist haloperidol (0.0; 0.025 or 0.05 mg/kg). Furthermore, to determine if this dopaminergic antagonist differentially affects maternal and sexual motivations when pups and male are not competing, we evaluated the effect of haloperidol in the preference of females for pups vs. a non-receptive female and for a male vs. a non-receptive female. In the preference test for pups vs. male, both doses of haloperidol decreased the time that females spent in pups' chamber while increased the time that they spent in male's chamber, resulting in a lack of preference between both incentives. Besides, haloperidol reduced the effort -attempts to get access to the stimuli- made by the females to obtain the pups. Conversely, 0.05 mg/kg of haloperidol did not affect the preference for both incentives when they were confronted to a non-receptive female. Together, these results indicate that the dopaminergic activity mediates pups' preference over male during the PPE and point toward a more relevant role of this system in females' behavioral output when incentives are competing.

1. Introduction

Maternal and sexual behaviors are highly motivated. This is reflected in the time and effort that females spent on getting access and interacting with the pups or a male [1–6]. The underlying neural circuitry of both motivations is partial overlapped, and includes the mesolimbic dopaminergic system (for maternal behavior see: [7,8] and for sexual see: [9,10], although: [11]). This system has been proposed as a general circuitry that regulates the activational aspects of motivated behaviors, particularly those related to the effort that individuals invest in achieving a certain goal [12,13].

Dopamine (DA) levels in the Nucleus Accumbens (NAcc) rise when mothers interact with pups [14–17], even when physical contact with them is precluded [18]. Also, DA rises in NAcc of sexually active females in the presence of a male [19,20], or even in the absence of interaction when the male is behind a barrier [20]. Moreover, the systemic administration of dopaminergic agonists at low dose promotes sexual [21,22] and maternal [23] responses. Conversely, DA depletions

in the ventral tegmental area or in the NAcc abolish maternal but not sexual behavior of female rats [24,25]. Also, while the systemic administration of low doses of dopaminergic antagonists drastically reduce the active components of maternal behavior [26,27], it does not affect female's sexual behavior [28]. Therefore, although the dopaminergic system has been implicated in the regulation of both motivated behaviors [8–10,29], data from pharmacological manipulations points toward a less relevant role of this system in the control of females' sexual motivation [11].

Interestingly, female rats exhibit a postpartum estrus (PPE) approximately twelve hours after delivery, and during this short phase they are simultaneously maternally and sexually motivated [30–32]. Therefore, this period allows us to explore how these two social motivations interact, as well as the neural substrate that underlies their expression and interaction. In a choice situation between pups and a male, we previously observed that PPE females choose the pups [33,34] concluding that, in this context, pups have a greater incentive value than the male. The preference for pups during the PPE seems to be

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mediated by a stronger maternal motivation, because the selective reduction of maternal motivation on the delivery day (by decreasing the time that mothers interact with their pups) shifts the preference of PPE females from the pups toward the male [34].

Based on the greater incentive value that pups have relative to the male for PPE females and on the evidence suggesting that the dopaminergic system has a greater involvement in the expression of maternal than sexual motivations, we hypothesize that antagonizing the dopaminergic neurotransmission of PPE females reduces the incentive value of pups relative to the male. To test this hypothesis, we determined the effect of the systemic administration of the dopaminergic antagonist haloperidol (HAL) on the preference for pups relative to a male of PPE females. It could also be speculated that if the dopaminergic system is differentially implicated in the regulation of maternal and sexual motivations, the administration of this dopaminergic antagonist will also differentially affect pups and males' preferences when these incentives are not competing between each other. Therefore, we also evaluated the effect of HAL on the preference of PPE females for pups vs. a non-receptive female (neutral social stimulus) and for a male vs. a non-receptive female.

2. Materials and methods

2.1. Animals

Three to five-month-old female and male Wistar rats were housed in a temperature and humidity-controlled environment under a 12 h light-dark cycle (lights on at 05:00 a.m.) with ad libitum access to water and rat chow. Animal care and experimental procedures were performed in accordance with the National Institutes of Health guide for the care and use of laboratory animals and the Uruguayan law (Law No 18611) for the use and care of laboratory animals. The Ethical Committee on Animal Care and Protocols of the Facultad de Ciencias approved this protocol (No 240011–002280-17).

2.2. Preference test

Preference between the pups and a male were performed in a transparent Y-shaped maze with three equal sized chambers (25 cm wide × 30 cm long × 18 cm high) at the end of each arm (10 cm wide × 60 cm long × 10 cm high). Two of the chambers contained either eight pups or a sexually active male, while the third chamber remained empty. For experiment II, one chamber contained an incentive stimulus - the pups or a male-, other contained a non-sexually receptive female (neutral social stimulus), and the third one remained empty. Each chamber had an acrylic transparent division with holes allowing the females to see, hear and smell the stimuli but not having contact with them. The location of the stimuli was counterbalanced in a random manner within a group.

On testing day, approximately twelfth hours after delivery and 30 min after drug administration, mothers were placed in the center of the maze and allowed to explore and habituate to the empty maze for 30 min. Immediately after, the stimuli were placed in the chambers and the cumulative time spent in each chamber and the number of entries were registered during a 20-min testing period. Also the attempts made to gain access to the stimuli (bites and scratches in perforated wall) were registered. The entire maze was cleaned with a 50% ethanol/water solution and dried thoroughly between test sessions.

Two complementary measures of females' preference were determined: 1- the number of females in each group exhibiting preference for the pups, the male or no preference, and 2. the total time that females spent in each chamber. Preference for a particular chamber was assigned if the female spent in this chamber more than the 50% of the time spent in the three chambers (pups, male and neutral), with the additional caveat that this time had to be at least 25% greater than the time spent in either of the two remaining chambers [26,33,34].

Additionally we determined the ambulatory activity of the females during the 20 min preference test as the total number of entries to the three arms and to the three chambers of the maze.

2.3. Experimental procedure

Pregnant females were allocated in individual cages on Day 20 of gestation and the presence of the litter was checked every hour during the light period from Day 22 of gestation. The litter was adjusted to four females and four males approximately one h after delivery.

Approximately 10 h after parturition, females were habituated to the experimental room for 1 h, and afterwards they were injected subcutaneously (SC) with vehicle or HAL solutions. After thirty minutes they were introduced in the Y-maze for habituation and thirty minutes later, the stimuli were introduced in the chambers and preference test was performed. Immediately after this test, females' sexual receptivity and maternal responsiveness were verified by assessing the expression of lordosis posture in response to male's mounting and of licking and retrieving of the pups in their home-cages. The preference task was conducted approximately 12 h after parturition to ensure maximal sexual activity of the females [30–32,35].

2.3.1. Experiment I. HAL effect on the preference of PPE females for pups over a male

To assess the influence of the dopaminergic neurotransmission on the preference for pups over a male observed during the PPE, primiparous females treated with the dopaminergic antagonist HAL (SC - 60 min: 0.0 n = 12, 0.025 mg/kg/ml n = 10, or 0.05 mg/kg/ml, n = 10) were tested for pups vs. male preference approximately 12 h after delivery. The HAL doses, route of administration and injection time were selected according to previous studies analyzing incentive motivations [26,36–38].

2.3.2. Experiment II. HAL effect on the preference of PPE females for the incentives- pups or male- over a neutral social stimulus

To evaluate if this dopaminergic antagonist affects the incentive value of these stimuli –pups and male- when they are not competing, we determined the effect of HAL on the preference for pups or a male when confronted to a neutral social stimulus (non-sexual receptive female). Therefore, primiparous PPE females were tested for pups vs. non-receptive (NR) female preference, or for male vs. NR female preference after been treated with HAL (0.0, n = 9 or 0.05 mg/kg, n = 8–9 per group). The dose of 0.05 mg/kg of HAL was selected based on its maximum effect on disrupting PPE females' preference for the pups in Experiment I (see Results below).

2.4. Statistical analysis

As most of the behavioral data do not fit to a normal distribution and variances were not homogeneous, data are expressed as medians and semi-interquartile ranges (SIQR) and were analyzed by means of non-parametric tests. Kruskal–Wallis one-way analysis of variance followed by Mann–Whitney *U* test were employed for comparisons of independent samples (between groups), while Friedman two-way analysis of variance followed by Wilcoxon matched pairs test were used for comparisons of dependent data (within groups) [39]. The putative existence of correlations between the attempts to gain access to the stimuli and the time spent in the chambers were tested by Spearman Rank Order Correlation test [39]. Multiple Exact Contingency Tables (3 × 2) test were used for comparisons of the distribution of preferences (for pups, male or no preference) among groups (Mehta and Patel, 1983), followed by Fisher Exact Probability test comparisons.

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