INCREASE WITH AGE IN THE HYPOTHALAMO-HYPOPHYSEAL THRESHOLD TO THE INHIBITORY ACTION OF ESTROGENS AND THE EFFECT OF PINEAL EXTRACT ON THIS PROCESS

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The dose of diethylstilbestrol propionate required to inhibit compensatory hypertrophy of the ovary induced by unilateral castration increases with the age of the rat. This indicates an increase with age in the threshold of the hypothalamo-hypophyseal complex to the inhibitory homeostatic effect of estrogens. An acetic acid extract of bovine pineal glands considerably potentiates the inhibitory effect of estrogens on compensatory hypertrophy of the ovary after hemicastration; consequently, pineal extract conjecturally increases the sensitivity of the hypothalamo-hypophyseal system to the inhibitory action of estrogens.

According to one hypothesis, activation of the sex cycle is connected with an increase with age in the resistance of the hypothalamo-hypophyseal centers to the inhibitory action of sex hormones [7]. There is, however, experimental and clinical evidence that gonadotropin production, which according to this hypothesis, increases as a result of deinhibition of the hypothalamo-hypophyseal system, is increased also after activation of the reproductive system, to reach a maximum after inactivation of the sex cycle with age [1, 2, 4, 6]. In order to explain this phenomenon it was postulated that gradual deinhibition of the gonadotropic function takes place through an increase in the hypothalamic threshold to the inhibitory action of estrogens, leading initially to activation and later to inactivation with age of the reproductive cycle [2].

Age changes in the hypothalamic threshold were accordingly investigated by determining the minimal dose of estrogen capable of completely inhibiting compensatory hypertrophy of the ovary in rats of each age group in response to unilateral ovariectomy.

The writers have shown previously that an acetic acid extract of bovine pineal glands increases the sensitivity of the hypothalamus to the inhibitory action of glucocorticoids [3]. Experiments described below in which a combination of pineal extract and estrogens was given to hemiovariectomized rats confirm the view that the pineal plays a regulatory role.

EXPERIMENTAL METHOD

Noninbred female albino rats of different ages, obtained from the Rappolovo Nursery, Academy of Medical Sciences of the USSR, were used. The minimal effective dose of diethylstilbestrol propionate (DES) completely inhibiting compensatory hypertrophy of the right ovary after removal of the left ovary was determined in each age group. Each dose of estrogen was tested on 5-10 animals. The first injection of DES was given immediately after the operation and later the substance was injected subcutaneously daily for 1 week. The following doses of estrogens were given: for rats aged 1 month 0.25, 0.5, 1, and 2 μg/week; rats aged 3 months 1, 2, 4, 8, and 16 μg/week; aged 12 months 4, 8, and 16 μg/week; aged 18 months 3, 6,

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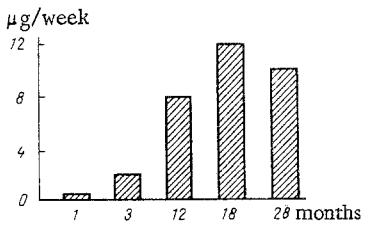

Fig. 1

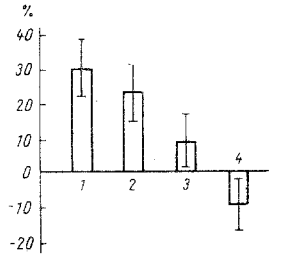

Fig. 2

Fig. 1. Relationship between dose of DES inhibiting compensatory hypertrophy of the ovary on age of rats. Abscissa, age of rats (in months); ordinate, dose of DES completely inhibiting compensatory hypertrophy of the ovary (in μg/week).

Fig. 2. Potentiation of inhibitory action of estrogens on compensatory hypertrophy of the ovary under the influence of pineal extract: 1) control; 2) pineal extract; 3) DES; 4) DES + pineal extract. Ordinate, compensatory hypertrophy of the ovary (in % of weight of removed ovary).

8, 12, 24, 48, and 96 μg/week; and rats aged 28 months 5, 10, 20, and 40 μg/week. The experiments with pineal extract were carried out on rats aged 5-6 months and weighing 180-200 g, receiving 4 μg DES and 7 mg pineal extract during the week after hemicastration. On the 8th day after the operation the animals were killed with ether, the right ovary was removed and weighed, and the degree of compensatory hypertrophy of the ovary was calculated.

To prepare the pineal extract an acetone powder of bovine pineal glands was extracted twice with 3% acetic acid solution at the rate of 50 ml to 2.5 g powder. The extract (100 ml) was fractionated on a column measuring 3 × 112 cm with Sephadex G-25 into three fractions absorbing in the ultraviolet region at $\lambda = 257.5$ nm. The lyophilized second fraction was used in the experiments.

EXPERIMENTAL RESULTS AND DISCUSSION

The degree of compensatory hypertrophy of the ovary in the control rats 1 week after hemicastration varied in different age groups from 30 to 56% of the weight of the removed ovary. As the results in Fig. 1 show the minimal inhibitory dose of DES rose gradually with increasing age: it was 24 times larger for rats aged 18 months than for those aged 1 month. A small decrease in the dose of estrogen inhibiting compensatory hypertrophy of the ovary from 12 to 10 μg per week was observed in old rats aged 28 months.

Injection of 1 mg pineal extract daily into the animals caused no significant inhibition of compensatory hypertrophy of the ovary (Fig. 2). However, if injected in combination with DES the pineal extract considerably potentiated the action of the estrogen in inhibiting compensatory hypertrophy of the ovary.

It is well known that hypertrophy of the residual ovary after hemicastration is due to the liberation of an excess of follicle-stimulating hormone into the blood stream in response to the resulting estrogen deficiency [5]. Administration of estrogens thus inhibits this process, evidently by inhibiting the hypothalamic and hypophyseal centers responsible for the increased activity to estrogen deficiency. The use of different doses of estrogens enables the sensitivity of these centers to the inhibitory effect of the sex hormones to be determined as a parameter of fundamental importance for gonadotropin-ovarian relations at each specific period of ontogenetic development. For instance, if the sensitivity of the hypothalamo-hypophyseal complex to the effects of estrogens is high, as it is in the animal before sexual maturity, the blood gonadotropin concentration lies below the level necessary for the development of ovarian function and cyclic regulation of the reproductive system. Later, the decrease in sensitivity of the hypothalamo-hypophyseal system to estrogens or, in other words, the increase in the hypothalamic threshold to inhibition leads to activation of the sex cycle and to the onset of the phase of sexual maturity.

Finally as ontogenetic development continues the resistance of the centers reaches a level at which the maximal output of ovarian hormones can no longer inhibit gonadotropin production to terminate the

estrogenic phase of the cycle and the onset of ovulation, as a result of which the rhythmic activity of the system comes to an end and, consequently, so also does the reproductive function. The increase in the dose of estrogens required to inhibit compensatory hypertrophy of the ovary in rats with age directly confirms the writers' earlier hypothesis that the development of resistance of the hypothalamic centers to inhibitory effects is a leading factor in the formation and aging of the endocrine system [2].

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