Delayed first cycle in intrauterine growth-retarded and postnatally undernourished female rats: follicular growth and ovulation after stimulation with pregnant mare serum gonadotropin at first cycle

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Abstract

In the present study we examined the consequences of intrauterine growth retardation and postnatal food restriction on the maturational process of sexual development by studying onset of first cycle. In addition, we investigated the effect of pregnant mare serum gonadotropin (PMSG) on ovarian growth and ovulation in intrauterine growth-retarded (IUGR) and postnatally food-restricted (PFR) rats. Intrauterine growth retardation was induced by uterine artery ligation on day 17 of gestation and food restriction was achieved by enlarging the litter to 20 pups per mother from day 2 after birth until weaning (day 24).

In control rats, vaginal opening and the first cycle took place on the same day. In IUGR rats, uncoupling occurred between vaginal opening and the first cycle. Vaginal opening was delayed (P<0.05) and the first cycle was even further delayed (P<0.01) compared with controls. Body weight in IUGR rats was lower (P<0.05) at vaginal opening, but at first cycle and after stimulation with 50 IU PMSG in the first cycle it was similar to that in controls. In the ovaries of IUGR rats, the numbers of primordial follicles (P<0.05), growing (P<0.01) and antral follicles (P<0.01), and the total number of follicles (P<0.01) were lower than in controls after stimulation with 50 IU PMSG at first cycle. The number of corpora lutea in the ovaries of the IUGR rats and the controls was similar and reflected superovulation.

In the PFR rats, vaginal opening occurred at the same time as in control rats, but at a lower body weight (P<0.01). First cycle was much delayed (P<0.01), by which time body weight was greater (P<0.01) than that of controls at first cycle. On the basis of the differences in weight and age between PFR rats and controls at first cycle, we performed two studies. In study A, ovaries were analysed histologically 42 h after stimulation with PMSG at first cycle of control rats and age-matched PFR rats. In study B, the ovaries of PFR rats at first cycle and age-matched control rats were examined 42 h after PMSG stimulation. In the ovaries of the PFR rats in study A, a greater total number of follicles (P<0.05) was observed, represented by a greater number of primordial follicles (P<0.01) and a lower number of antral follicles (P<0.05), including corpora lutea. The number of corpora lutea in the ovaries of the PFR rats was significantly lower than that in controls (P<0.01). The total number of follicles in the ovaries of the PFR rats of study B did not differ from the age-matched controls after PMSG stimulation at first cycle, and neither did the number of the follicles in the different classes.

We conclude that, in IUGR rats at first cycle, PMSG can induce multiple follicular growth and development followed by superovulation comparable to that in controls, despite a decreased total number of follicles in the ovaries. However, in PFR rats of the same age, the ovary is not capable of responding adequately to PMSG, despite a greater total number of follicles. Stimulation with PMSG at first cycle resulted in follicular growth and superovulation comparable to those in age-matched controls. Undernutrition in different critical time periods around birth in the rat leads to ovarian development in such a way that, in both groups, an increased risk of reduced reproductive capacity can be expected.


Introduction

In humans and animals, the start of puberty is the achievement of interactions between the higher central nervous system, the hypothalamus, the pituitary gland and the ovaries – that is, the neuroendocrine–reproductive axis. In the female rat, vaginal opening and ovulation take place when the hypothalamic–pituitary–ovarian axis...
becomes fully mature (Ojeda et al. 1980, 1983, Halasz et al. 1988). In normal female rats, the oestrous cycle and ovulation occur at the same time as vaginal opening occurs. Depending on its extent, undernutrition during the period before weaning can uncouple these events (Kennedy & Mitra 1963, Glass & Swerdlo 1980). Kennedy & Mitra (1963) have shown that female rats undernourished before weaning had delayed vaginal opening, accompanied by a significantly lower body weight. The first oestrous cycle occurred when the undernourished rats reached the same body weight as that of control rats at vaginal opening. In addition, mating behaviour was often absent, even after the start of normal cycling (Kennedy & Mitra 1963). It is well established that malnutrition during critical periods in early life has implications for further development (Glass & Swerdlo 1980, Gluckman et al. 1996, Lucas 1998). With respect to puberty, we have shown earlier that intrauterine growth retardation results in a delayed onset of puberty in female rats, in contrast to postnatal food restriction, which leads to onset of puberty at the same age as in control rats (Engelbregt et al. 2000a). We defined onset of puberty as the age in days at which vaginal opening occurred. In addition, intrauterine growth-retarded (IUGR) rats have a significantly lower number of follicles in the ovaries at vaginal opening compared with controls, whereas postnatally food-restricted (PFR) rats have a normal number of follicles, but an impaired follicle maturation. Both growth-retarded groups do not ovulate at onset of puberty, in contrast to control rats, which exhibited ovulation and vaginal opening at the same time (Engelbregt et al. 2000b). These findings indicate that the perinatal period appears to be a 'critical period' for the maturational process of sexual development in the rat, and that undernutrition during different time periods may affect ovarian development in different ways.

Pregnant mare’s serum gonadotrophin (PMSG) has been widely used to induce ovulation and superovulation in the immature rat and superovulation in the mature rat (McCann et al. 1974). The activity of PMSG is species-dependent, and comparable to the functions of follicle-stimulating hormone (FSH), luteinizing hormone (LH), or both, so PMSG can induce complete gonadotropic stimulation of the reproductive tract (Moore & Ward 1980). In the present study, we examined the effect of PMSG on follicular growth, follicular development and ovulation in control, IUGR and PFR rats. First we examined the start of the oestrous cycle. On the basis of these findings, we determined the time at which PMSG stimulation takes place.

Materials and Methods

For all experiments, approval was obtained from the Animal Welfare Committee (DEC) of the VU Medical Center at Amsterdam.

IUGR rats

Timed pregnant Wistar rats were obtained from Harlan CPB (Horst, the Netherlands) and housed under a constant light–darkness cycle with lights on from 0600 h to 1800 h and controlled temperature (20–22 °C). Intrauterine growth retardation was induced by bilateral ligation of the uterine artery on day 17 of gestation according to a modification of the method of Wigglesworth (1964). At day 21–22, the pups were born spontaneously and defined as IUGR if their weight on day 2 after birth was less than 5.3 g, corresponding to −2s.d. of the mean of control pups, born from sham-operated dams. In the IUGR group, four or five pups were suckled by one mother and in the control group the litter size was kept at six pups per mother, brothers and sisters being kept together with their own mother, justified by the fact that male and female rats do not differ in weight gain until weaning.

PFR rats

Postnatal undernutrition was achieved by enlarging the litter to 20 pups per mother from day 2 after birth until weaning, which in our laboratory is day 24.

Onset of puberty and first cycle

After weaning at day 24, three females of the same treatment group and the same weight were kept from each cage, and given unlimited access to food and water. From day 30 onwards, the females were inspected daily for vaginal opening. Onset of puberty was defined as the age (in days) at which vaginal opening occurred. Cyclic stages of the ovaries were studied by daily vaginal smears after vaginal opening.

PMSG stimulation test

Stimulation with PMSG was carried out in two different studies. Study A was performed with controls and IUGR rats in their first cycle and PFR rats of the same age as controls. In study B, PFR rats in their first cycle and age-matched controls were investigated.

In study A, 50 IU PMSG (Sigma Chemical Co., St. Louis, USA) was injected intraperitoneally in IUGR rats and control rats on dioestrous of the first cycle at 1600 h, whereas PFR rats were injected at 1600 h 2 days after vaginal opening. PFR rats in study B were injected on dioestrous of the first cycle at 1600 h and were compared with age-matched controls.

Forty-two hours after stimulation with PMSG, at 1000 h, the rats were killed with an intraperitoneal injection of pentobarbitone.

Ovarian histology and follicle counts

The left ovary was dissected, its weight recorded and the ovary was fixed in Bouin’s fluid for 24 h and embedded in
paraffin wax. Our observation of equal follicle counts in both ovaries in a previous study (Engelbregt et al. 2000) enabled us to sample only one ovary in the present study. Serial sections of 10 µm were stained with haematoxylin and eosin, and in each fifth section the number of follicles was counted by use of a microscope. The follicles were classified as primordial (types 1–3b), growing (types 4–5b) and antral (types 6–8) according to the description by Pedersen & Peters (1968). To avoid double-counting, in the growing class only those follicles that showed the nucleus of the oocyte were counted and in the antral class the follicles were compared with previous sections. The corpora lutea, which are in fact ‘post-antral follicles’, were counted in the same way as the follicles in the antral class.

Statistical analysis

Data are expressed as mean ± s.e.m. Statistical analyses were performed using analysis of variance, followed by Dunnett’s test for multiple comparison of the two treated groups with controls. Student’s t-test was performed to compare the PFR group at first cycle with the controls. Differences were considered statistically significant at \( P \leq 0.05 \).

Results

IUGR rats

The body-weight characteristics of IUGR and control rats at day 2, day 24 and vaginal opening are shown in Table 1. According to the definition of intrauterine growth retardation, body weight was significantly lower in IUGR rats than in controls at day 2 after birth \( (P<0.01) \). At weaning on day 24, it was significantly lower \( (P<0.01) \) relative to controls. This study confirms our findings in a previous study (Engelbregt et al. 2000a) that, at vaginal opening, the age was significantly delayed in IUGR rats \( (P<0.05) \) and body weight was significantly lower \( (P<0.05) \), compared with those in controls.

Table 1  Body weight (BW) characteristics of control, intrauterine growth-retarded (IUGR) and postnatally food-restricted (PFR) rats at day 2, day 24 and vaginal opening (VO), and time of vaginal opening

<table>
<thead>
<tr>
<th></th>
<th>Control A</th>
<th>IUGR</th>
<th>PFR A</th>
<th>Control B</th>
<th>PFR B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number BW (g)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 2 after birth</td>
<td>6.4 ± 0.1</td>
<td>4.3 ± 0.8**</td>
<td>6.5 ± 0.5</td>
<td>6.5 ± 0.2</td>
<td>6.8 ± 0.2</td>
</tr>
<tr>
<td>Day 24 (weaning)</td>
<td>60.5 ± 1.8</td>
<td>53.0 ± 1.8**</td>
<td>27.7 ± 1.3**</td>
<td>70.7 ± 1.0</td>
<td>43.8 ± 1.3***</td>
</tr>
<tr>
<td>Day of VO</td>
<td>115.4 ± 3.2</td>
<td>103.7 ± 3.3*</td>
<td>70.2 ± 2.8**</td>
<td>126.0 ± 2.7</td>
<td>101.6 ± 2.5***</td>
</tr>
<tr>
<td>Day of VO</td>
<td>36.2 ± 0.5</td>
<td>37.8 ± 0.7*</td>
<td>36.1 ± 0.5</td>
<td>36.1 ± 0.4</td>
<td>35.6 ± 0.4</td>
</tr>
</tbody>
</table>

Overall, at each time point of measurement until the day when they were killed, body weight in the IUGR rats was significantly lower than that in controls (Fig. 1A).

First cycle was delayed even further than vaginal opening in IUGR rats compared with controls \( (P<0.01) \), but body weight was not different between them at their first cycle, nor was it at the time when they were killed (Table 2). In addition, neither ovarian weight nor ovarian weight adjusted for body weight differed between IUGR rats and controls.

As seen in Table 3, after stimulation with PMSG in the first cycle, the total number of follicles in the ovaries of IUGR rats \( (P<0.01) \) and the number of primordial \( (P<0.05) \), growing \( (P<0.01) \) and antral follicles \( (P<0.01) \) were significantly lower than in controls. The number of corpora lutea did not differ from that in controls. As corpora lutea are in fact ‘post-antral follicles’, we added their count to that of the antral follicles of the ovaries in order to obtain the total number of antral follicles. This number was significantly lower in IUGR rats than in controls \( (P<0.05) \). Figures 2A and B show the ovaries of a control and an IUGR rat respectively, after stimulation with PMSG at first cycle, in which superovulation is clearly recognisable by the high number of corpora lutea.

PFR rats

The body-weight characteristics of PFR and control rats of study A and study B at day 2, day 24 and at vaginal opening are shown in Table 1. At day 2 after birth, body weight in the PFR rats did not differ from that in controls, but at day 24 (weaning) and at the age of vaginal opening, it was significantly lower \( (P<0.01) \). The age at vaginal opening did not differ between PFR rats and controls, which confirmed the results of our previous study (Engelbregt et al. 2000a).

Figure 1A shows the growth curve of the PFR rats in study A until they were killed. At all time points of measurement until the day on which they were killed, except day 2 after birth, body weight in the PFR rats was significantly lower than that in controls.
At the time they were killed, the PFR rats in study A exhibited body and ovarian weights that were significantly lower than those of controls ($P<0.01$; Table 4). However, after adjusting for body weight, ovarian weight was significantly greater ($P<0.01$). In study A (Table 3), after stimulation with PMSG 2 days after vaginal opening, the number of primordial follicles in the ovaries of the PFR rats was significantly greater ($P<0.01$) than that in controls at first cycle, as was the total number of follicles ($P<0.05$). The number of growing and antral follicles did not differ from that in controls. However, the number of corpora lutea in the ovaries was significantly lower than that in controls ($P<0.01$). Adding the number of corpora lutea to the number of antral follicles, the number of ‘total antral follicles’ was significantly lower ($P<0.05$). Figure 2C shows the ovary of a PFR rat from study A stimulated with PMSG 2 days after vaginal opening, in which fewer corpora lutea are observed compared with controls.

In comparison with study A, in study B the body weight of PFR rats was significantly lower than that in controls at all time points, except day 2 after birth (Fig. 1B). As shown in Table 4, first cycle was significantly delayed in PFR rats ($P<0.01$) and body weight was significantly greater ($P<0.01$) compared with controls at their first cycle. However, at the time they were killed, PFR rats had body weights that were significantly lower ($P<0.01$) than those of age-matched controls. Ovarian weight was also significantly lower in the PFR rats ($P<0.01$) but, after adjustment for body weight, ovarian weight did not differ between PFR rats and controls. Table 3 shows the number of follicles after stimulation with PMSG in the first cycle. The number of follicles in the different classes did not differ from that in controls, as was the case for the total number of follicles.

**Discussion**

**IUGR rats**

Our data show that, in IUGR rats compared with controls, not only did a significantly delayed vaginal opening occur,

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**Table 2** Results for control and IUGR rats at first cycle and at time killed after PMSG stimulation

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>IUGR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Day of first cycle</td>
<td>36.2 ± 0.5</td>
<td>40.1 ± 0.6**</td>
</tr>
<tr>
<td>BW (g)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day of first cycle</td>
<td>115.4 ± 3.2</td>
<td>113.0 ± 3.7</td>
</tr>
<tr>
<td>Day killed</td>
<td>134.9 ± 3.9</td>
<td>127.9 ± 5.1</td>
</tr>
<tr>
<td>Ovarian weight (mg)</td>
<td>30.4 ± 1.4</td>
<td>28.9 ± 0.9</td>
</tr>
<tr>
<td>(100 g BW)</td>
<td>21.9 ± 1.1</td>
<td>22.8 ± 0.9</td>
</tr>
</tbody>
</table>

Values are expressed as means ± s.e.m. BW, body weight. **$P<0.01$** compared with controls.

At the time they were killed, the PFR rats in study A exhibited body and ovarian weights that were significantly lower than those of controls ($P<0.01$; Table 4). However, after adjusting for body weight, ovarian weight was significantly greater ($P<0.01$).

In study A (Table 3), after stimulation with PMSG 2 days after vaginal opening, the number of primordial follicles in the ovaries of the PFR rats was significantly greater ($P<0.01$) than that in controls at first cycle, as was the total number of follicles ($P<0.05$). The number of growing and antral follicles did not differ from that in controls. However, the number of corpora lutea in the ovaries was significantly lower than that in controls ($P<0.01$). Adding the number of corpora lutea to the number of antral follicles, the number of ‘total antral follicles’ was significantly lower ($P<0.05$). Figure 2C shows the ovary of a PFR rat from study A stimulated with PMSG 2 days after vaginal opening, in which fewer corpora lutea are observed compared with controls.

In comparison with study A, in study B the body weight of PFR rats was significantly lower than that in controls at all time points, except day 2 after birth (Fig. 1B). As shown in Table 4, first cycle was significantly delayed in PFR rats ($P<0.01$) and body weight was significantly greater ($P<0.01$) compared with controls at their first cycle. However, at the time they were killed, PFR rats had body weights that were significantly lower ($P<0.01$) than those of age-matched controls. Ovarian weight was also significantly lower in the PFR rats ($P<0.01$) but, after adjustment for body weight, ovarian weight did not differ between PFR rats and controls.

Table 3 shows the number of follicles after stimulation with PMSG in the first cycle. The number of follicles in the different classes did not differ from that in controls, as was the case for the total number of follicles.
but also an even further delayed onset of the first oestrous cycle, indicating an uncoupling of these two events. These findings are explained by the fact that, in IUGR rats, malnutrition in utero may change the endocrine programming, which might result in a disturbed timing of onset and sequelae of pubertal development.

In an earlier study (Houdijk et al. 2000), we showed that body weight and somatic growth were significantly decreased in IUGR rats compared with controls, at least until 100 days of life. At the time of first cycle, body weight was equal to that in control rats at the time of vaginal opening and first cycle, which confirms the results of Kennedy & Mitra (1963) who found that, in rats undernourished before weaning, first cycle occurred when the rats achieved the same body weight as controls at vaginal opening and first cycle. However, in common with others, we do not think that body weight is an important factor for attaining puberty, because weight is more related to age than it is to pubertal development (Wilens & Naftolin 1978, Engelbregt et al. 2001).

Vaginal opening is the first visible sign that pubertal development is taking place. Therefore, as is common in the literature, we defined vaginal opening as marking the onset of puberty, although pubertal development has already started earlier. Gruaz et al. (1998) suggested that, in fact, vaginal opening may be only a sign of the increase in oestrogen secretion in the rat, and does not reflect the state of reproductive capacity and the occurrence of oestrous cycles.

We have shown earlier that, at vaginal opening, the number of follicles in the ovary of IUGR rats was significantly lower than that in controls (Engelbregt et al. 2000b), indicating that malnutrition in utero is a detrimental insult at a time critical to the differentiation of the germ cells into oocytes, which might have a permanent effect on the number of follicles. This may explain the delayed onset of vaginal opening in these rats, because the threshold of oestrogens needed for cornification of the cells of the vagina is reached at a later time. Despite a decreased total number of follicles in the ovaries of IUGR rats, PMSG was able to induce an increased multiple follicular growth and development followed by superovulation, comparable to those in controls. The follicles were able to grow and develop in a way comparable to that in control rats, reflected in the weight of their ovaries – similar to that in controls.

In the IUGR rats, PMSG given on dioestrous in the afternoon may act like FSH by inducing follicular growth and so (indirectly) stimulating oestradiol, followed by the occurrence of the LH peak and subsequent ovulation (Aguado & Ojeda 1985, Uilenbroek et al. 1997). It is well known that oestrogens have a crucial role in the stimulation of follicular development: in their presence, a low dose of FSH can induce full follicular development and is able to increase the number of developing follicles (Uilenbroek et al. 1997). Another explanation for the superovulation in the IUGR rats might be that PMSG enhances the magnitude of the normal endogenous FSH peak, occurring on the day of pro-oestrous.

Sometimes PMSG must be given in combination with human chorionic gonadotrophin (hCG); without hCG administration, the release of endogenous LH might be insufficient to induce superovulation or even ovulation. On the basis of the results of our own study and that of others, the effect of PMSG would seem to depend either on the type and dose of the PMSG preparation, or on the strain and the age of the rats (Moore & Ward 1980). In IUGR rats, 50 IU PMSG can induce multiple follicular growth and development followed by superovulation, comparable to those in controls, despite the presence of a lower number of follicles in the ovaries.

Induced intrauterine growth retardation takes place during a period of germ cell increment, a process occurring in the human fetus in the second trimester of gestation. Therefore we hypothesise that IUGR in the female rat might be comparable, at least in part, to second-trimester undernutrition in humans, resulting in a lower number of follicles. A decreased number of follicles at birth could be associated with fertility problems at later ages, such as premature ovarian failure, which is defined as a syndrome characterized by menopause before the age of 40 years. Our study should give rise to consideration of the possibility that fetal developmental disorders in the human might play a part in the origin of premature ovarian failure.
In the PFR rats, we did not observe any sign of an oestrous cycle in the expected period after onset of puberty. The first oestrous cycle in these rats occurred almost 2 months after vaginal opening. Although, at first cycle, body weight in the PFR rats was almost twice that of controls at first cycle, from birth until first cycle at any time of measurement, body weight was significantly lower than that in age-matched controls. In an earlier study, we showed that, at onset of puberty, a significantly greater number of follicles was observed in the ovaries of the PFR rats, and a significantly greater number of primordial follicles in particular (M J T Engelbregt et al., unpublished observations). Vaginal opening occurred at the normal time, as in controls, probably because of the constant outflow of oestrogens from these follicles, leading to attainment of the threshold concentration required for cornification of the cells of the vagina. However, complete maturation of the neuroendocrine–reproductive axis subserving ovulatory oestrous cycles was delayed. The question arises whether the ovary is capable of responding adequately to PMSG at time of vaginal opening. After PMSG, we observed, in particular, follicular growth and development from primordial to growing follicles, in comparison with the follicle pool at vaginal opening (M J T Engelbregt et al., unpublished observations), suggesting that the delay in follicular development observed in the ovaries at vaginal opening is not completely overcome by the administration of PMSG. It could be possible that the metabolic conditions in these rats are unfavourable after early postnatal malnutrition. Therefore we suggest that postnatal undernutrition may cause a central effect that can lead to delayed sexual maturation at time of vaginal opening. This might result in suppression of release of LH-releasing hormone from the hypothalamus, followed by a decline in gonadotropin secretion (Hiney et al. 1991, 1996). Alternatively, postnatal undernutrition may affect the ovary itself, leading to an impairment of the maturation of ovarian follicles, which could not be overcome by a high dose of PMSG. This results in a low number of corpora lutea found in the ovaries of the PFR rats, in contrast to those of IUGR rats and controls. Lastly, both the central neuroendocrine unit and the ovary might be affected.

In PFR rats at their first cycle, the adult pattern of follicular growth and maturation, as seen in age-matched control rats, was achieved, which confirms that full maturation and response to PMSG requires elapse of time that is not related to body weight gain per se – the PFR rats in study B were much heavier than the controls at the time of first cycle.

Because the rat is born immature and follicle maturation takes place after birth, we hypothesise that the PFR rats undernourished soon after birth might be, at least in part, comparable to the human IUGR status in the third trimester of gestation, the period of development of the gonadal axis in humans. Our results are partly analogous to those from human studies showing that intrauterine growth retardation in girls leads to an earlier onset of puberty and a reduced ovarian size at the time of puberty (Ibáñez et al. 2000a, b). Girls with precocious pubarche

**Figure 2** Ovaries of (A) control and (B) IUGR rats after stimulation with PMSG at first cycle, and (C) non-cycling PFR rats of the same age as controls. The arrows indicate corpora lutea. Bar represents 250 μm.
and a low birth weight have an increased risk for anovulation from late adolescence onward (Ibáñez et al. 1999). The greater number of follicles in the ovaries of the PFR rats may reflect the recruitment of a larger cohort and the impairment of follicle maturation after stimulation with gonadotropins, as also observed in women with polycystic ovaries (van der Meer et al. 1998). The latter group of women can develop normal regular cycles later in life, a phenomenon that parallels the late start of oestrous cycles seen in the PFR rats at adult age.

We conclude that, despite a decreased total number of follicles in the ovaries of pubertal IUGR rats, PMSG can induce multiple follicular growth and development followed by superovulation, as compared with controls. However, the lower total number of follicles may lead to an increased risk of having a reduced reproductive capacity later in life. In pubertal PFR rats, PMSG cannot overcome the impaired development of follicles that exists at the onset of puberty; at adult age, this impairment is abolished. This means a delayed age for conception. McGuire et al. (1995) showed that rats under nutrient restriction in utero and until weaning demonstrate reduced reproductive capacity, a delayed age for conception, and smaller litter size. However, the experiments in that study were performed by dietary treatment of the dams, and food restriction to the mother may produce effects other than those selectively related to undernutrition of the offspring (Harding 2001).

Our findings underlie our hypothesis that ‘critical periods’ exist around birth in the rat, during which food deprivation results in different effects on the hypothalamic–pituitary–ovarian axis, resulting in different effects later in life.

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References


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