THE EFFECT OF PROLACTIN ON MAMMARY GLAND CARCINOMA IN RATS AND MICE

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M.-Kh. B. Chalov

Laboratory of Experimental Hormone Therapy (Chief, Dr. N. I. Lazarev),
Institute of Experimental and Clinical Oncology (Director, Acting Member
of the Academy of Medical Sciences of USSR, Prof. N. N. Blokhin),
Academy of Medical Sciences of USSR, Moscow
(Presented by Active Member AMN SSSR, L. M. Shabad)
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It has been established in the Laboratory of Hormone Therapy at the Institute of Experimental and Clinical Oncology that proliferative processes in normal [9, 10] and tumorous tissue [4] of the mammary gland depend on the increased content in the organism of not only estrogens, but also of the follicle-stimulating hormone of the hypophysis. These findings have led to a formulation of rational methods of estrogen and androgen therapy of mammary gland cancer in order to inhibit the production of the follicle-stimulating hormone [5-8]; these methods are being successfully applied in the clinic [11-13]. It is known that in addition to estrogens and androgens, prolactin also has the ability to inhibit the production of the follicle-stimulating hormone [1, 16].

The present investigation deals with the problem of the effect of the anti-tumor action of prolactin.

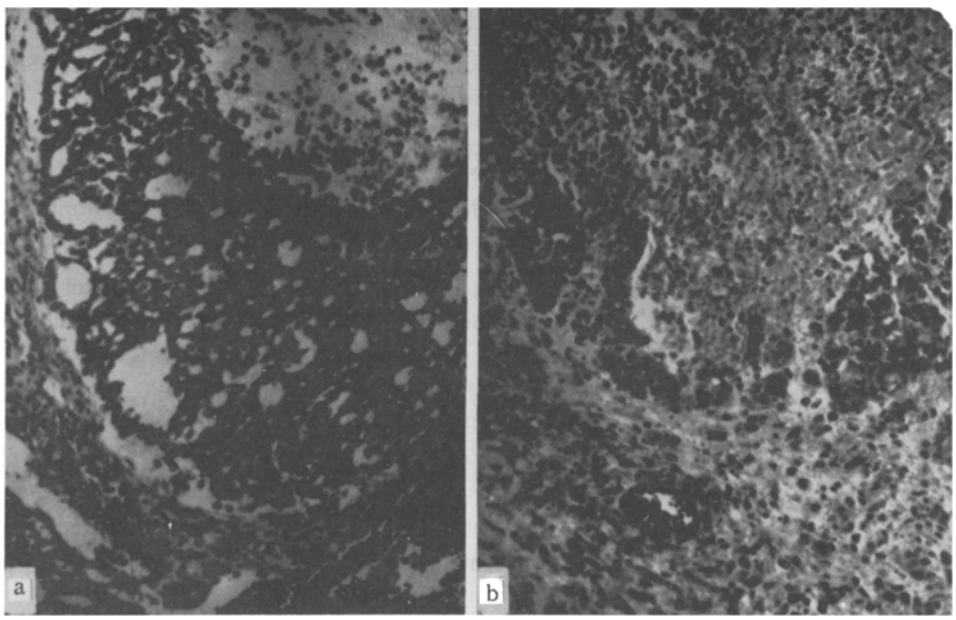

Fig. 1. Rat mammary gland carcinoma RMK-1. a) Control; b) effect of 10 mg of prolactin during 20 days.

TABLE 1. Effect of Different Doses of Prolactin on the Growth of Transferable Rat Mammary Gland Carcinoma and on the Changes in the Production of the Follicle-Stimulating Hormone

Rat group no.	No. of rats	Prolactin (in mg)	Mean weight of tumor (in g)	Percentage inhibition of tumor growth	Index of follicle-stimulating hormone content
1	20	–	32.7	–	4.4
2	30	10.0	11.7	60.5	2.5
3	30	1.0	19.1	41.8	3.3
4	10	0.2	25.4	22.6	–

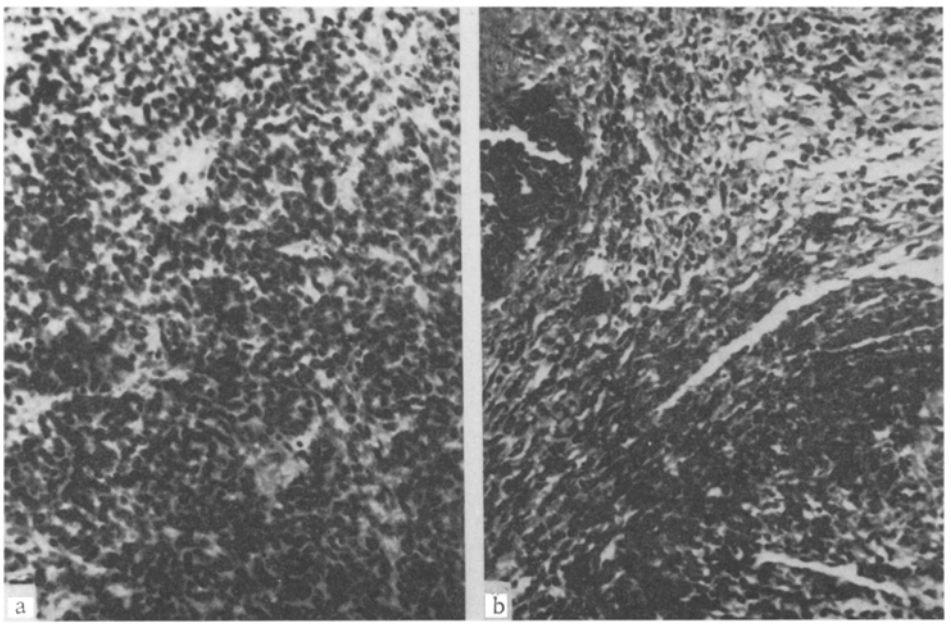

Fig. 2. Spontaneous mammary gland adenocarcinoma in non-pedigreed mice. a) Control; b) effect of 10 mg of prolactin during 25 days.

METHODS

Investigations were made on non-pedigreed 1 month old female rats with transferable mammary gland cancer (RMK-1) [2, 3] and on non-pedigreed mice with spontaneous mammary gland tumors.

In our experiments we have used commercial prolactin which was precipitated from solution with sodium chloride (15 g per 100 ml of prolactin solution). The precipitate was suspended in saline in a concentration, so that the required dose of the preparation was contained in 0.2 ml of suspension. The prolactin suspensions were injected subcutaneously in daily doses of 0.2 and 10 mg. In rats the injections were started 7-9 days after transferring the RMK-1 cancer, when the tumor reached the size of a bean, and were continued for 20 days. In mice in which the size of the tumor varied from 0.8 to 2 cm in diameter, but was approximately the same in the experimental and the control groups, the prolactin injections were continued for 25 days.

At the end of experiments the animals were killed and the tumors were weighed. The percentage of inhibition of tumor growth was calculated as a ratio of the difference of tumor weights in the control and experimental groups, multiplied by 100, to the weight of tumors in the control group.

Simultaneously the content of the follicle-stimulating hormone in the hypophysis was determined in all the animals. This was done by determining the change of weight of the uterus of baby mice which had been injected

TABLE 2. Inhibition of Growth of Spontaneous Mammary Gland Carcinoma in Non-Pedigreed Mice and Changes in the Production of the Follicle-Stimulating Hormone Under the Effect of Prolactin

Mouse group no.	No. of mice	Prolactin (in mg)	Mean wt. of tumors (in g)	Percentage inhibition of tumor growth	Index of follicle-stimulating hormone content
1	13	–	6.3	–	3.8
2	20	10	2.5	60.3	2.3

for 3 days with a saline suspension of acetone powder of hypophyseal tissue of control and experimental rats and mice, in doses of 1 rat hypophysis or 2 mouse hypophyses per 1 baby mouse. The mice were killed 72 h after the first injection. The index determining the follicle-stimulating hormone content in the hypophysis was expressed by a ratio of the weight of the reproductive organs of a baby mouse, multiplied by 1000, to the total body weight.

For histological studies fragments of tumors were fixed in 20% formalin, embedded in paraffin, sectioned and stained with hematoxylin-eosin.

In the experiment on the effect of prolactin on transferable rat mammary gland carcinoma (RMK-1) a total of 90 animals divided into 4 groups were used. Rats in group No. 1 served as controls, those in group No. 2 received 10 mg of prolactin each, in group No. 3, 1 mg each, and in group No. 4, 0.2 mg each.

RESULTS

The results obtained in experiments with rats are presented in Table 1 from which it will be seen that prolactin clearly inhibits the growth of the rat mammary gland carcinoma, and at the same time lowers the content of the follicle-stimulating hormone in the hypophysis. This effect depends on the prolactin dose: the higher the dose, the stronger the inhibition of the growth of tumor and the lower the content of the follicle-stimulating hormone in the hypophysis.

We have determined that the inhibition of the growth of mammary gland carcinoma in rats under the effect of prolactin is accompanied by a considerable increase in the density of the tumors. Histological studies have shown that tumors in control rats resembled a typical macroalveolar carcinoma of the mammary gland and consisted mainly of large alveoli lined with epithelial sheets of variable heights, with the alveoli separated from each other by narrow strands of connective tissue. In the tumors of prolactin-treated rats there were foci of resorption of the tumor as seen in heterotransplants, and large areas of the tumor tissue were replaced by fibrous connective tissue, which accounts for the increased density of such tumors, (Figs. 1a, b).

Thus, as had been anticipated, the effect of prolactin considerably decreases the follicle-stimulating hormone content in the hypophyses of rats with transferrable mammary gland carcinoma, and in this way produces an inhibition of the growth of the tumor.

In the experiment on the effect of prolactin on spontaneous mammary gland tumors of non-pedigreed mice, a total of 33 animals were used, divided into the control and experimental groups. The control mice were not treated with prolactin. The mice in the experimental group received prolactin in doses of 10 mg.

It will be seen from Table 2 that prolactin inhibits tumor growth and production of the follicle-stimulating hormone in mice as well as in rats.

Tumors in mice which were treated with prolactin were also considerably denser, some of them became ulcerated and in some mice they became detached. In 3 out of 20 mice in the experimental group the tumors became detached and the damaged skin became repaired with scar tissue.

The microscopical study of tumors in the control mice has shown that these tumors most often resembled the solid type adenocarcinoma, in which the stromal elements were weakly defined. In the prolactin-treated mice there were very extensive necrotic areas as well as areas of tumor resorption and replacement of the dead tumor tissue by fibrous connective tissue, which in some places penetrated into non-necrotic tumor tissue (Figs. 2a, b).

Thus, we were able to determine that the effect of prolactin in rats with transferable mammary gland carcinoma RMK-1 and in mice with spontaneous mammary gland tumors produced a clear relationship between the percentage of inhibition of tumor growth and the content of the follicle-stimulating hormone in the hypophysis. This confirmed the preliminary theoretical hypothesis.

We were not able to find in the literature any investigations in which the effect of prolactin on the inhibition of mammary gland tumor was studied simultaneously with the follicle-stimulating hormone content in the hypophysis, although attempts to interpret the effect of prolactin in combination with corticosteroids or with stilbestrol on the growth of transferrable mammary gland carcinomas of rats and mice are known [13-15]. According to these authors prolactin produced an insignificant inhibition of the growth of mammary gland tumors.

The results obtained by us on the prolactin therapy of transferable rat mammary gland carcinoma and of spontaneous mouse mammary gland tumors indicate that prolactin may prove to be a new active agent useful for the treatment of human mammary gland carcinoma.

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