CAUSES OF RESUMPTION OF GROWTH OF MAMMARY GLAND CARCINOMA METASTASES DURING HORMONE THERAPY

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UDC 618.19-006.6-085.361-06:618.19-006:6-033.2

As a result of hormone therapy for metastases of mammary gland carcinoma, as a rule only a temporary improvement is observed, and despite continued treatment this is followed by resumed growth of the metastases, leading to death of practically all the patients. Discovery of the causes of this resumed growth of the metastases during continued hormone therapy is extremely important at the present time, for measures could then be taken to eliminate them and thus to prolong the remissions. One such cause has been found by comparing data from endocrinology and hormone therapy. It has been shown, for example, that during prolonged and continuous treatment with a particular hormone the endocrine functions dependent on it undergo modification (are stimulated or inhibited) only temporarily, after which, despite the continued administration of this hormone, adaptation takes place to it and the normal functions are restored. Despite this, hormone therapy is given continuously for many months or even years. In the light of the author's data [4, 5] proliferative processes in both normal and malignant tissues of the mammary glands are controlled by the combined action of estrogens and follicle-stimulating hormone (FSH), while the antitumor effect of estrogen therapy is due to the complete inhibition of FSH production. The following hypothesis may therefore be put forward: in the course of prolonged and continuous estrogen therapy, the secretion of FSH by the pituitary is stopped only temporarily, leading to the development of a remission, after which the follicle-stimulating function of the pituitary becomes adapted to estrogens and secretion of FSH is resumed, leading to resumption of growth of metastases of the mammary gland carcinoma [4, 5].

The present investigation was carried out to study the validity of this hypothesis.

EXPERIMENTAL METHOD

Experiments were carried out on 380 noninbred albino rats receiving synestrol (diethylstilbestrol dipropionate) in clinically adequate doses (200 μg daily) either as a suspension in aqueous alcohol or as pellets of compressed synestrol weighing 5 mg and implanted twice monthly subcutaneously. Every 10 or 20 days, 5 rats from each of the control and experimental groups were sacrificed and the FSH content in their pituitary was studied. A suspension was prepared from the pituitary of each rat in physiological saline, and this was injected in equal parts daily for 3 days into infantile female mice in a dose of 1 pituitary per mouse. The mice were sacrificed 96 h later and the uterus with the ovaries was weighed. To allow for individual variations, the weight of the uterus with the ovaries was divided by the body weight of the mouse, and the quotient was multiplied by a thousand, to give a convenient index for comparing the results obtained. Some endocrinologists regard an increase in the weight of the mouse uterus as a reflection of the content, not only of FSH, but of all gonadotropins taken together – FSH together with luteinizing hormone – in the material tested. However, it has recently become clear that this point of view is incorrect, because highly purified FSH in fact leads to an increase in the weight of the uterus while highly purified LH causes no reaction whatever [8]. The authors have also recently shown that highly purified LH, possessing extremely high activity (0.1 μg causes superovulation in rats), in a dose of 100 μg causes no increase in the weight of the uterus of infantile mice, and, consequently, the increase in weight of the mouse uterus reflects the presence of FSH only in the material tested.

Laboratory of Hormone Therapy, Institute of Experimental and Clinical Oncology, Academy of Medical Sciences of the USSR, Moscow (Presented by Active Member of the Academy of Medical Sciences of the USSR N. N. Blokhin). Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 64, No. 11, pp. 118-121, November, 1967. Original article submitted May 21, 1967.

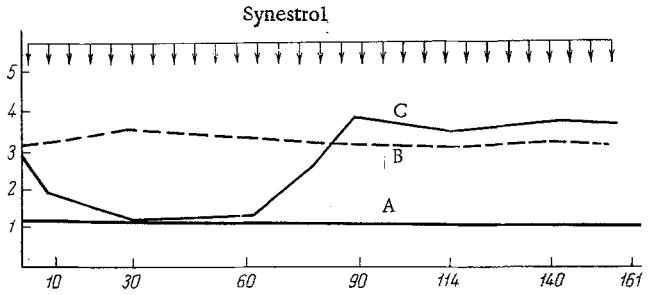

Fig. 1. Onset of adaptation of follicle-stimulating function of the pituitary to prolonged administration of synestrol. A) Dynamics of weight of uterus of intact infantile mice; B) dynamics of weight of uterus of mice receiving pituitary of rats of control group (showing constancy of FSH content in pituitary); C) dynamics of weight of uterus of mice receiving pituitary of experimental rats (showing that during prolonged administration of synestrol the FSH content in the pituitaries of the rats at first fell temporarily, and then rose despite continued action of synestrol). Here and in Figs. 2 and 3: abscissa—days of experiment; ordinate—weight of uterus (in indices).

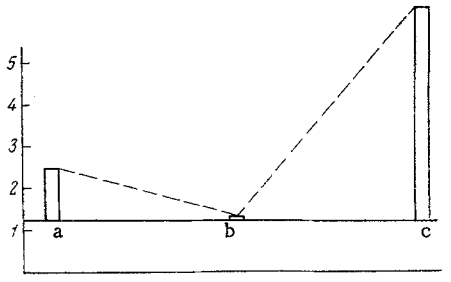

Fig. 2. Content of FSH extracted from the urine of patients with mammary gland carcinoma before treatment (a), during remission as a result of synestrol therapy (b), and during recurrence after remission (c).

EXPERIMENTAL RESULTS

In the first experiment the dynamics of the FSH content was studied in the pituitary of rats receiving synestrol as a suspension in aqueous alcohol in a daily dose of 200 μg. Control investigations of the FSH content in the pituitaries after 10 and 30 days (Fig. 1) showed that during this time the FSH content in the pituitary fell appreciably, and by the 30th day from the beginning of the experiment none could be found in the glands. No FSH could be detected in the pituitaries thereafter until the 60th day. However, during the next 30 days, FSH reappeared in the pituitary, and its content exceeded the initial level by the 90th day; an increased FSH content in the pituitary was observed for a long period of time (until the 161st day of observation [2]).

Hence, the results obtained confirm the hypothesis that synestrol, given to patients in clinically adequate doses, at first completely inhibits FSH secretion, but later, despite continued administration of synestrol in the same dose, large quantities of FSH are again found in the pituitary. Does this mean, however, that the resumption of FSH secretion alone is adequate to cause resumption of growth of metastases from a mammary gland carcinoma?

It should be emphasized that in the authors' other investigations, a clear correlation was frequently revealed between the stimulation or inhibition of growth of mammary gland carcinoma, on the one hand, and an increased or decreased FSH content in the organism on the other hand. For example, as a result of synestrol treatment, in all rats in which a decrease in the FSH content in the pituitary was found, inhibition of growth of primary mammary gland carcinoma was observed, and the more marked the depression of FSH secretion, the more marked also inhibition of growth of the carcinoma [3]. Conversely, if FSH secretion was stimulated, the rate of growth of the mammary gland carcinoma was increased [6]. In clinical investigations also, as a rule no FSH was found in the urine of 16 patients in a state of remission during synestrol therapy, whereas in 7 patients in whom synestrol therapy was ineffective, large quantities of FSH were always excreted in the urine [1]. That is why the result obtained indicating resumption of FSH secretion in rats after prolonged treatment with synestrol suggested that in patients with mammary gland carcinoma undergoing prolonged synestrol therapy, and in whom growth of metastases had resumed, the FSH content would be increased.

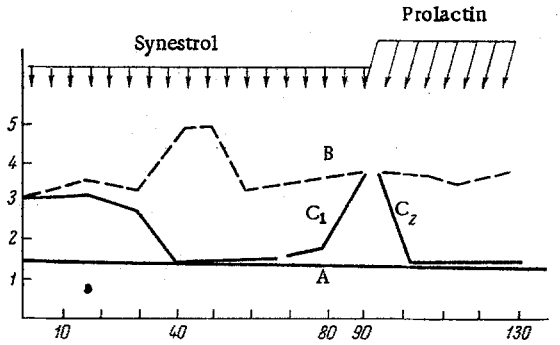

Fig. 3. Inhibition by prolactin of follicle-stimulating function of pituitary adapted to prolonged administration of synestrol. A) Dynamics of weight of uterus of intact infantile mice; B) dynamics of weight of uterus of mice receiving pituitary of control rats; C_1—dynamics of weight of uterus of mice receiving pituitary from experimental rats treated with synestrol; C_2—dynamics of weight of uterus of mice receiving pituitary of rats treated initially with synestrol and later with prolactin.

To study this problem, the FSH content in the urine was investigated in three groups of patients with mammary gland carcinoma: 2 patients before treatment, 3 patients receiving synestrol therapy and in state of remission, and 4 patients in whom synestrol therapy at first produced a remission but this had been followed by resumed growth of metastases. The gonadotropic hormones were isolated from the urine by Loraine's method and their follicle-stimulating activity was estimated from the increase in weight of the uterus of infantile mice. The results obtained are given in Fig. 2, showing that no FSH was found in the urine of the patients in a state of remission (b), whereas the FSH content in the urine of the patients with resumed growth of metastases (c) was much higher than in the urine of the patients before treatment (a).

Since synestrol, in its biological activity, is equal to the most active fraction of the endogenous estrogens—estradiol—it is evident that when FSH secretion is resumed as a result of adaptation to synestrol, the content of estrogens in the body must reach a high level on account of the exogenous synestrol; this creates highly favorable conditions for increased proliferation of the mammary gland carcinoma cells and, evidently, the rapid aggravation of the clinical manifestations observed in such patients is not fortuitous.

In that case, when and how is the follicle-stimulating function of the pituitary, adapted to synestrol, prevented or again inhibited?

To study this problem, the basic assumption was made that adaptation of FSH secretion to synestrol should be regarded as a phenomenon of immunologic nature and, in particular, that adaptation must be strictly specific in relation to the inhibitor, just as antibodies are to antigen. It could therefore be expected that replacement of synestrol by another inhibitor of FSH secretion of different nature would lead to further depression of the adapted FSH secretion.

This problem was studied in experiments on rats, reproducing the scheme of the first experiment, but after sacrifice of the control rats had revealed the presence of adaptation of the follicle-stimulating function to synestrol, the experimental rats were treated with prolactin, which also depresses FSH secretion, although it differs essentially in its structure from synestrol. Admittedly, in this experiment panhysterectomized rats were used in order to avoid high mortality of the experimental rats from pyometra caused by synestrol, and the synestrol was implanted in pellets of 5 mg twice monthly to bring the experimental conditions close to clinical, but these differences in the methods used were not in any way reflected in the eventual results of the experiments. The prolactin used in this experiment was manufactured by the Leningrad Meat Combine, and given in a dose of 10 mg daily per rat for 30 days.

The results of this investigation are illustrated in Fig. 3. Before FSH secretion became adapted to synestrol, the dynamics of the FSH content in the pituitary was similar to that determined previously, although the FSH content in the rats of the control group was considerably higher than in the animals in the first experiment: the increased FSH content was attributable to panhysterectomy. The rats (40 animals) with adapted follicle-stimulating function of their pituitaries were divided into two groups. The animals of our group were left as controls, and those of the other group (experimental) received prolactin daily. It is clear from Fig. 3 that prolactin caused complete inhibition of FSH secretion adapted to synestrol [7].

FSH secretion, resumed because of adaptation to the prolonged action of synestrol, was thus completely suppressed again by the action of prolactin. Could, however, the repeated depression of the adapted FSH secretion cause inhibition of growth of mammary gland carcinoma? To answer this question, a mammary gland carcinoma was transplanted into rats with depressed and resumed FSH secretion. It was found that the rate of growth of the carcinoma was greater in the rats with resumed adapted FSH secretion than in control rats (mean weight of tumor 24 and 17 g respectively), whereas in rats whose FSH secretion was inhibited for the second time by the action of prolactin the rate of growth of the carcinoma was again clearly retarded (mean weight of tumor 5 g).

Future experience will show whether this scheme of hormone therapy of recurrent mammary gland carcinoma is justified in clinical practice, but clinicians with experience of hormone therapy are already familiar with cases in which replacement of one hormone by another has led to a marked improvement in the condition of patients with mammary gland carcinoma in advanced stages of the disease.

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