Regression of Spontaneous Mammary Tumors in Rats by Ergot Drugs[1] (36036)

S. K. QUADRI AND JOSEPH MEITES

Department of Physiology, Michigan State University, East Lansing, Michigan 48823

Recently we observed that 2 ergot drugs, ergocornine methane sulfonate[2] (ERG) and 2-Br-α-ergokryptine (ERK) inhibited prolactin secretion (1–4) and induced profound regression of carcinogen-induced mammary adenocarcinomas in rats without altering the estrous cycle (1, 5). We now report inhibition by ERG and ERK of growth of *spontaneous* mammary tumors in old female rats. Spontaneous mammary tumors in female rats appear in the postreproductive phase of life (6, 7), and unlike the carcinogen-induced mammary adenocarcinomas, they are usually benign fibroadenomas and occur as a single tumor per rat.

Materials and Methods. Sprague-Dawley female rats (Spartan Research Animals, Haslett, Mich.), 12 months of age or older, were obtained at variable periods of time after appearance of a single spontaneous mammary tumor. Tumor diameter in individual rats varied from 1.6 ± 0.1 to 4.2 ± 0.3 cm. The rats were randomly divided into one control group, 4 groups given ERG and 4 groups given ERK. The drugs were injected daily intraperitoneally in doses of 0.05, 0.10, 0.20, or 0.40 mg/100 g of body weight in a solution containing 96% physiological saline and 4% ethanol of 70% strength. Control rats were injected daily only with the saline–ethanol vehicle. The largest diameter of each tumor was measured once weekly with calipers. After 4 weeks of treatment, all injections were discontinued and the tumors were measured for an additional period of 4 weeks. The rats were housed in an air-conditioned, temperature-controlled (75 ± 2°F) room and were fed a standard laboratory diet supplemented with oranges and carrots.

Results. Figures 1 and 2 show that all doses of ERG and ERK induced marked regression of mammary tumor diameter during the 4 week treatment period. Inhibition of tumor growth, observed even 1 week after treatment in each of the groups, was highly significant compared with tumor growth in the control group. Average tumor diameter in all groups given ERG for 4 weeks decreased from 2.81 ± 0.3 to 2.0 ± 0.2 cm, and in the ERK-treated rats from 2.66 ± 0.4 to 1.54 ± 0.3 cm. By contrast, the control group showed a gain in average tumor diameter from 2.81 ± 0.5 to 3.91 ± 0.6. There was no obvious relationship between dose of ERG or ERK injected and mammary tumor inhibition, but this may be due to the considerable variability in initial tumor size and to the small number of rats used per dose. After treatment with ERG or ERK was terminated, growth of the mammary tumors promptly resumed. Tumor growth 1 week after cessation of drug treatment exceeded that of the controls, except for the group previously given 0.05 mg of ERK daily. Thereafter tumor growth rate proceeded at about the same rate as in the control rats.

Discussion. Ergocornine and ergokryptine both induced significant regression of spontaneous mammary tumors in old female rats similar to that previously observed in rats with carcinogen-induced mammary tumors (1, 5). Both drugs appeared to be almost equally effective in decreasing size of the spontaneous mammary tumors, in contrast to the greater effectiveness of erocornine in suppressing growth of carcinogen-induced mammary tumors (5). Measurement of individual tumors indicated that the 2 drugs produced greater inhibition of growth of the smaller than of the larger tumors, and in some cases

[1] This study was aided in part by NIH Grants CA 10771 and AM 04784 and by a grant from Eli Lilly and Co., Indianapolis, IN.

[2] We thank Professor E. Fluckiger and Dr. M. Taeschler for ergocornine methanesulfonate and 2-Br-α-ergokryptine.

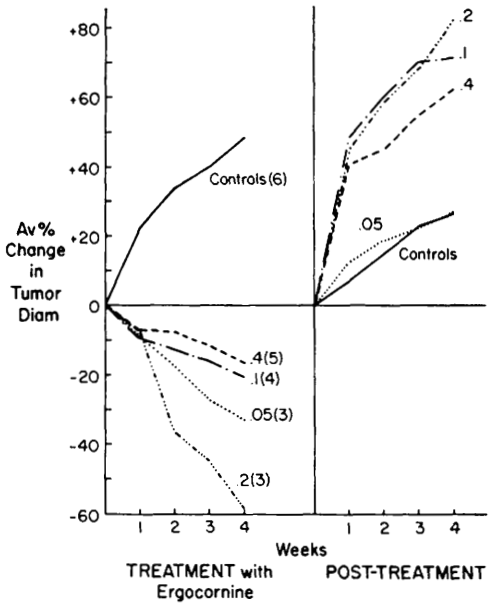

FIG. 1. Regression of mammary tumor diameter induced by ergocornine during 4-week treatment period. Dose (μg) and total number of rats are indicated for each group. Note that in the post-treatment period, tumors of all except one previously injected group grew at a faster rate during the first week than in the controls.

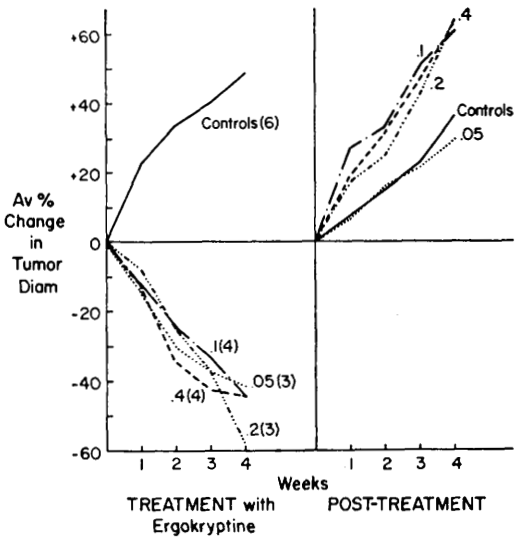

FIG. 2. Regression of mammary tumor diameter induced by ergokryptine during 4-week treatment period: Dose (μg) and total number of rats are indicated for each group. Note prompt resumption of mammary tumor growth in posttreatment period.

elicited complete disappearance of the smaller tumors. We have observed a similar action of these drugs in relation to size of the carcinogen-induced mammary tumors (5). Growth of the mammary tumors resumed quickly after termination of drug treatment, and surpassed that of the control rats. This is believed to reflect increased prolactin secretion and action on the tumors after drug removal.

Although blood prolactin levels were not measured in the present study, we have demonstrated previously that similar doses of the 2 drugs significantly reduce serum and pituitary prolactin concentrations in Sprague–Dawley rats (1–4). In addition, ERG decreased pituitary and serum prolactin in rats with carcinogen-induced mammary tumors (1). Earlier we reported that several treatments that raise blood prolactin levels, *i.e.*, placement of lesions in the hypothalamus or grafting of extra pituitaries underneath the kidney capsule, accelerate development and growth of spontaneous (6, 7) or carcinogen-induced (8) mammary tumors in female rats. Contrawise, procedures that depress blood prolactin concentration, *i.e.*, hypophysectomy, ovariectomy or adrenalectomy, inhibit development of mammary tumors in rats (9). Prolactin is believed to be an essential hormone, together with estrogen, for mammary tumor development and growth (10).

Summary. Daily injection of ergocornine or ergokryptine for 4 weeks induced marked regression in growth of spontaneous mammary tumors in old female rats. After termination of drug treatment, prompt resumption of mammary tumor growth was observed. Both drugs are believed to inhibit mammary tumor growth by depressing secretion of pituitary prolactin.

1. Nagasawa, H., and Meites, J., Proc. Soc. Exp. Biol. Med. **135**, 469 (1970).

2. Lu, K. H., Koch, Y., and Meites, J. Endocrinology, **89**, 229 (1971).

3. Wuttke, W., Cassell, E., and Meites, J., Endocrinology **88**, 737 (1971).

4. Quadri, S. K., Karande, K. A., and Meites, J. unpublished data.

5. Cassell, E., Meites, J., and Welsch, C. W.,

Cancer Res. 31, 1051 (1971).

6. Welsch, C. W., Jenkins, T. W., and Meites, J., Cancer Res. 30, 1024 (1970).

7. Welsch, C. W., Clemens, J. A., and Meites, J., Cancer Res. 29, 1541 (1969).

8. Clemens, J. A., Welsch, C. W., and Meites, J., Proc. Soc. Exp. Biol. Med. 127, 969 (1968).

9. Sterental, A., Dominguez, J. M., Weissman, C., and Pearson, O. H., Cancer Res. 23, 481 (1963).

10. Furth, J., and Clifton, K. H., Cancer 10, 842 (1957).

Received July 6, 1971. P.S.E.B.M., 1971, Vol. 138.