



## Sexual behavior in lactating rats: Role of estrogen-induced progesterone receptors

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### ABSTRACT

Lactation is associated with suppression of reproductive function, the duration of which depends on the number of young suckled and food availability. Although previous studies have documented increasing responsiveness to the positive feedback effects of estrogen on luteinizing hormone (LH) secretion with time postpartum, changes in the ability of estrogen to stimulate sexual behavior across these time points and the influence of food restriction on response to estrogen have not been investigated. Thus, we compared the ability of exogenous estrogen administration to stimulate proceptive and receptive behavior in ad libitum fed and food restricted rats on Days 15 and 20 postpartum. Because the ability of estrogen to induce sexual behavior depends on activation of both estrogen receptors and estrogen-induced progesterone receptors, a second study compared estrogen and progesterone-ir within the VMH and MPOA in similar groups. Finally, we investigated the role of the high levels of progesterone typical of lactation in the suppression of estrogen-induced sexual behavior by transient blockade of the progesterone receptor using RU486. As expected there was an increase across time in the ability of estrogen to stimulate sexual behavior that correlated with an increased ability of estrogen to induce progesterone receptors in the MPOA that was most evident in ad libitum fed rats. RU486 administration concomitant with estrogen administration increased solicitation behavior and was most effective in ad libitum fed rats suggesting an inhibitory role of progesterone on estrogen-induced sexual proceptivity in lactating rats.

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### Introduction

In a variety of mammals lactation is accompanied by suppression of reproductive function (Lamming, 1978). Typically the length of this period of anovulation is a function of the number of young nursed and/or the availability of food (McGuire et al., 1992; Woodside, 1991; Woodside and Popeski, 1999). For example, in ad libitum fed rats nursing litters of eight pups the period of lactational diestrus lasts for 20–21 days (Hansen et al., 1983) but is prolonged by almost a week if the rats are food restricted for the first 2 weeks postpartum (Woodside and Jans, 1995).

Lactational infertility in rats is accompanied by low levels of circulating estrogen (Smith and Neill, 1977), and a reduction in sensitivity to exogenously administered estrogen (Abizaid et al., 2003, 2004; Coppings and McCann, 1979; Smith, 1978). Maintenance of the corpora lutea formed following postpartum ovulation results in high plasma progesterone levels that peak around Day 10 postpartum (Gonzalez-Fernandez et al., 2008; Grota and Eik-Nes, 1967; Takiguchi et al., 2004; Tomogane et al., 1969). Physiologically, high levels of progesterone decrease the ability of estrogen to induce a preovulatory luteinizing surge in lactating rats. (Abizaid et al., 2003; Woodside, 1991). Progesterone concentrations are also negatively associated

with the ability of estrogen to induce progesterone receptors in the anteroventral periventricular area (AVPV) of ad libitum fed and food restricted rats, an effect that is blocked by ovariectomy or RU486 (Abizaid et al., 2003). Returning to full reproductive capacity entails appropriate behavior as well as ovulation, yet comparatively few studies have examined the effect of lactation on the mechanisms underlying sexual behavior. Those that have done so have focused on the induction of sexual behavior in early lactation (Clarke and Roy, 1984; Sodersten et al., 1983). Sodersten et al. (1983) reported that a single dose of estradiol benzoate with or without progesterone administration failed to stimulate sexual behavior in rats on Day 6 postpartum. Responsivity was restored if pups were removed, prolactin release was suppressed with bromocryptine, or if rats were ovariectomized. Progesterone replacement to ovariectomized postpartum rats resulted in a suppression of responsivity, but only if females continued to receive suckling stimulation or prolactin levels were maintained by domperidone treatment. Clarke and Roy (1984) found that repeated estrogen administration (10 µg/day for 3 days) induced a high level of receptivity in lactating rats on Days 5–9 postpartum that was not increased by supplementing estrogen administration with progesterone. Together, these studies suggest that during the first half of lactation female rats show estrogen-stimulated lordosis behavior following repeated estrogen administration or when the influences of progesterone and/or prolactin were eliminated. In neither of these studies was proceptive behavior measured and whether there are changes in the ability of estrogen to

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stimulate sexual behavior that correlate with the return of ovulation was not addressed.

We have demonstrated previously that food restricting rats for the first 2 weeks postpartum extends the length of lactational infertility (Woodside, 1991). This state is accompanied by a longer period of elevated circulating progesterone levels (Woodside, 1991) as well as a prolongation of both suppression of pulsatile luteinizing hormone release (Walker et al., 1995) and hyporesponsivity to estrogen positive feedback (Abizaid et al., 2003). How combining restriction of food availability with lactation might affect the ability of estrogen to stimulate sexual behavior, however, has not yet been investigated.

In the current studies we used the dose of estrogen described by Clarke and Roy (1984) to compare the ability of exogenous estrogen administration to stimulate both sexual receptivity and proceptivity between food restricted and ad libitum fed rats on Days 15 and 20 postpartum. If the pattern of estrogen responsiveness in the neural circuits underlying sexual behavior are similar to those involved in initiating the LH surge then one would expect that ad libitum fed rats would show a greater response to exogenous estrogen on Day 20 than on Day 15 postpartum and that food restricted rats would show lower levels of sexual behavior, than ad libitum fed rats on Day 20 postpartum. Given that food deprivation has been shown to suppress choice of a male partner over food in female hamsters (Schneider et al., 2007), we hypothesized that solicitation behaviors as well as rejection of the male would be most affected by food restriction.

The performance of both lordosis and solicitation behavior depends on the activation of steroid receptors in specific brain areas. The lordosis response depends primarily on the activation of ER $\alpha$  in the ventromedial hypothalamus (VMH) (Meisel et al., 1987; Rubin and Barfield, 1980) and is potentiated by activation of progesterone receptors in the same area (Rubin and Barfield, 1983). On the other hand, the display of proceptive behavior is reduced by lesions of the medial preoptic area (MPOA) (Hoshina et al., 1994) and is dependent for its full expression on progesterone receptor activation (Erskine, 1989). In the second experiment, therefore, we compared levels of estrogen receptor alpha immunoreactivity in the VMH and MPOA between food restricted and ad libitum fed rats on Days 15 and 20 postpartum. Further, as the ability of estrogen to induce progesterone receptors within the AVPV was suppressed in food restricted lactating rats PR levels in both the VMH and MPOA of estrogen treated rats were also assessed. Our hypothesis was that the time course of restoration of solicitation behavior would be associated with increases in ER $\alpha$  and PR levels within these areas.

The possibility that the blockade of progesterone receptors during estrogen priming might facilitate the ability of estrogen to stimulate sexual behavior, in the same way that this manipulation increases the ability of estrogen to stimulate a surge in LH (Abizaid et al., 2003), was examined in the third experiment. In this study, the effects of administering the progesterone receptor blocker RU 486 concurrent with estrogen treatment on sexual proceptivity and receptivity, in both ad lib fed and food restricted lactating rats on Day 15 postpartum were investigated.

## General methods

### Subjects

Female Wistar rats were obtained from Charles River Breeding Farms (St. Constant, Quebec) and weighed 220–240 g at the start of the experiment. Following 1 week of acclimation to the animal facility, females were mated by group housing with a sexually experienced male of the same strain. When pregnancy became obvious, females were individually housed in polypropylene cages (45 × 25 × 20 cm) with wood chip bedding. On the day following parturition (Day 1 postpartum) litters were culled to 8 pups and females were assigned to food restricted or ad libitum fed groups.

In all experiments intact male Wistar rats served as stimulus males. Each male received 10 tests of sexual behavior with a receptive female and only those males that initiated vigorous copulatory activity with females within 1 min of being placed inside the testing chamber were used in the experiment. All male training sessions took place within the same testing chamber that was used in the experiments.

Rats were maintained on a 12:12 light/dark cycle with lights on at 2400 h and off at 1200 h. Temperature was maintained at 20 ± 2 °C. With the exception of lactating females in the food restricted group all rats had ad libitum access to food throughout the experiments. Food restricted rats received a daily ration equivalent to 50% of the food eaten on that day by ad libitum fed rats. All experimental procedures were approved by the Concordia University Animal Care Committee according to the guidelines set by the Canadian Council on Animal Care.

### Tests of sexual behaviors

Testing began during the dark phase. On the assigned day of testing females were placed in an open field chamber (H: 48 cm, W: 49 cm, L: 55 cm) lined with Beta chip bedding with a stimulus male. Behaviors were videotaped for 30 min using a Panasonic video camera mounted on a tripod allowing the inside of the testing chamber to be viewed. Videotapes were scored subsequently for both female and male sexual behavior by an observer blind to group assignment. Latency and frequency data were generated for solicitations (incidents of the female making a head-wise orientation to the male followed by a runaway) hops and darts, and rejection responses as described by Coria-Avila et al. (2006). The lordosis posture was categorized on a scale of 1 (slight dorsiflexion), 2 (moderate dorsiflexion) and 3 (full dorsiflexion) using the scale of Hardy and Debold (1971). In addition to an overall reflex score, the frequencies of each posture were analyzed, as described by Coria-Avila et al. (2006). Latency and frequency data were also generated for male behaviors (mounts, intromissions, and ejaculations) during the test.

### Experiment 1 Estrogen-stimulated sexual behavior in ad libitum fed and food restricted lactating rats

To evaluate the ability of estrogen to stimulate sexual behavior in ad libitum fed and food restricted rats in late lactation, rats in each of these diet conditions were tested for sexual behavior on either Day 15 (AL15,  $N = 8$ ; FR15  $N = 6$ ) or Day 20 postpartum (AL20,  $N = 8$ ; FR 20,  $N = 8$ ). All rats received three daily subcutaneous injections of 10  $\mu$ g estradiol benzoate (EB) in 0.1 ml sesame oil (Clarke and Roy, 1984) and were tested for sexual behaviors on the fourth day. Data were analysed using a 2 (days postpartum) × 2 (diet condition) ANOVA for independent groups.

### Experiment 2 Estrogen and progesterone receptor levels in the MPOA and VMH of ad libitum fed and food restricted lactating rats

To evaluate the possibility that estrogen's ability to stimulate receptive and proceptive behavior in ad libitum and food restricted lactating rats correlated with changes in estrogen receptor number, estrogen receptor alpha immunoreactivity was compared among ad libitum and food restricted lactating rats on Days 15, and 20. The ability of estrogen to induce progesterone receptors in these areas was assessed by comparing progesterone receptor immunoreactivity among groups of oil- and estrogen-primed ad libitum fed and food restricted lactating rats at the same time points. Estrogen treatment was identical to that used in experiment 1.

### Immunocytochemistry for ER $\alpha$

Rats were overdosed with sodium pentobarbital (50 mg/rat) between 10:00 and 11:00 h, and were transcardially perfused with

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