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Normal Puberty Onset in Female Rats Treated with Antiprogesterone RU486 during Juvenile Period

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The significance of the increased progesterone plasma levels after day 21 on the onset of puberty in female rats is unclear. To analyze this question, female rats were injected from day 21 to 32 with the potent antiprogestagen RU486 (1 mg/day) or vehicle. Treatment with RU486 did not modify either the age at which vaginal opening or first estrus occurs. Vaginal cycles were regular. Animals sacrificed on day 40 or 50 showed reduced uterus weight, whereas body, pituitary, adrenal and ovaries were not affected. These results evidence that antagonization of progesterone action during the juvenile phase did not affect the onset of puberty.

Key words: Puberty, Progesterone, RU486, Vaginal opening, First estrus, Estradiol.

Progesterone plasma levels increased in female rats during juvenile period (3) while *in vitro* experiments have demonstrated a direct stimulatory effect of progesterone on LHRH release in immature female rats (8). Therefore, the exact role of progesterone on the onset of puberty remains unclear: it has been suggested that the precocious puberty induced by prolactin (6) could be mediated through an action at the adrenal level enhancing progesterone secretion (1, 2, 12), but progesterone administration delayed puberty (5). Antiprogesterone RU486 (RU486) is a potent antagonist of progesterone with no agonistic actions (11) and if given from day 1 to 15 it advanced vaginal opening by 1 or 2 days (17). As progesterone levels increased during the third and fourth weeks of life (3) we have analyzed the effects of administration of RU486 during this period on the puberty onset in female rats.

Materials and Methods

Twelve female rats were sc injected daily between days 21 and 32, with 0.1 ml of

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olive oil, and other 12 rats with 1 mg of RU486 (11β-(4-dimethylaminophenyl-17β-hydroxy,17α-(prop-1-ynyl)-estra-4,9-dien-3-one) dissolved in olive oil. They were inspected once a day for vaginal opening, and vaginal smears were taken daily and rats were sacrificed in diestrus at different days (40-41 or 50-51). Adrenals, ovaries, uteri and pituitaries were dissected and weighed, and estradiol in plasma samples was measured by using a Kit from Diagnostics Products Corporation. Values are given as means ± SEM. Statistical differences were analyzed by Student «t» test.

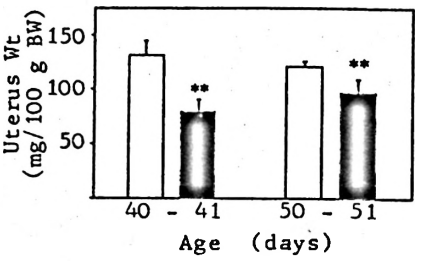

Fig. 1. *Uterine weights in female rats treated with vehicle (□) or RU486 (■).*
Each group consisted of 5-7 animals. Values are given as means ± SEM. ** $p \leq 0.01$ vs vehicle-injected group.

Results

Vaginal opening and first estrus occurred at a similar age in females treated with RU486 or vehicle. After vaginal opening 4-5 days regular cycles were observed. Uterus weight was significantly reduced after treatment with RU either on day 40-41 or 50-51 (fig. 1). Changes in ovarian weight and estradiol plasma levels were not-significant.

Discussion

The interaction between prolactin and adrenal in the control of the onset of puberty seems to be unclear. Progesterone delayed vaginal opening (5) and induction of precocious puberty by pregnant mare serum injections resulted in increased progesterone secretion and changes in the daily rhythm of progesterone observed in prepubertal rats (13, 14). Our results evidence that endogenous progesterone secretion during the third and fourth weeks was not necessary to normal puberty onset and that delayed puberty after progesterone administration (5) may be a pharmacological finding.

RU486 given at an earlier age (from days 1-15 to 4-18) interferes with normal ovarian cyclicity and reduced fertility (17). This effect may be explained through the protective effect of neonatal progesterone against the effects on the central nervous system of the high circulating concentrations of estrogen during infantile period (16), since it is well known that neonatally given estrogens induce sterility (7).

Adult rats treated with RU486 showed normal uterine weight and a tendency to increase estradiol secretion (15). Present results evidence, on the contrary, that RU486 administration to prepubertal female rats decreases uterine weights. Since estradiol levels were similar at decapitation, the decreased uterine weight may be caused by the antagonization of progesterone and/or by a reduced estradiol secretion during treatment with RU486, perhaps due to the decreased LH secretion previously described (4). RU486, by blocking the protective effect of progesterone on the negative feedback exerted by high circulating estrogens on LH secretion during juvenile phase (9, 10), may reduce LH secretion, which in turn decreases estradiol secretion causing uterine atrophy.

In conclusion, present results show that antagonization of progesterone action during juvenile period does not interfere

with the normal onset of puberty in female rats.

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Resumen

Se estudia el desarrollo puberal en ratas hembras tratadas con la antiprogesterona RU486 (1 mg/día). Las ratas tratadas desde la edad de 21 a 32 días presentan la apertura vaginal y el primer estro a una edad similar que los animales inyectados con vehículo, siendo regulares los ciclos vaginales posteriores. Los animales tratados con RU486 y sacrificados en el día 40 o 50, muestran atrofia uterina, sin cambios en los pesos corporal, ovárico, adrenal e hipofisario. Estos resultados indican que la antagonización de la progesterona durante el período juvenil no interfiere con el normal desarrollo puberal.

Palabras clave: Pubertad, Progesterona, RU486, Apertura vaginal, Primer estro, Estradiol.

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