Enhanced Regression of DMBA-induced Mammary Cancers in Rats by Combination of Ergocornine with Ovariectomy or High Doses of Estrogen

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SUMMARY

The effects of either ergocornine (EC), ovariectomy (Ovx), or high doses of estradiol benzoate (EB) alone, or combinations of EC and Ovx or EC and EB on growth of 7,12-dimethylbenz(a)anthracene-induced mammary cancers were investigated in female Sprague-Dawley rats. After the cancers reached at least 1 cm in their largest diameter, the rats were ovariectomized or were given daily injections of EC (0.2 mg/100 g body weight) or EB (20 µg/rat) or were treated with combinations of EC and Ovx or EC and EB. By the end of 3 weeks, the combined treatments reduced mammary tumor size and number to a greater degree than any single treatment. The greater effectiveness of the combined treatments is believed to be due to the more complete inhibition of prolactin release produced by EC, together with the loss of estrogen resulting from Ovx or to the peripheral interference with prolactin action by high doses of EB.

INTRODUCTION

Prolactin and estrogen are the 2 most important hormones involved in DMBA-induced mammary carcinogenesis and growth in the Sprague-Dawley female rat (3, 5). Estrogen is believed to act in large part by stimulating prolactin secretion by the pituitary, and it does not produce mammary tumors in the absence of the hypophysis (3, 5, 7). Procedures that result in elevated prolactin release, including placement of lesions in the median eminence or administration of drugs such as methyldopa, reserpine, or haloperidol, produce increased growth of existing mammary cancers. On the other hand, treatments that reduce prolactin release, including placement of lesions in the median eminence or administration of drugs such as methyldopa, reserpine, or haloperidol, produce increased growth of existing mammary cancers. The other hand, treatments that reduce prolactin release, including administration of ergot drugs, 3-(3,4-dihydroxyphenyl)-L-alanine or iproniazid, result in inhibition of mammary cancer growth. Ovariectomy or administration of high doses of estrogen also produce inhibition of established mammary cancer growth in rats. High doses of estrogen actually elevate blood prolactin levels in rats but also interfere with peripheral stimulation by prolactin of mammary tumor growth (4).

The purpose of this investigation was to determine whether combined treatment with Ovx and EC, or high estrogen and EC, would be more effective for induction of inhibition of carcinogen-induced mammary cancer growth than any single treatment alone. Although Ovx reduces prolactin secretion and high doses of estrogen interfere with prolactin stimulation of mammary tumor growth, it was considered possible that more complete inhibition of prolactin release by EC might contribute further to suppression of mammary cancer growth.

MATERIALS AND METHODS

Virgin Sprague-Dawley female rats were obtained from Holtzman Co., Madison, Wis. They were housed in an air-conditioned, temperature- (75 ± 1°F) and light- (14 hr of light from 5 a.m. to 7 p.m.) controlled room and were fed a diet of Wayne Lab Blox pellets (Allied Mills, Inc., Chicago, Ill.) and water ad libitum. At 55 to 56 days of age, each rat received an injection, via the tail vein, of a single dose of 1 ml of a lipid emulsion containing 5 mg of DMBA, kindly supplied by Dr. P. Schurr, The Upjohn Co., Kalamazoo, Mich. Approximately 60 days later, when each rat had developed at least 1 mammary tumor 1 cm in diameter or larger, the rats were divided into 6 groups and given daily s.c. injections for 3 weeks as follows: Group 1, intact controls, 0.2 ml of a 0.85% NaCl and 3% ethanol solution; Group 2, 0.2 mg EC/100 g body weight, injected in 0.2 ml of the 0.85% NaCl-ethanol solution; Group 3, bilateral Ovx and 0.1 ml corn oil; Group 4, 20 µg EB/rat in 0.1 ml corn oil; Group 5, bilateral Ovx and 0.1 ml corn oil; Group 6, 0.2 mg EC/100 g body weight + Ovx; Group 6, 0.2 µg EC/100 g body weight + 20 µg EB/rat.

Every 7 days during the treatment period of 3 weeks, the rats were placed under light ether anesthesia and the
largest diameter of each tumor was measured with vernier calipers. Both number of tumors per rat and body weight also were recorded. At the end of the 3-week treatment period, the average number of tumors that had disappeared or were in a state of regression or continued growth was categorized under each treatment. Significance of differences between any 2 groups was evaluated by Student's t test.

RESULTS

The effects of different treatments on mammary cancer growth are shown in Table 1. In the intact controls there was an increase in average tumor diameter from 2.8 ± 0.6 to 3.7 ± 0.7 cm (mean ± S.E.) and an increase in average tumor number from 2.7 ± 0.6 to 3.9 ± 0.6 tumors per rat. In contrast, there was regression of mammary tumors, both in size and number, in all experimental groups. In the EC group, average tumor diameter decreased from 4.2 ± 1.0 to 1.8 ± 0.5, and average tumor number decreased from 2.6 ± 0.5 to 1.6 ± 0.31. In the Ovx group, average tumor diameter decreased from 3.7 ± 0.7 to 2.1 ± 0.7 and average tumor number decreased from 2.9 ± 0.5 to 1.5 ± 0.4. The same values in the EB group decreased from 5.0 ± 0.6 to 2.0 ± 0.5 and from 3.0 ± 0.4 to 1.7 ± 0.2. The combination of EC and Ovx decreased average tumor diameter from 3.9 ± 0.5 to 1.1 ± 0.2 and decreased average tumor number from 3.3 ± 0.4 to 1.4 ± 0.3; the same values in the EC and EB group decreased from 3.7 ± 0.7 to 0.8 ± 0.2 and from 2.6 ± 0.5 to 0.9 ± 0.2. Thus the combination treatments were more effective than any of the single treatments.

To obtain a better evaluation of the effectiveness of the different treatments, percentage changes in average tumor diameter and average tumor number induced by the different treatments were calculated. The combinations of EC + Ovx or EC + EB evoked reductions of 72.6 and 78.9%, respectively, in average tumor diameter, compared with decreases of 52.2% by EC, of 41.8% by ovariectomy, and of 60.7% by EB alone. The combination treatments also caused greater decreases in the average number of tumors, of 56.5% by EC + Ovx and of 65.5% by EC + EB, compared with 38.7% by EC, 47.9% by ovariectomy, and 43.3% by EB.

The effects of the different treatments on the individual tumors are shown in Table 2. In the intact controls, no tumors disappeared by the end of the treatment period, only 3 were found to be regressing, and a total of 28 were in a state of active growth. In contrast, in all experimental groups, an overwhelming majority of tumors had either disappeared or were in a state of regression by the end of the treatment period. However, in each of the 3 groups given single treatments of EC, Ovx, or EB, a total of 6 to 8 tumors remained unchanged in size or continued to grow. In contrast, no tumors were growing by the end of the treatment period in the rats given the combinations, and only 1 tumor remained unchanged in size in a rat given EC + EB.
**DISCUSSION**

This study shows that a combination of EC and Ovx or of EC and EB was more effective in producing regression of DMBA-induced mammary tumors than either EC, Ovx, or EB alone. The combinations produced not only greater reductions in average tumor diameter and average tumor number, but completely suppressed mammary tumor growth and prevented development of new tumors. In the rats that received single treatments, some of the tumors remained unresponsive to the treatments while others showed growth stasis without any visible regression. In contrast, all except 1 tumor responded to the combination treatments with a decrease in tumor size and number. This study confirms earlier reports that EC, Ovx, or large doses of EB can inhibit mammary tumor growth in rats (1, 4, 6), but it also demonstrates that combined therapy is more effective than any single treatment alone.

Ergot drugs act directly on the pituitary and also via the hypothalamus to inhibit prolactin release (2, 5). Ovx inhibits mammary tumor growth by removing estrogen stimulation on the mammary tumor tissue and by decreasing prolactin secretion (3, 5). Large doses of estrogen inhibit mammary tumor growth by blocking the peripheral stimulating action of prolactin on the tumor tissue, although prolactin secretion is increased (4). We believe that greater suppression of mammary tumor growth was achieved by the combination of EC and Ovx or high EB and EC because of the more complete inhibition of prolactin release by the ergot drug. The dose of EC used, 0.2 mg/100 g body weight, previously was shown by us to reduce serum prolactin in intact female Sprague-Dawley rats to levels below those during the estrous cycles (5). These observations suggest that a similar combination of an ergot drug and Ovx or high estrogen may be more beneficial for treating hormone-responsive human breast carcinomas than single endocrine therapy.

**REFERENCES**


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