AGE INCREASE IN THE THRESHOLD OF SENSITIVITY OF THE TONIC REGION OF THE HYPOTHALAMIC SEX CENTER TO INHIBITION BY ESTRADIOL IN FEMALE RATS

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To study the sensitivity of the hypothalamic sex center to the inhibitory action of estrogens, estradiol-17β was injected into the third ventricle of hemicastrated rats. The dose of estrogen needed to inhibit compensatory hypertrophy of the ovary by 50 and 100% in old animals (14-16 months) was 4 to 5 times greater than in young rats (3 months). The results point to an age increase in the threshold of sensitivity of the tonic region of the hypothalamic sex center to inhibition by estrogens and they can be used to explain the mechanisms of the age increase in gonadotropin secretion and the termination of reproductive function. KEY WORDS: aging, hypothalamus, estradiol, reproductive function.

On the basis of Hohlweg's classical experiments [11], Donovan and Van der Werff ten Bosch [7] put forward their idea of the mechanism of age activation of reproductive function. According to this idea, the key factor in this mechanism is an increase in the resistance of the hypothalamus to the inhibitory action of estrogens. The presence of this phenomenon was confirmed by other investigations on rats, both female and male [14, 16]. However, the change in hypothalamic sensitivity to sex hormones was studied in these investigations in the period directly linked with puberty. This left unanswered the question of whether changes in hypothalamic sensitivity continue in the adult animal, i.e., after activation of the reproductive function. Indirect evidence was given previously [3] on the role of increased hypothalamic activity in the mechanism of age termination of the reproductive function. It was shown later in the writers' laboratory that the dose of estrogens required to inhibit compensatory hypertrophy of the ovary due to unilateral castration increases with an increase in the age of the rat [1]. It must be specifically emphasized that this increase in the inhibitory dose of the estrogen took place after the completion of sexual maturation and was observed until the termination of reproductive function. Similar results were obtained in experiments to study the effect of estrogens on the postcastration rise in LH [9, 15]. Considering that compensatory hypertrophy of the ovary is induced by follicle-stimulating hormone (FSH), the secretion of which in turn, after unilateral castration, is controlled by a mechanism of negative feedback between the sex hormone level and the tonic region of the hypothalamic sex center [6, 13], the results could be interpreted as evidence of an increase in the threshold of sensitivity of the corresponding hypothalamic center to the inhibitory action of estrogens. These results confirmed the earlier view that the same mechanism initially leads to age activation, and later to age inactivation of reproductive function [3]. At the same time, these experimental approaches did not allow reliable conclusions to be drawn regarding the age increase in the hypothalamic threshold of sensitivity to the inhibitory action of estrogens, for estrogens may play an essential role at the pituitary level. In addition, after subcutaneous injection of estrogens their distribution in the body may be significantly affected by age changes in body weight, which do not correlate with changes in the weight of the brain. In the present investigation a method of injecting the estrogen directly into the cavity of the third ventricle was therefore used.

EXPERIMENTAL METHOD

Experiments were carried out on 93 female rats aged 3 and 14-16 months, with regular estrous cycles. Hemicastration was performed on all the animals. By means of a stereotaxic apparatus 5 μl of physiological

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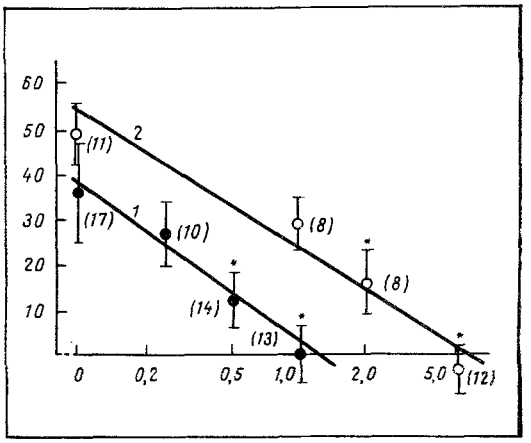

Fig. 1. Relationship between age and dose of estradiol required to inhibit compensatory hypertrophy of the ovary in hemicastrated rats. Rats aged: 1) 3 months, 2) 14-16 months. Number of animals in group given in parentheses. Values indicated are M ± m. *) Difference from control significant, $P < 0.05$. Ordinate, degree of compensatory hypertrophy of ovary, %; abscissa, dose of estradiol, μg.

saline or the same volume of a solution of estradiol-17β in different concentrations was injected at the same time into the third ventricle of the rats. Estradiol (Roussel, UCLAF) evaporated from a standard alcoholic solution was dissolved immediately before use in 1 N hydrochloric acid and neutralized with 1 N caustic soda to pH 7.34. The animals were killed on the eighth day after the operation, the residual ovary was weighed, and the degree of compensatory hypertrophy of the ovary determined. The experimental results were subjected to statistical analysis by Student's t-test and Wilcoxon's U-criterion to determine the significance of the differences.

EXPERIMENTAL RESULTS

As the results in Fig. 1 show, the dose of estradiol required to inhibit compensatory hypertrophy of the ovary by 50 and 100% in old rats was 4 to 5 times greater than the dose required for young animals.

Compensatory enlargement of the residual ovary after hemicastration is known to be due to an increase in the secretion of FSH-releasing hormone by the hypothalamus into the portal system of the pituitary and, correspondingly, to increased FSH secretion in response to the primary fall in the blood estrogen level [6, 13]. Administration of estradiol inhibits this mechanism, evidently at the hypothalamic level. These findings point to an age increase in the threshold of sensitivity of the tonic region of the hypothalamic sex center, controlling the folliculotropic function of the pituitary, to inhibition by estrogens. These observations agree with earlier findings after subcutaneous injection of estrogens [1]. In the experiments of Babichev [2] an age decrease in the sensitivity of the hypothalamic neurons to estradiol was demonstrated by an electrophysiological method, and this would correlate with the increase in the threshold of sensitivity of the hypothalamus to its controlling stimulus.

An increase in the threshold of sensitivity to the action of sex hormones, it should be noted, must arise not only in the tonic, but also in the cyclic region of the sex center, which is under the control of a positive feedback mechanism [4, 5]. Results confirming this view were recently published by Meites et al. [12].

An increase in the hypothalamic threshold of sensitivity to the action of estrogens is thus observed during ontogeny in the systems of both tonic and cyclic regulation of reproductive function, thus permitting a single mechanism for the activation and inactivation of the cyclic activity of the ovaries. It is important to note that the action of many external agents leading to the termination of reproductive function, such as continuous illumination, for example, is also realized on account of an increase in the hypothalamic threshold [10]. In the early stages of ontogeny the androgen-like hormones of the adrenal cortex have also been shown to participate in this process [8].

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CHANGES IN RAT LIVER LYSOSOMES DURING STIMULATION OF REGENERATION IN THE INJURED ORGAN BY TRITON WR-1339

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The effect of a single dose of the lysosomotropic agent Triton WR-1339 on the properties of the liver lysosomes of rats with chronic toxic hepatitis and on the course of the pathological process was investigated. The compound was shown to promote the more rapid restoration of liver structure and function. The possible mechanism of the beneficial effect of Triton WR-1339 is discussed. KEY WORDS: lysosomes; toxic hepatitis; Triton WR-1339.

Changes in the lysosomes under pathological conditions are connected both with the development of injury and with the formation of intracellular mechanisms leading to compensation of the disturbances and restoration of the normal structure and function of the organ [3, 5, 7, 11]. The writers showed previously that chronic toxic hepatitis, developing during loading of the vacuolar system of the liver cells by Triton WR-1339 (Triton), is distinguished by the milder development of zones of necrosis and collagenization of the tissue [1]. This effect may be due either to a decrease in the severity of injury to the organ or the more intensive development of repair processes.

To study this problem the effect of Triton on the development of repair processes in the liver of rats with chronic toxic hepatitis was studied.

EXPERIMENTAL METHOD

Male Wistar rats weighing 180-200 g were used. Chronic toxic hepatitis was induced by inhalation of CCl_4 for three weeks [1]. Triton in a dose of 85 mg/100 g body weight was injected intraperitoneally 24 h after the last inhalation of the poison. The animals were decapitated 3, 7, and 14 days after the end of the course of

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