UTERINE DECIDUALIZATION IN RATS GIVEN TESTOSTERONE PROPIONATE NEONATALLY

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There has been little success in inducing a decidual reaction in the uteri of adult female rats given androgen neonatally. Burin, Thevenot-Duluc & Mayer (1963) reported a positive reaction after scratching the antimesometrial lining and giving progesterone (5 mg) daily for 8 days, but the incidence of success, the age of the animals, and the criteria for decidualization were not given. Barraclough (1967) reported that 25% of adult females given HCG to induce ovulation, and reserpine to sustain pseudopregnancy, produced a positive decidual reaction. All other reports are negative. The reasons for failure are not clear. Lack of oestrogen-binding capacity has been documented (McGuire & Lisk, 1969) and may play an important rôle; the availability of progesterone receptors in the uteri of such females is unknown.

In the present study, attempts were made to induce a decidual cell reaction in the uteri of adult females of various ages given different doses of testosterone propionate (TP) at 5 days of age. Holtzman strain female rats were given 50 µg, 250 µg or 1250 µg TP on the 5th day after parturition. A decidual reaction was induced in adult females by scratching the entire antimesometrial length of one uterine horn; the contralateral horn served as the control. A 300% increase in weight of the former over the latter was considered significant (DeFeo, 1963). Progesterone was administered subcutaneously dissolved in 0.1 ml sesame oil, as was oestradiol benzoate (OB) when it was used. Animals were killed on the 10th day after treatment began.

Young adults were given progesterone for 9 days and were killed on the 10th day (Table 1). Uterine trauma on Day 6 elicited a response in all rats (Groups 2A and 3A). The need for progesterone was indicated by the lack of response with oil or with early withdrawal of treatment. The 2 mg dose of progesterone was used in all further tests. The progesterone apparently caused a reduction in gonadotrophin from the pituitary because ovarian weight was reduced (Groups 2A and 3A versus 4A and 5A).

A positive response was obtained in about 25% of 3- to 4-month-old females given 1250 µg TP neonatally (Table 1). Again, oestrogen did not increase the incidence of positive responses. The steroid treatment reduced the ovarian weight of the rats in three of the four groups. These results are similar to those

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Table 1. The induction of decidualata in rats treated neonatally with androgen

Group	Day of trauma	No. of rats responding/ no. treated	Ovarian wt	Control horn	Traumatized horn (range)	Treatment
A. 2 months old*	6	8/8	—	75.6 ± 3.4	571 ± 31 (406 to 656)	Prog., 2 mg, Days 1 to 9
	6	9/9	18.4 ± 1.6	81.9 ± 4.3	538 ± 59 (352 to 804)	Prog., 2 mg, Days 1 to 5 + 4 mg, Days 6 to 9
	6	5/5	19.4 ± 1.1	74.3 ± 3.3	464 ± 31 (372 to 554)	Prog., 2 mg, Days 1 to 5 + 1 mg, Days 6 to 9
	6	0/3	32.4 ± 6.7	179 ± 7.7	215 ± 5.2 (209 to 225)	Prog., 2 mg, Days 1 to 5
	1	0/5	30.2 ± 2.4	137 ± 18	202 ± 21 (132 to 261)	None
B. 3 to 4 months old†	5	0/4	35.9 ± 1.9	168 ± 21	190 ± 20	None
	6	2/8	30.9 ± 1.4	158 ± 13	436 ± 64 (199 to 738)	Prog., 2 mg, Days 1 to 9
	6	3/15	21.2 ± 0.8	111 ± 5.8	363 ± 33 (140 to 568)	Prog., 2 mg, Days 1 to 9 + OB, 0.1 µg, Day 5
	5	2/7	25.3 ± 1.5	127 ± 8	312 ± 85 (100 to 672)	Prog., 2 mg, Days 1 to 9
	5	1/7	26.8 ± 1.9	134 ± 2.8	480 ± 64 (266 to 786)	Prog., 2 mg, Days 1 to 9 + OB, 0.1 µg, Day 4
C. 6 to 8 months old	6	0/4	31.2 ± 1.2	169 ± 3.5	226 ± 19 (180 to 270)	Prog., 2 mg, Days 1 to 9
	6	0/9	27.4 ± 1.5	147 ± 6.9	233 ± 9 (174 to 320)	Prog., 2 mg, Days 1 to 9
	6	0/9	30.8 ± 1.8	162 ± 5.2	246 ± 14 (172 to 320)	Prog., 2 mg, Days 1 to 9 + OB, 0.1 µg, Day 5
	6	0/8	30.3 ± 1.6	155 ± 7.7	247 ± 16 (174 to 320)	Prog., 2 mg, Days 1 to 9
	6	0/8	29.0 ± 1.5	158 ± 3.7	298 ± 18 (211 to 394)	Prog., 2 mg, Days 1 to 9 + OB, 0.1 µg, Day 5

Ovarian and uterine weights are expressed as Mean ± S.E.M. in mg. OB = oestradiol benzoate; Prog. = progesterone.

* Testosterone propionate (250 µg) administered on Day 5 of age.

† Normal females ovariectomized 4 weeks before traumatization.

‡ Testosterone propionate (1250 µg) administered on Day 5 of age.

§ Testosterone propionate (250 µg) administered on Day 5 of age.

¶ Testosterone propionate (50 µg) administered on Day 5 of age.

obtained by Barraclough (1967) who used animals treated neonatally with 1000 μg TP.

Rats 6 to 8 months old failed to give a positive response when given progesterone, even when 0.1 μg OB was added on the day before traumatization (Table 1). Females treated with 50 μg TP on Day 5 also failed to produce a decidual reaction when they were of this age.

No decidualization techniques have been conclusively proved to have physiological significance, but they do permit identification of the endocrine conditions which prepare the uterus for blastocyst implantation and also give an indication of uterine sensitivity to hormonal stimuli (DeFeo, 1967). The general lack of success in obtaining a response in females treated with TP is probably related to the dose used, and to the age of the animals. When young, the females treated with 250 μg TP gave responses equal to those of normal females. Kramen (1974) has demonstrated successful implantation in young animals given 50 μg TP. The total failures seen in all females 6 to 8 months old, however, indicate that the uterine capacity to form a decidual reaction is lost quite early in these animals. With the high dose of TP, most uteri were incapable of the response at 3 to 4 months of age.

The reasons for the failure to elicit a decidual response are not clear, but uterine histology provides some clues. Before 3 months of age, the uterine epithelium of females treated with TP shows simple, tall columnar cells with basal nuclei and some vacuolization. Stromal glands with low columnar to cuboidal epithelium are sparsely distributed among the dense, fibrous and reticular stroma. The vaginal epithelium in these animals shows stratified squamous proliferation characteristic of constant vaginal oestrus. As the animals age, the uterine lining takes on the appearance of the vaginal epithelium showing metaplasia from columnar to stratified squamous; the latter appears at about 3 months and is essentially complete by 5 months of age. Hyperplasia and/or metaplasia of the uterine epithelium has been noted in rodents treated with androgens (Takewaki, 1965). In some cases, the transformation will occur even in the absence of the ovaries. The possibility of a direct effect of androgen upon the uterine response to subsequent hormonal stimulation cannot be overlooked.

Changing endocrine levels in ageing females treated with androgens may also be involved in the failure to elicit a decidual reaction. The endocrine environment is presumed to be stable. The only hormonal changes that could be correlated with an effective dose of TP and age of the animals are serum prolactin concentrations. These increase with age and with the dose of TP given on Day 5 (Mallampati & Johnson, 1973). The rôle of prolactin in uterine physiology is unclear, and must await further investigation.

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