TRANSPLACENTAL ACTION OF SEX HORMONES IN EMBRYOGENESIS AND EARLY POSTNATAL DEVELOPMENT OF RATS

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UDC 612.64/.65-06:577.175.6

KEY WORDS: sex hormones; embryogenesis; postnatal development.

Some synthetic sex hormones (estrogens, progestins, and androgens), if given for various purposes during pregnancy, may have a teratogenic, masculinizing, sterilizing, or carcinogenic action on the progeny [1, 4].

In order to study the transplacental action of androgens and estrogens on embryogenesis and early postnatal development, experiments were carried out on noninbred rats.

EXPERIMENTAL METHOD

More than 200 pregnant rats were used in the experiments: 53 received testosterone propionate, 84 received estrogens, and the rest were controls (Table 1). The hormones were injected on the last 3 days of pregnancy (the 19th,* 20th, and 21st days) subcutaneously as a suspension in aqueous alcohol or as an aqueous solution in sessional doses of: testosterone propionate 1, 5, 10, and 50 mg, dihydrostilbestrol (DHS) 0.2 mg, diethylstilbestrol (DES) 0.2 and 1 mg, and sigetin† 0.2, 2, and 20 mg.

EXPERIMENTAL RESULTS

Large doses of hormones (except sigetin) often caused a disturbance of pregnancy and parturition: the mothers died during parturition, gave birth to dead and nonviable young rats, and some ceased lactation early. Small doses of sigetin did not disturb pregnancy or lactation, but after injection of 20 mg lactation in two of six rats ceased after 2 weeks.

The mean number of healthy young rats in the litter in the experimental groups was the same as in the control. The mortality among the young rats in the first month of life after transplacental action of the hormones was significantly increased compared with the control only after administration of sigetin and a large dose of DES. The sex ratio on removal of the young rats from their mothers 1 month after birth was about the same in all groups (Table 1).

Under the influence of nearly all sex hormones, irrespective of the dose injected, the body weight of the newborn rats was appreciably reduced, and only sigetin did not have this effect. DHS and DES led to an increase in the weight of the uterus and ovaries by two or more times, and after the largest dose of sigetin their weight increased by 30%. Testosterone propionate caused no significant change in weight of the uterus. The weight of the testes, seminal vesicles, and prostate was increased after administration of the androgen in a dose of 5 mg. The weight of the seminal vesicles and prostate was reduced by DES and a small dose of sigetin, and the weight of the testes was increased after administration of 0.2 mg of DES (Table 2).

In newborn rats exposed to the transplacental action of DHS and DES, marked dilatation of the subcutaneous blood vessels was observed, and the nipples were significantly enlarged in the females.

*The 19th day of pregnancy in rats corresponds to the 14th week of pregnancy in man [3].
†Dipotassium salt of disulfomeso-4,4-diphenylhexane (Translator's note).

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0007-4888/80/9011-1597$07.50

TABLE 1. Transplacental Action of Sex Hormones on the Course of Pregnancy and Parturition, and on Lactation and Early Postnatal Development of the Young in Rats

Acting hormone	Dose, mg	Number of pregnant rats					Number of young rats born	
		total	number with pathology				total	number dying during first month of life
			total	death during birth	stillborn	cessation of lactation		
Control	—	71	9 (13%)	0	6 (8%)	4 (6%)	525	62 (12%)
Testosterone propionate	1,0	42	10 (24%)	6 (14%)	2 (5%)	3 (7%)	218	48 (17%)
	5,0	5	3	2	1	0	8	2
	10,0	3	1	1	0	0	22	1 (9%)
	50,0	3	1	1	1	0	23	6 (26%)
Dihydrostilbestrol	0,2	30	18 (60%)	6 (20%)	7 (23%)	5 (17%)	117	16 (14%)
Diethylstilbestrol	0,2	11	8 (73%)	3 (27%)	5 (45%)	2 (18%)	55	3 (5%)
	1,0	25	21 (84%)	10 (40%)	8 (32%)	6 (24%)	28	10 (36%)
	0,2	6	0	0	0	0	58	16 (28%)
Sigetin	2,0	6	1	0	1	0	70	36 (52%)
	20,0	6	2	0	0	2	61	26 (43%)

TABLE 2. Body Weight and Weight of Reproductive Organs of Newborn Rats after Transplacental Action of Sex Hormones

Acting hormone	Dose, mg	Females				Males					
		number of animals	mean weight of			number of animals	mean weight of				
			body, g	uterus with ovaries, mg			body, g	testes, mg		seminal vesicles and prostate, mg	
				absolute	relative			absolute	relative	absolute	relative
Control	—	33	6,0±0,1	4,2±0,2	0,7	21	6,4±0,1	3,5±0,2	0,55	6,3±0,5	0,98
Testosterone propionate	1,0	14	5,3±0,3	4,2±0,2	0,79	15	5,6±0,2	3,7±0,5	0,66	5,6±0,4	1,0
	5,0	9	5,4±0,2	4,8±0,4	0,89	14	5,9±0,2	4,3±0,5	0,73	9,6±1,0	1,62
	10,0	8	5,5±0,1	4,6±0,8	0,84	10	5,6±0,1	3,6±0,2	0,64	7,3±1,0	1,3
	50,0	11	4,8±0,2	4,5±0,5	0,94	15	5,0±0,2	3,1±0,2	0,62	5,8±0,7	1,16
Dihydrostilbestrol	0,2	17	5,4±0,2	8,4±0,6	1,56	13	5,2±0,2	3,6±0,2	0,69	5,7±0,4	1,1
Diethylstilbestrol	0,2	17	5,6±0,2	8,7±0,3	1,56	13	5,5±0,2	4,5±0,3	0,82	4,9±0,4	0,89
	1,0	10	4,3±0,3	7,0±0,7	1,63	16	4,0±0,2	3,0±0,1	0,68	3,7±0,2	0,84
Sigetin	0,2	9	5,8±0,1	4,4±0,3	0,76	16	6,2±0,1	3,7±0,2	0,6	4,1±0,3	0,66
	2,0	12	5,8±0,1	3,8±0,5	0,66	14	6,1±0,1	3,4±0,1	0,56	6,2±0,2	1,02
	20,0	15	5,8±0,2	5,5±0,2	0,95	9	6,4±0,1	3,8±0,4	0,59	5,6±0,2	0,88

In 273 females estrous cycles were studied after the age of 3 months: in 102 offspring of control rats, in 43 offspring of mothers receiving the androgen, 37 from those receiving DHS, 30 receiving DES, and 61 receiving sigetin.

By the age of 15 months testosterone propionate increased the frequency of constant estrus in the various subgroups of the female progeny up to 50-77% compared with 21% in the control. After 4-5 months constant estrus was observed in 9% of female offspring of the control rats and in 70 and 27% of the offspring of mothers receiving DHS and DES respectively during pregnancy. The frequency of constant estrus in female progeny 7-8 months after transplacental exposure to a large dose of DES was 100% compared with 17% in the control. Sigetin lowered the frequency of constant estrus: after 4-5 months its frequency in different subgroups of the young female rats ranged from 0 to 5%, and after 1 year from 30 to 50%.

Furthermore, in female rats exposed to the transplacental action of the androgen, DHS, and DES masculinization of the external genitalia was observed. Enlargement of the clitoris and underdevelopment of the vagina was observed in 100% of rats after DHS and in 84% after DES. In animals dying accidentally, at autopsy suppurative inflammation of the oviducts, uterus, and ovaries was frequently observed. In the other rats the ovaries were small, no corpora lutea were found in them, only atretic follicles. Often the uterus of such rats was atrophic, despite a positive estrous reaction of the vagina.

Females exposed to the transplacental action of DHS and DES were sterile throughout life. They never became pregnant, even if kept together with males for a month or more. After sigetin most rats reproduced normally even after 1 year, in agreement with the observations of Kosheleva [2].

Testosterone propionate caused masculinization in 47 females. In six males unilateral cryptorchidism was observed, and in five atrophy of the testes. DHS and DES caused atrophy of the testes, their appendages, and the prostate in many males, and in two males they caused additional development of a vagina.

These investigations thus showed that administration of synthetic sex hormones (except sigetin), capable of passing through the placental barrier, to rats on the last 3 days of pregnancy led to frequent disturbance of the course of pregnancy, parturition, and lactation. The sex hormones had a masculinizing and sterilizing action on the progeny of the rats. Sigetin had no significant effect on embryogenesis and the progeny retained their normal ability to conceive.

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CHARACTERISTICS OF STAGES OF THE PREIMPLANTATION PERIOD OF LABORATORY MOUSE EMBRYOS

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UDC 591.31-932.34

KEY WORDS: duration of cleavage stages; hybrid mice.

Definite differences have been found in the times of cleavage of mouse embryos of different strains [3, 6]. However, there have been few studies of this problem.

The object of the present investigation was to make a more detailed study of the duration of each cleavage division in mouse embryos.

EXPERIMENTAL METHOD

Experiments were carried out on (CBA × C57BL)F_1 hybrid mice from the Rappolovo Nursery. Exact dating of the beginning of pregnancy [4], and synchronization of ovulation and fertilization of the ova in animals of each group were used. The embryos were studied throughout the cleavage period every 2 h starting from the time of insemination of the female. Blastomeres were counted either on total preparations or on air-dried films [5]. The duration of the individual stages of development was determined by calculating the ratio between the number of embryos at particular stages of cleavage and the total number of embryos studied at that time.

EXPERIMENTAL RESULTS

Zygote. Penetration of the spermatozoon into the cytoplasm of the ovum took place 4-5 h after insemination, and after 19-20 h (Table 1) the majority of embryos had completed the 1st cleavage division. It can therefore be concluded that the unicellular stage lasts about 14-16 h.

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(Presented by Academician of the Academy of Medical Sciences of the USSR P. N. Veselkin.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 90, No. 11, pp. 609-611, November, 1980. Original article submitted March 6, 1980.

0007-4888/80/9011-1599$07.50