Treatment of neonatal rats with progesterone alters the capacity of the uterus to form deciduomata

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Summary. Progesterone, given to rats on Days 7–9 after birth, abolishes the capacity of the adult uterus to form a deciduoma. Treatment on Days 3–5 reduces the response and on Days 13–15 has no effect.

Introduction

The formation of “nuclear bodies” in the rat uterine epithelial cells during the 8–10-day period after birth has led us to suggest that these nuclear structures might represent chromatin changes corresponding to a critical stage in the development of the uterus (Le Goascogne & Baulieu, 1977). Such a suggestion was substantiated by the observation that progesterone treatment on Days 7–9 which reduced the normal appearance of nuclear bodies also completely prevented the formation of deciduomata in the 3-week-old rat uterus traumatized after progesterone plus oestradiol treatment, while treatment with diethylstilboestrol on Days 7–9 increased the number of nuclear bodies and had no effect or even a facilitatory one on the decidual response (Sananès & Le Goascogne, 1976).

It was of interest to know whether progesterone treatment permanently altered the uterine capacity to form a deciduoma or whether the inhibitory effect was only transient and decidualization could be induced in the adult.

Materials and Methods

The neonatal rats of the Sprague–Dawley strain received a subcutaneous injection of 3 mg progesterone (in sesame oil) on 3 consecutive days as indicated in Table 1, while the control rats were given injections of vehicle alone.

The effects of the neonatal progesterone treatment were checked when the rats were 2 months old and adult (weighing 170 g). After bilateral ovariectomy 10 days earlier, the following hormone treatment was started. Subcutaneous injections of 5 mg progesterone (Roussel-Uclaf, France) in 0.15 ml sesame oil were given for 7 consecutive days at 16:00 h. On the 4th day of treatment, the rats received 150 ng oestradiol (Roussel-Uclaf) subcutaneously and, 18 h later, 100 µl sesame oil were instilled into one uterine horn, after laparotomy under ether anaesthesia, for induction of the decidual response. The animals were killed by decapitation under ether anaesthesia 3 days later and the uterine horns were removed, trimmed of fat and extraneous connective tissue, weighed and fixed for histology.

Results

The decidual response was completely abolished in animals from Group III (Pl. 1, Fig. 1). The deciduogenic capacity of the uterus in Group II was impaired since only 2 of the 6 animals responded. The decidual responses in these 2 animals were histologically similar to those obtained in the controls and their mean weight was 290 mg (the low mean weight of 189 mg reported in Table 1 represents the 4 animals which did not respond). Progesterone injections on Days 13–15 (Group IV) had no inhibitory effects on the capacity of the uterus to respond to a deciduogenic stimulus and the degree of decidual response was similar to that in Group I. The deciduoma was formed in the antimesometrial region of the uterus and laterally (Pl. 1, Fig. 2). The decidual cells, 3 days after induction of the decidual response, were large and typically binucleated (Pl. 1, Fig. 4) with very little intercellular space, unlike the uterine stromal cells of animals from Group III (Pl. 1, Fig. 3). Deciduomata were not formed in the contralateral horns, which did not receive an oil stimulus, in any of the groups (Pl. 1, Figs 5 and 6).

Table 1. The effect of progesterone treatment (5 mg/day) of neonatal rats on the formation of deciduomata in the adult

Group	No. of rats	No. with deciduomata	Mean $\pm$ s.e.m. weight of uterine horns (mg)
I Controls	6	6	550 $\pm$ 40
II Progesterone, Days 3–5	6	2	189 $\pm$ 38
III Progesterone, Days 7–9	6	0	72 $\pm$ 10
IV Progesterone, Days 13–15	11	11	545 $\pm$ 56

The weight of the contralateral uterine horns (not receiving the oil stimulus) of animals in Group I was 66 $\pm$ 6 mg.

Discussion

Progesterone given between Days 3 and 9 of post-natal life significantly reduced or abolished the subsequent ability of the uterus to decidualize. The mechanism of this effect is not understood and it cannot be decided from these experiments whether the hormone acts directly on the uterine cells or indirectly via systemic endocrine changes. Over the period that progesterone is effective, plasma oestrogen levels are reported to rise whereas progesterone levels remain low (Meijs-Roelofs, Uilenbroek, de Jong & Welschen, 1973; Weisz & Gunsalus, 1973; Morera, Audi & Saez, 1974; Döhler & Wuttke, 1975; Morera, Audi, Bertrand & Saez, 1978). Nuclear bodies

PLATE 1

Fig. 1. Lack of a decidual response in the oil-instilled uterine horn of an animal from Group III. Masson's trichrome, $\times 65$.

Fig. 2. Decidual reaction in the antimesometrial region of the oil-instilled uterine horn of a rat from Group IV. Masson's trichrome, $\times 65$.

Fig. 3. Enlargement of the antimesometrial region of the uterine horn of a rat from Group III showing the spaced stromal cells which are more compacted beneath the epithelium. Giemsa, $\times 290$.

Fig. 4. Typical aspect of the binucleated decidual cells of the antimesometrial region of the uterine horn of an animal from Group IV. Giemsa, $\times 290$.

Fig. 5. Non-instilled contralateral horn of the same animal as in Fig. 1. Masson's trichrome, $\times 65$.

Fig. 6. Non-instilled contralateral horn of the same animal as in Fig. 2. Masson's trichrome, $\times 65$.

PLATE 1

(Facing p. 272)

form in the uterine epithelium at this time (Le Goascogne & Baulieu, 1977) when oestradiol receptor concentration becomes maximal (Gorski, Sarff & Clark, 1971; Michel, Jung, Baulieu, Aussel & Uriel, 1974) and their number is increased by diethylstilboestrol administration and reduced by progesterone administration (Le Goascogne & Baulieu, 1977). Possibly the anti-decidual effects of neonatal progesterone arise by antagonizing endogenous oestrogens and the formation of nuclear bodies, so permanently altering the sensitivity of the luminal epithelial cells. The critical period of sensitivity to progesterone extends from about Day 3 of post-natal life to some time after Day 10, and is certainly over by Days 13–15. Endogenous progesterone levels are reported to rise after Day 10 (Morera *et al.*, 1974, 1978; Döhler & Wuttke, 1975; Meijs-Roelofs, de Greef & Uilenbroek, 1975).

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