Relation Between Growth of Carcinogen-Induced Mammary Cancers and Serum Prolactin Values in Rats[1] (37080)

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Prolactin is essential for development and growth of carcinogen-induced and spontaneous mammary tumors in rats. Reductions in prolactin secretion induced by hypophysectomy, ovariectomy or administration of drugs that decrease prolactin release (*l*-dopa, iproniazid, pargyline, ergot drugs, etc.), result in reduced mammary tumor growth (1–3). Elevations in prolactin secretion, produced by placing lesions in the median eminence of the hypothalamus, by implantation of minute amounts of estrogen in the median eminence, by administration of prolactin or drugs that increase prolactin release such as reserpine, haloperiodol or methyldopa, accelerate growth of mammary tumors in rats (1, 3). Estrogen also is needed for mammary tumor development and growth in rats, and is believed to function by stimulating prolactin secretion by the pituitary and by acting synergistically with prolactin directly on the mammary tissues (1–3).

In view of the importance of prolactin for growth of mammary tumors in rats, it was of interest to determine the relation of blood levels in prolactin to growth of carcinogen-induced mammary cancers. The results indicate that mammary cancers can grow in size and number in the presence of normal serum prolactin values.

Materials and Methods. At 50–55 days of age, 50 Sprague-Dawley female rats (Spartan Research Animals, Haslett, MI) were each given a single intravenous injection of a suspension of 5 mg of 7,12-dimethylbenz(*a*) anthracene (DMBA)[5], according to the method of Huggins (4). The rats were examined for appearance of mammary cancers once weekly. The number of palpable cancers were counted and largest diameter of each cancer was measured with calipers. Vaginal smears were examined from each rat at approximately 9 AM daily during the experimental period of 165 days. The rats continued to cycle normally after development of the cancers. Beginning about 45 days after the appearance of cancers and approximately at monthly intervals thereafter, blood samples (about 0.5 ml) were collected from the femoral vein under light ether anesthesia at about 2 PM on a day of estrus. The day of estrus was chosen to avoid variability in serum levels of prolactin due to the estrous cycle. The serum was assayed for prolactin by a standard radioimmunoassay (5). Prolactin results are expressed in terms of NIH-P-B1 (5).

Results. Table I shows that 24 out of 50 rats developed mammary tumors by 45 days, 46 rats had mammary tumors by 75 days, and all 50 rats developed mammary tumors by 105 days after DMBA treatment. The average latency period for the appearance of these

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TABLE I. Relation Between Growth of DMBA-Induced Mammary Cancers and Serum Prolactin Concentration.

After DMBA inj. (days)	No. of rats with tumors	Av no. of tumors/rat	Av tumor diam (cm)	Av serum PRL concn (ng/ml)
45	24	1.5 ± 0.3	0.7 ± 0.1	117 ± 17[b]
75	46	4.8 ± 0.7	0.9 ± 0.1	115 ± 14
105	50	5.7 ± 0.8	1.1 ± 0.1	124 ± 17
135	21	7.4 ± 0.9	1.1 ± 0.3	102 ± 13
165	14	6.8 ± 0.8	1.4 ± 0.2	91 ± 21

[a] Standard error of mean.

[b] Serum prolactin values on the day of estrus in normal Sprague-Dawley rats range from 60 to 170 ng/ml (6).

DMBA-induced cancers was 55 ± 3.1 days, in agreement with previous results from our laboratory (3). The average number of cancers per rat increased steadily and reached a maximum by 135 days, and average tumor diameter reached maximum size at 165 days. Many of the tumors became ulcerated after 105 days, and these were subsequently eliminated from this experiment. It can be seen that average serum prolactin concentration in the tumor-bearing rats remained about the same at each bleeding interval throughout the experimental period. None of the serum prolactin values differed significantly from each other.

Discussion. These results demonstrate that DMBA-induced mammary cancers increase in size and number in Sprague–Dawley rats in the presence of normal serum prolactin concentrations. The prolactin values in these tumor-bearing rats are in agreement with serum prolactin levels found in normal cycling Sprague-Dawley rats on the day of estrus (6). These results do not negate the importance of prolactin for growth of DMBA-induced mammary cancers in rats, but indicate only that normal serum prolactin levels are sufficient to permit growth of these cancers. As previously indicated, a reduction in blood prolactin levels results in inhibition or regression of mammary tumor growth, whereas an elevation of blood prolactin results in accelerated mammary tumor growth (1, 3). It also is of interest that when an increase in prolactin secretion is induced prior to the appearance of mammary cancers in DMBA-treated rats, the ensuing stimulation to mammary growth protects the mammary tissues against the action of the carcinogen and inhibits mammary cancer development (1, 3).

The present observations may not apply to development of spontaneous benign mammary tumors commonly seen in old Sprague-Dawley female rats. In our Sprague-Dawley female rats 2 yr of age or older, the incidence of such spontaneous mammary tumors is 50% or greater (3). Old female Sprague-Dawley rats have pituitary (7) and serum levels of prolactin (Shaar, Euker, Riegle and Meites, unpublished data) that are significantly higher than in 3–4 month old cycling female rats of the same strain. The development of spontaneous mammary tumors in these old rats apparently is associated with the increase in prolactin secretion. Elevations of blood prolactin levels in young female Sprague-Dawley rats induce early appearance of these mammary tumors (8, 9), whereas administration of drugs that inhibit prolactin secretion prevents their development even in old age (Quadri and Meites, unpublished data).

Summary. Mammary cancers were induced in fifty 50–55 day old female Sprague-Dawley rats by a single intravenous injection of 5 mg 7,12-dimethylbenz(*a*)anthracene (DMBA). Total mammary cancers and average cancer diameter per rat were measured once weekly. Beginning about 45 days after the appearance of mammary cancers and approximately at monthly intervals thereafter, for a total of 165 days, serum prolactin was measured by radioimmunoassay. Although the average number of mammary cancers increased from an initial 1.5 ± 0.5 to a maximum of 7.4 ± 0.9 per rat, and

average tumor diameter increased from 0.7 ± 0.1 to 1.4 ± 0.2 cm, serum prolactin concentrations remained within the normal range and did not change significantly from month to month. These observations indicate that growth of DMBA-induced mammary cancers in Sprague-Dawley rats can proceed in the presence of normal blood prolactin values.

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