ESTROGENS AS INHIBITORS OF THE INFLUENCE OF GROWTH HORMONES ON THE MOBILIZATION OF FREE FATTY ACIDS

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At the present time, estrogens are widely used in the treatment of cancer of the mammary and prostate glands. The mechanism of their therapeutic action has not been definitely elucidated. Undoubtedly estrogens exert an inhibiting influence on the activity of a number of hypothalamic centers and the secretion of certain hormones of the anterior pituitary [1]. In particular, they inhibit the secretion of the growth hormone, the significance of which for the development of the tumoral process has been experimentally demonstrated [5]. It is believed that antagonistic interrelationships of this type between the estrogen level and the secretion of growth hormone also play a role in physiological processes. Thus, the stoppage of growth of the skeleton is explained by sexual maturation and by an estrogen inhibition of the secretion of growth hormone during the process of maturation. All these facts have been established in experimental and clinical investigations. The hypothesis has also been advanced that the sex hormones can change the sensitivity of the receptor organs with respect to the action of growth hormone [1]. The data that we obtained show that actually, in addition to the central action, an antagonism exists between the effect of the somatotropic hormone and the estrogens at the level of the peripheral tissues. An effect of this type has also been observed with respect to the action of somatotropin on the growth of the epiphysary cartilage after the simultaneous introduction of large doses of estrogens [8]. It should be mentioned that when physiological doses of the hormones are used, no antagonism exists between the action of the estrogens and the action of the growth hormone; rather, there is a synergism with respect to the influence on the reproductive system (uterus [4], mammary gland [7]), as well as on the growth of the epiphysary cartilage [8].

In this work we studied the influence of the so-called therapeutic doses of estrogen on the action of the growth hormone. The latter was evaluated according to the mobilization of nonesterified (free) fatty acids, i.e., an effect that is just as characteristic of somatotropin and its influence on growth.

EXPERIMENTAL PROCEDURE

The growth hormone was isolated from the human pituitary according to the method of Raben [6]. In our experiments we used somatotropin obtained in 3 separate preparations from acetonized pituitaries. The free fatty acids were determined according to the method of Dole [2]. In the experiment we used nonpedigreed white male rats, about 150 g in weight (in one case, the weight was about 250 g). A week before the introduction of the growth hormone, part of the animals received subcutaneous implantations of a tablet with 5 mg of synestrol. The growth hormone was injected intraperitoneally in a dose of 1.5-2 mg per animal in alkaline physiological solution. The animals were killed by decapitation 3-4 days after the injection of the growth hormone; the blood was collected in heparinized test tubes. In each series of experiments we used 4 groups of animals: the rats of the first group received synestrol and physiological solution, 2nd group—synestrol and growth hormone (experimental group); the 3rd group included intact animals that received physiological solution, while the 4th included intact animals that received growth hormone (control). Four series of experiments were conducted, using 80 animals.

Influence of Growth Hormone and Synestrol on the Level of Free (Nonesterified) Fatty Acids (NEFA) in the Serum

Series of Expts.	Aver. wt. of animals (in g)	Group of animals	No. of animals in group	Aver. value of NEFA content (in μ-equiv/liter)	Inc. in NEFA content (in %)	P
I	150	1	8	415.5	9.8	0.001
		2	8	456.6		
		3	8	334.5	72.6	
		4	8	574.8		
II	150	1	4	311.5	7.7	0.01
		2	4	335.7		
		3	4	378.1	65.6	
		4	4	626.2		
III	250	1	4	384.5	62.2	0.067
		2	4	639.1		
		3	4	399.6	100.5	
		4	4	801.3		
IV	150	1	4	544.3	4.0	0.05
		2	4	566.6		
		3	4	611.8	46.6	
		4	4	898.5		

EXPERIMENTAL RESULTS

The data presented in the Table show that the ability of the growth hormone to increase the free fatty acid content is eliminated or substantially reduced under the action of somatotropin against a background of therapeutic doses of estrogens.

The results obtained indicate the necessity for bringing in supplementary data for the evaluation of the antitumoral action of estrogens in processes in which the participation of the growth hormone is presumed. It seems especially interesting to us to investigate patients with uterine cancer along this line. The dose of estrogen that we used—5 mg per 0.15 kg of weight of the rat—corresponds to approximately 2.5 g of synestrol when converted to the average human weight (75 kg). Thus, the phenomenon that we noted is detected in the case of therapeutic doses of synestrol.

The secretion of active estrogens is reduced during senescence, both in males and females; during this same period, the frequency of the number of endocrine-dependent tumors increases. It is of interest to determine whether this is a result of intensification of the action of growth hormone against a background of a reduced estrogen level. The appearance of acromegaloid features in senescence corresponds to this.

From this standpoint, the concept that the cessation of longitudinal growth of the skeleton is related only to the central inhibitory influence of estrogens on the secretion of growth hormone may be in need of reexamination. At the present time there are no data indicating that the level of somatotropin in the blood serum of adult humans is significantly lower than in young humans [3], and that the cessation of longitudinal growth is related precisely to this. It should be verified whether the high estrogen level after sexual maturation is a factor that changes the rate of growth under the influence of somatotropin.

It is also essential to determine whether analogs of the estrogens, devoid of the intrinsically estrogenic effects, the so-called pituitary inhibitors, are capable of exerting the competitive action described. This would make it possible to introduce a supplementary criterion in searches for new pituitary inhibitors.

It may be that the results that we obtained in the 3rd series of experiments should be subjected to a supplementary study. As can be seen from the table, in this experiment no complete inhibition of the action of the growth hormone was observed. Both in the animals that received injections of synestrol and in the control group, an increase in the free fatty acid content was observed. It may be that the weakening of the inhibitory effect of estrogen is related to a more intense action of the growth hormone than usual. This is manifested in the fact that in the control

animals, the introduction of somatotropin gave rise to a 100% increase in the free fatty acid content, i.e., a substantially greater increase than in any other experiment that we conducted. According to our hypothesis, although it naturally will require verification, the increased effectiveness of the growth hormone observed in this experiment may be related to the fact that the experiment was conducted on older animals. It is of interest to determine whether the sensitivity to the action of somatotropin actually increases with age.

SUMMARY

It is shown in the paper that implantation in rats of a 5 mg synestrol tablet (equivalent to an average therapeutic dose of the preparation used in treating milk-duct carcinoma in man) eliminates or reduces the growth hormone's capacity of raising the level of free fatty acids in blood serum. The paper discusses at some length the importance of this antagonism phenomenon necessitating a more profound study which would include the development of acromegaloid features with aging, as well as investigating the issues arising from the antagonism to other properties of the growth hormone, the studies involving the use of both the estrogens and the hypophyseal inhibitors.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.
