ROLE OF PROLACTIN IN THE DEVELOPMENT OF MAMMARY GLAND TUMORS INDUCED BY DIMETHYLBENZANTHRACENE

I. I. Dedov and N. A. Demina

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In recent years the role of prolactin in the pathogenesis of mammary gland tumors has been a topic for intensive research. Nevertheless it is not yet clear whether the development of a neoplasm of the mammary gland is the result of the combined action of estrogens and prolactin, or whether estrogens, by inhibiting the production of prolactostatin in the hypothalamus, stimulate liberation of prolactin and thereby facilitate its carcinogenic action on parenchymatous cells.

The object of the present investigation was to study the action of prolactin on mammary gland tumors induced by dimethylbenzanthracene in rats with different estrogen levels.

EXPERIMENTAL METHOD

Experiments were carried out on female Wistar rats aged 55-60 days. 7,12-Dimethylbenzanthracene (DMBA), dissolved in dimethyl sulfoxide, was injected intravenously in a dose of 6 mg per animal. After 2 months, the 76 animals with palpable mammary gland tumors (0.5 cm in diameter) were divided into five groups. The rats of group 1 served as the control. To create an experimental model with a high level of endogenous prolactin, the pituitary stalk was divided in the rats of group 2. This operation, like destruction of the median eminence, is known to cause sharp stimulation of prolactin secretion [1, 3]. A combined operation was performed on the rats of group 3: 4 days after division of the pituitary stalk, their ovaries were removed. Castrated rats formed group 4. The rats of group 5 were treated with chlorpromazine. By reducing the monoamine concentration in the hypothalamus drastically, chlorpromazine induces a prolonged rise of the prolactin level and, at the same time, it lowers the concentration of pituitary gonadotrophic hormones and of sex steroids [3]. Chlorpromazine was injected intramuscularly in a dose of 5 mg per animal daily for 4 weeks. The total dose was 100 mg.

The pituitary stalk was divided by a method devised by the authors. To prevent restoration of the portal system of the pituitary circulation after division of hypothalamo-hypophyseal connections, a steel plate was inserted into the zone of division. The tumors were

TABLE 1. Development of Mammary Gland Tumors Induced by DMBA in Female Rats with Exposure of their Endocrine System to Various Factors

Group of animals	Number of animals	Number of animals with tumors	Number of mammary gland tumors per animal (M ± m)
1	15	10 (66,7%)	1,4±0,02
2	17	15 (88,2%)	2,3±0,03
3	15	5 (33,3%)*	1,1±0,02
4	12	2 (16,7%) †	1,0±0,02
5	17	13 (76,5%)	1,8±0,03

*$P < 0.01$ compared with group 2.
†$P < 0.02$ compared with control and group 2.

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TABLE 2. Estradiol, TSH, and Thyroxine Levels in Blood Plasma of Female Rats Exposed to Various Factors (M ± m)

Experimental conditions	Estradiol, pg/ml	TSH, ng/ml	Thyroxine, μg/100 ml
Control (intact)	48,6±3,2	142,6±12,2	6,8±0,4
Control + DMBA	54,2±2,8	132,5±14,6	5,1±0,4
Division of pituitary stalk (90 days, control)	26,8±1,2	52,6±3,2*	2,8±0,1*
Division of pituitary stalk + DMBA	20,4±2,2*	57,2±4,6*	3,3±0,1*
Chlorpromazine			
maximal growth of tumors	26,8±2,5	85,5±9,2	3,6±0,3
period of regression	52,4±4,6	128,4±14,5	5,2±0,3

*$P < 0.05$ compared with control.

Legend. Each group consists of five animals.

measured every week for 3 months after the operation. Concentrations of estradiol, thyroid stimulating hormone (TSH), and thyroxine were determined by a radioimmunologic method in blood plasma collected during sacrifice of the animals.

EXPERIMENTAL RESULTS

Of the total number of mammary gland tumors 92% were carcinomas of different kinds and 8% were fibroadenomas. The dynamics of development of the mammary gland tumors is shown in Tables 1 and 2 and in Fig. 1, and data are given on the hormone levels against the background of which this development took place. A high prolactin level caused by division of the pituitary stalk, even against the background of a reduced estrogen concentration, was shown to stimulate growth of mammary gland carcinomas induced by the carcinogen to a considerable degree. The number of tumors per animal was greater in the group of rats with a divided pituitary stalk, and they grew faster than in rats of the other experimental groups (Table 1, Fig. 1).

Ovariectomy sharply reduced the effect of division of the pituitary stalk. Meanwhile, the development of mammary gland carcinoma took place more rapidly in animals undergoing the combined operation (division + castration) than in animals undergoing only division of hypothalamo-hypophyseal connections. Chlorpromazine, like division of the pituitary stalk, stimulated tumor development (Fig. 1). Characteristically growth of the tumors was activated actually during administration of the drug. After the injections of chlorpromazine had ceased, rapid regression of the tumors took place. Whereas during the period of rapid tumor growth the levels of estrogen, TSH, and thyroxine in the animals were significantly reduced, during regression the concentrations of these hormones were restored practically to normal (Table 2). Consequently, the combined action of estrogens and prolactin is the optimal condition for stimulation of growth of mammary gland tumors. Synergism of action of estrogens and prolactin is not only effective in maintaining growth of tumors already induced by chemical carcinogens, but it is also the principal factor in the pathogenesis of spontaneous mammary gland tumors. In fact, the main cause of development of mammary gland carcinoma in women is an anovulatory or disturbed sex cycle, during which hyperestrogenization coincides with a high blood prolactin level. If the sex cycle is normal, this interference between biological effects of prolactin and estrogens on the mammary gland does not take place; prolactin exerts its action in the lutein phase of the cycle in conjunction with progestins.

The mechanism of the pathogenetic action of prolactin in the development of mammary gland tumors is evidently more complex than has hitherto been considered. For instance, after division of the pituitary stalk or administration of reserpine or sedatives, stimulation of tumor growth cannot be explained purely by the action of prolactin [3]. Secretion of prolactin in situations mentioned above is sharply activated, but under these circumstances there is a marked fall in the levels of most pituitary trophic hormones and hormones of the peripheral endocrine glands controlling many different metabolic processes (Table 2). The stimulating action of prolactin on tumors is exerted only in this endocrine situation. If, for example, the pituitary stalk was divided before administration of DMBA, a lower yield of tumors was found in the animals [2]. According to the authors cited, a high prolactin level preceding injection of DMBA has a protective action on the parenchymatous cells of the mammary gland and increases their resistance to the blast-transforming effect of carcinogens.

It is clear that the role of prolactin and other hormones in the etiology and pathogenesis of mammary gland tumors requires further study. Nevertheless, even at this stage, the

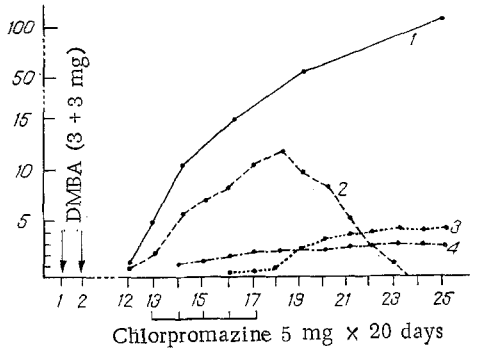

Fig. 1. Development of mammary gland carcinoma induced by DMBA in female rats with different hormonal status. Abscissa, time of observation (in weeks); ordinate, volume of tumor (in cm^3); 1) division of pituitary stalk; 2) chlorpromazine; 3) control; 4) division of pituitary stalk + ovariectomy.

blood prolactin and estrogen concentrations can be chosen as criteria for the identification of groups of women with a high risk of development of hormone-dependent mammary gland tumors and for the choice of methods of their treatment. To break this pathological hormonal chain (prolactin + estrogens) and, in particular, for the treatment of mastopathies, substances suppressing prolactin secretion (ergot alkaloids and, in particular, parlodel, L-dopa, etc.) must be combined with antiestrogens.

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EFFECT OF MISCLERON (CLOFIBRATE) ON INDUCTION OF INTESTINAL TUMORS BY DIMETHYLHYDRAZINE IN RATS

L. M. Bershtein, K. M. Pozharisskii, and V. M. Dil'man

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In harmony with views on the role of disturbances of lipid and carbohydrate metabolism in the creation of conditions promoting tumor growth [1, 2], the hypolipidemic drug Miscleron (clofibrate) has been used for several years for the correction of these disturbances in cancer patients suffering, in particular, from carcinoma of the colon and rectum [3]. Besides these considerations, support for the validity of this therapeutic approach has recently been obtained from a steady flow of information on cholesterol and certain of its derivatives and the bile acids as promotors of carcinogenesis in the large intestine [5, 8]. However, the use of hypolipidemic agents such as cholestyramine and candicidin in experiments on rats not only did not inhibit the development of tumors of the large intestine under the influence of azoxymethane, but actually potentiated this process [15]. Meanwhile, in an international investigation conducted over the last few years by Professor Oliver, to study primary prevention of ischemic heart disease by clofibrate, it was shown that the number of myocardial infarcts not ending fatally was significantly reduced in the group of subjects taking the drug, and on standardization of the data for age, the number of malignant neoplasms developing (including those in the gastrointestinal tract) did not differ significantly from the control values, i.e., in subjects receiving a placebo [7].

Laboratory of Endocrinology and Laboratory of Experimental Tumors, N. N. Petrov Research Institute of Oncology, Ministry of Health of the USSR, Leningrad. (Presented by Academician of the Academy of Medical Sciences of the USSR A. P. Avtsyn.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 90, No. 9, pp. 350-352, September, 1980. Original article submitted September 26, 1979.

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