



# Prepubertal ovariectomy modulates paced mating behavior but not sexual preference or conditioned place preference for mating in female rats



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## HIGHLIGHTS

- Ovaries were removed from female rats before or after puberty.
- As adults rats were tested on sexual preference & place preference for paced mating.
- Prepubertal ovariectomy led to increased locomotor activity and withdrawal.
- Sexual preference and mating-induced reward did not differ due to ovariectomy timing.
- Results add to understanding of peripubertal ovarian hormones on sexual behavior.

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## ABSTRACT

The present study investigated whether the presence or absence of peripubertal ovarian hormones affects sexual preference and conditioned place preference for paced mating in adult female rats primed with 10  $\mu$ g estradiol benzoate and 1 mg progesterone. Ovariectomy (OVX) occurred either before or after pubertal development, and 4 weeks later rats began a series of behavioral tests. Rats with ovaries removed before the pubertal timeframe (Prepubertal OVX) were more active, more likely to withdrawal from the male compartment, and did not discriminate between mounts and intromissions during paced mating relative to rats with ovaries during puberty (Adult OVX). Both Adult OVX and Prepubertal OVX rats showed a higher preference for the male when hormone primed vs. oil treated and a conditioned place preference for paced mating behavior. The results of the present study demonstrate that some, but not all, aspects of female sexual behavior require ovarian hormones during puberty.

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## 1. Introduction

According to the classic view of rodent sexual differentiation, male-typical development requires testosterone, or testosterone aromatized to estradiol, during a distinct sensitive period just before and after birth, whereas female-typical development is the default occurring in the absence of perinatal gonadal hormones [1–4]. However, evidence increasingly shows that the ovarian hormone, estradiol, actively shapes the female brain. Aromatase knockout (ArKO) female mice, incapable of synthesizing estradiol because of lifelong aromatase deficiency, exhibit lower levels of the receptive posture lordosis as adults in response to estradiol and progesterone, no preference for a male sexual partner over a female partner, and diminished investigation of volatile conspecific odors relative to wild-type mice [5–7]. Reduced lordosis is also observed

in adult, hormone-primed female rats that received ovariectomy between postnatal day 1 (P1) and P15 [8,9]. In addition, adult female rats given the estrogen receptor modulator tamoxifen from P1–5 show reduced lordosis in response to estradiol + progesterone, but not enhanced male sexual behavior in response to testosterone [10]. The effect of tamoxifen on female, but not male, sexual behavior suggests that tamoxifen acted as an estrogen receptor antagonist in that study, although tamoxifen is also known to have agonist properties [11]. These data support the idea that ovarian hormones actively contribute to female-typical development of brain and behavior.

Exposure to ovarian hormones just before or during puberty, considered to occur from roughly P28–55 in female rats [12,13], can augment adult lordosis if estradiol exposure early in life is reduced or eliminated. Adult receptivity in hormone-primed female rats that had been ovariectomized on P1 is rescued partially by estradiol administered between P10–20, and more so by estradiol between P30–40 (i.e., during puberty) [9,14]. Estrogen administration to ArKO mice from P15–25, but not P5–

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15, leads to more lordosis in adulthood after hormone treatment [5]. Hamsters ovariectomized before puberty also show altered adult receptive behavior, although in the opposite direction from mice and rats, an effect reversed by pubertal estradiol [15,16]. Additional support pointing to puberty as an important time for female sexual differentiation comes from findings showing that prepubertal ovariectomy prevents female-typical development of several sexually dimorphic brain regions [17,18]. Collectively, these studies indicate that ovarian hormones acting around the time of puberty influence the display of lordosis in adulthood, however the organizational effects of ovarian hormones on more complex sexual behaviors are still not well understood [19].

The study of female sexual behavior has shifted from a focus on the lordosis posture to include a more dynamic, comprehensive analysis of reproductive behaviors to better understand factors contributing to sexual motivation and reward [20]. When tested in an environment that permits the female rat to control proximity to the male rat, a sexually receptive female rat will control the timing of a sexual encounter by exhibiting a pattern of approach and withdraw from a sexually active male rat called paced mating behavior [21]. The two main measures of paced mating behavior, contact-return latency (the time elapsed before the female rat returns to the male following receipt of a sexual stimulation) and percentage of exit (the likelihood of withdrawal following each type of sexual stimulation), increase with receipt of more intense sexual stimulations ( $M < I < E$ ) [22]. Contact-return latency has been proposed to reflect sexual motivation whereas percentage of exits has been proposed to reflect sensory discrimination [23]. Sexual motivation can more directly be assessed in rats using a sexual preference test, also called a sexual incentive motivation task, in which experimental rats have a choice between two conspecifics, a sexual partner or a non-sexual, social partner [22,24–26]. Female rats will express a conditioned preference for cues associated with mating, indicating that mating is rewarding to female rats [27,28].

The few studies available that have examined female rodent sexual behaviors other than lordosis suggest that ovarian hormones around the time of puberty shape adult sexual motivation. Rats ovariectomized between P15 and 35 show lower levels of solicitation behaviors [8,29,30] that are considered to indicate sexual motivation [31–33]. Preference for male vs. female odors is enhanced in ArKO mice given estradiol from P15–25, but not P5–15, relative to untreated knockouts [5]. However, the studies did not specifically target the pubertal period when manipulating gonadal hormones and did not use behavioral paradigms that capture the complete repertoire of female sexual behavior. The gap in the literature regarding the role of pubertal ovarian hormones in adult female sexual behavior prompted us to test whether the absence of ovaries across the peripubertal period of development would disrupt later paced mating behavior, sexual preference, and conditioned place preference for mating in adult, hormone-primed female rats.

## 2. Methods

### 2.1. Subjects

Sexually naïve female Long-Evans rats were obtained from Harlan Laboratories (Indianapolis, IN) and kept in a temperature-controlled vivarium on a reverse light-dark cycle (12:12 h, lights off 1100 h). Rats were group housed in clear polycarbonate homecages with commercial rat food pellets and water freely available. Stimulus Long-Evans males were sexually experienced and approximately five months of age. Juvenile females arrived before puberty on postnatal day (P) 24 and adult females on P57–64. Female rats were ovariectomized under ketamine (50 mg/kg; Butler Schein, Port Washington) and xylazine (2.5 mg/kg; Butler) either before puberty at P25 (Prepubertal OVX,  $n = 23$ ) or after puberty at P57–64 (Adult OVX,  $n = 23$ ). Hormones were administered subcutaneously in a sesame oil vehicle; rats received 10 µg estradiol benzoate (EB) followed 44 h later by 1 mg of progesterone (P;

Sigma, St. Louis). Four weeks after ovariectomy Prepubertal OVX rats received two cycles of EB + P to induce vaginal opening (Fig. 1). Adult OVX rats also received two cycles of EB + P so that both groups received comparable exposure to EB + P prior to behavioral testing. EB + P was administered to subjects to prime them for mating tests, which began five weeks after surgery. Behavioral testing occurred under dim red lighting during the dark portion of the light-dark cycle. All animal procedures were approved by the Institutional Animal Care and Use Committee at Carleton College and were in accordance with the National Institutes of Health Guide for care and use of laboratory animals.

### 2.2. Apparatus and procedures

#### 2.2.1. Sexual preference and paced mating arena

Clear Plexiglas® arenas (112.5 × 37.5 × 32 cm high) with pine bedding covering the floor were used for sexual preference and paced mating tests as described previously [25,34–36]. Each arena was divided into three equally sized compartments (36.5 × 31.7 cm) using two pairs of Plexiglas® partitions (36.5 × 32 cm). One partition was clear with a five cm hole in each bottom corner and one partition was solid and opaque. For sexual preference tests wire mesh dividers bisected each outer compartment and the stimulus rats, a sexually vigorous male and an EB + P treated female rat, were sequestered behind the mesh divider in each outer compartment. Prior to the start of testing, the opaque partitions were placed next to the clear partitions to confine the experimental rat to the center compartment. Once the test began, the female rat was permitted to freely enter and exit an outer compartment through the clear partition. The week before behavior tests began, experimental rats were habituated to the arena twice, for 15 min each time. Before being used in paced mating tests, male stimulus rats were trained to stay in an outer compartment by tapping them on the nose if they attempted to pass through the clear partition.

#### 2.2.2. Sexual preference procedure

Immediately prior to each test the arena was thoroughly cleaned with 70% ethanol and fresh pine shavings were added to cover the floor. Male stimulus rats received an intromission with a stimulus female to ensure sexual vigor before the sexual preference test. The experimental rat acclimated in the center compartment while the stimulus rats acclimated in the outer compartments behind the wire mesh divider for five minutes before the test started.

The test began when the experimenter removed the opaque dividers granting the experimental rat access to both outer compartments where exchange of olfactory, visual, and auditory information but not physical contact was possible. Following the sexual preference test, experimental rats were tested in a separate Plexiglas arena (39.5 W × 22.9 L × 31.1 cm H) to 10 mounts with an intact male to confirm that the hormone injections induced sexual receptivity. Lordosis response to each sexual stimulation was scored on a 4-point scale from 0 to 3 [37] and used to calculate a lordosis quotient (LQ), the number of lordosis responses of 2 or 3 divided by the number of mounts received × 100. Hormone-primed rats with a LQ < 70 were considered non-receptive and excluded from analysis.

During the 10-min test, time of entries and exits of the experimental rat to and from each side compartment was recorded live by trained observers. The following measures were calculated for each subject: (1) male preference score, defined by time spent with the male divided by time spent with either of the stimulus animals; (2) social score, defined by time spent with either of the stimulus animals divided by total test time; and (3) activity, defined as the sum of entries into and exits from the side compartments [25].

#### 2.2.3. Paced mating behavior procedure

The experimental rat acclimated in the center compartment while sexually vigorous male stimulus rats acclimated in the outer compartments for 5 min. The paced mating test began by removing one opaque

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