Effects of LSD, Pargyline and Haloperidol on Mammary Tumor Growth in Rats[1] (36949)

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Prolactin and estrogen are essential for development and growth of mammary tumors in rats (1, 2). Treatments that result in increased prolactin secretion accelerate growth of mammary tumors in rats, whereas treatments that depress prolactin secretion inhibit mammary tumor growth. Thus placement of bilateral lesions in the median eminence, grafting of pituitaries underneath the kidney capsule, injections of reserpine or a mestranol-norethynodrel combination, all of which increase prolactin secretion, hasten growth of carcinogen-induced mammary tumors in rats (1, 3, 4). Contrawise, administration of ergot drugs (5, 6), iproniazid (7) or *l*-dopa (8), all of which depress prolactin secretion, result in inhibition of mammary tumor growth. The present study assesses the effects of lysergic acid diethylamide (LSD) and pargyline, both depressors of prolactin release (9, 10), and of haloperidol (11), a drug that elevates serum prolactin, on growth of carcinogen-induced mammary tumors in rats.

Materials and Methods. Sprague-Dawley virgin female rats (Spartan Research Animals, Haslett, MI), 55 days old, were injected iv with a single dose of 5 mg of 7,12-dimethylbenzanthracene (DMBA)[2] dissolved in a fat emulsion. In our laboratory this procedure results in development of mammary adenocarcinomas with an average latency period of 55–60 days (1, 2). About 10 wk after injection of DMBA, when each rat had at least one mammary tumor 1 cm in diameter, the rats were randomly divided into 4 groups and injected sc daily for 3 wk as follows:

Group 1, controls, 0.1 ml saline–corn oil emulsion/100 g body weight.

Group 2, 2.5 mg pargyline[3] in 0.1 ml saline/100 g body weight.

Group 3, 50 μg haloperidol[4] in 0.1 ml corn oil/100 g body weight.

Group 4, 0.5, 1 and 2 μg LSD[5] in 0.1 ml saline–corn oil emulsion/100 g body weight during the first, second and third weeks, respectively.

Body weight, number of tumors per rat and the largest diameter of each tumor (measured by calipers) were recorded once weekly. Treatment with the drugs was terminated at the end of 3 wk and the same measurements were recorded for an additional 3 wk. All animals were housed in an air-conditioned room (75 ± 2°F), with 14 hr of artificial light and 10 hr of darkness daily. The animals were fed Wayne Lab Blox (Allied Mills, Chicago, IL) and tap water *ad libitum*. Significance of difference between any 2 groups was determined by Student's *t* test.

Results. The effect of the different treatments on tumor growth and body weight are shown in Table I. Mammary tumors in the control group showed a steady increase in size and number during the treatment period, reaching 6.3 ± 0.8 cm in average tumor diameter and 5 ± 1.3 in average tumor number per rat by the end of the third week of treatment. By contrast, pargyline treatment completely inhibited tumor growth and caused a decrease in average tumor diameter (4.2 ± 0.8 cm) and average tumor number (2.8 ± 0.4). There was no inhibition of tumor growth in the LSD-treated group during the first 2 wk of treatment, but during the third week the dose of LSD was raised to 2 μg/100 g body weight and no further increase was observed in average tumor diameter or aver-

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age tumor number. In contrast to the pargyline- and LSD-treated groups, there was marked stimulation of tumor growth in the haloperidol-treated group. Average tumor diameter increased to 12.2 ± 3.2 cm and average tumor number reached 8.0 ± 1.4 by the third week of treatment. None of the treatments had any marked effects on body weights by the end of 3 wk. Although a significant ($p < .05$) decrease in average body weight occurred in the pargyline-treated rats initially, most of the rats showed a gain in body weight during the last week of treatment.

Tumor growth during the posttreatment period is shown in Table II. The control group continued to show a progressive increase in average tumor diameter and average tumor number similar to that observed during the treatment period. By contrast, there was a complete reversal of the growth pattern in the experimental groups, with a marked increase in both tumor diameter and tumor number in the rats previously treated with pargyline or LSD, and only minimal increases in tumor growth in the rats previously treated with haloperidol.

Figures 1 and 2 show average percentage changes in tumor diameter and tumor number per rat during and after the treatments. In the control group there was an average gain of 40.8% in tumor diameter and 42.3% in tumor number during the treatment period, and similar gains during the posttreatment period. Tumors in the pargyline-treated group showed a loss of 30.8% in tumor diameter and 26.7% in tumor number during the treatment period, but gained 132.4 and 132.1%, respectively, during the posttreatment period. Tumor diameter in the LSD-treated group increased by 27.1% and tumor number by 15.4% during the first 2 wk of treatment period, but when the dose of LSD was raised to 2 μg/100 g of body weight during the third week it resulted in a 7% reduction in tumor diameter and no further increase in tumor number. On termination of LSD treatment, there was a gain of 108.8% in tumor diameter and 97.9% in tumor number by the end of the third week. Tumor diameter and tumor number in the haloperidol-treated group increased by 340.1 and

TABLE I. Effect of Central-Acting Drugs on Growth of DMBA-Induced Mammary Tumors in Rats.

Treatment (no. of rats)	Av tumor diameter (cm) (wk): 0	1	2	3	Av no. of tumors/rat 0	1	2	3	Av body wt (g) 0	3
Controls (9)	4.5 ± 0.7[a]	4.9 ± 0.7	5.6 ± 0.6	6.3 ± 0.8[b]	3.5 ± 0.1	3.8 ± 0.9	4.5 ± 1.2	5.0 ± 1.3[b]	275.3 ± 5.3	278.9 ± 8.9
Pargyline (8)	6.1 ± 0.4	5.4 ± 0.6	4.3 ± 0.7	4.2 ± 0.8[b]	3.8 ± 0.3	3.8 ± 0.4	2.8 ± 0.5	2.8 ± 0.4[b]	281.2 ± 5.8	260.8 ± 6.9[b]
LSD (7)	4.9 ± 0.8	5.8 ± 0.7	6.3 ± 0.8	5.9 ± 0.8	4.0 ± 1.3	4.6 ± 1.3	4.6 ± 1.6	4.6 ± 1.4	277.8 ± 8.2	265.6 ± 7.2
Haloperidol (6)	2.7 ± 0.4	5.4 ± 0.8	7.3 ± 1.5	12 ± 3.2[b]	2.2 ± 0.8	4.5 ± 0.8	5.7 ± 1.2	8.0 ± 1.4[b]	291.7 ± 7.3	290.5 ± 8.3

[a] Mean ± standard error.
[b] Significantly different from week 0.

TABLE II. Growth of DMBA-Induced Mammary Tumors During Posttreatment Period.

Treatment	Av tumor diameter (cm)				Av tumor no./rat				Av body wt (g)	
(wk):	0	1	2	3	0	1	2	3	0	3
Controls	6.3 ± 1[a]	6.3 ± 1.1	6.8 ± 1.3	8.4 ± 1.4	5.0 ± 1.3	5.0 ± 1.4	5.1 ± 1.5	7.0 ± 1.4	278.5 ± 8.2	291.8 ± 9.3
Pargyline	4.2 ± 1.3	7.0 ± 1.4	8.1 ± 1.3	9.8 ± 1.8	2.8 ± 0.8	4.8 ± 1.2	5.8 ± 1.2	6.5 ± 1.3	260.6 ± 5.3	279.6 ± 9.1
LSD	4.6 ± 0.8	5.8 ± 0.9	8.1 ± 1.4	10.8 ± 1.5	5.9 ± 0.7	6.3 ± 0.6	7.3 ± 0.9	9.1 ± 1.8	265.3 ± 4.8	273.2 ± 5.6
Haloperidol	12.2 ± 1.4	12.1 ± 1.8	12.3 ± 2.2	13.1 ± 3.8	8.0 ± 1.8	8.5 ± 2.2	9.5 ± 2.2	9.5 ± 2.5	290.3 ± 8.2	298.4 ± 9.2

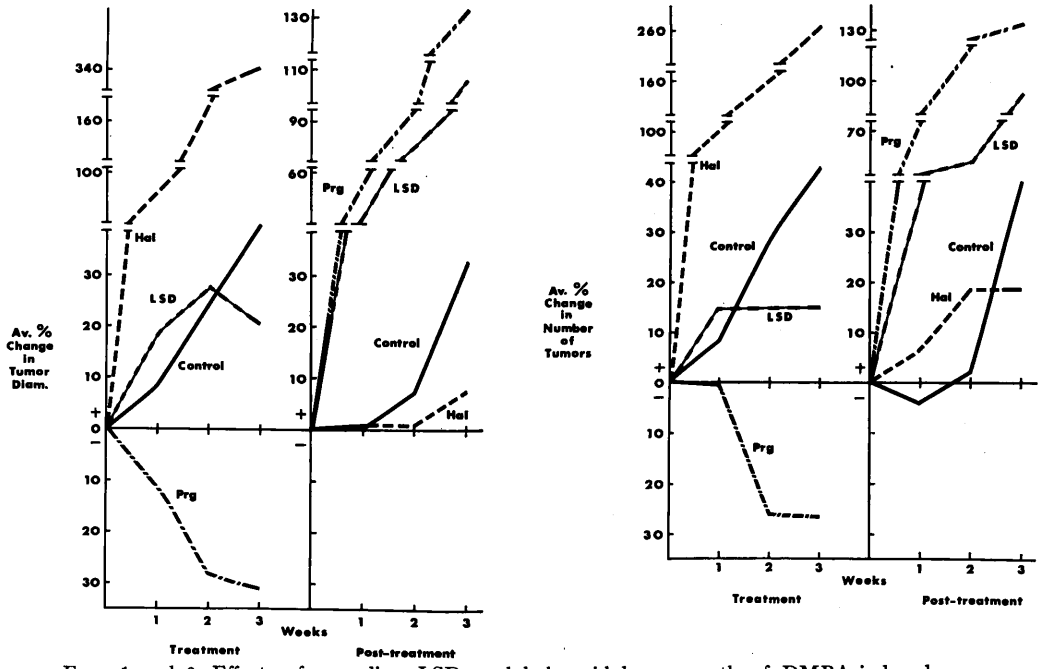
[a] Mean ± standard error.

255.4%, respectively, during the treatment period, but only by 7.0 and 18.3%, respectively, during the posttreatment period.

Discussion. The present observations provide further evidence for the importance of prolactin in mammary tumor growth in rats. Pargyline produced a significant reduction in tumor size and tumor number. No new tumors appeared during the course of treatment with pargyline. It is possible that a more prolonged treatment with this drug would have led to even a greater decrease in tumor size and number. LSD in doses of 0.5 and 1 μg/100 g body weight was not effective in reducing mammary tumor growth, but when the dose was raised to 2 μg/100 g body weight there was a decrease in tumor size and tumor number. Inasmuch as rats are relatively resistant to the actions of LSD (12), it is possible that higher doses would have been even more effective in reducing tumor growth. Haloperidol produced a remarkable increase in tumor size (greater than 300%) and tumor number (about 260%). Haloperidol was reported to greatly increase prolactin release (11) and to stimulate mammary lobuloalveolar growth and induce a prolonged state of diestrus in rats (13).

It is of interest that after treatment with these drugs was terminated, the rats previously given pargyline and LSD showed a pronounced acceleration in growth of mammary tumors that exceeded that of the controls. This is believed to reflect the removal of inhibition to prolactin secretion. On the other hand, the rats formerly given haloperidol showed a marked reduction in tumor growth that was below that of the controls. This undoubtedly reflects the removal of the stimulus to prolactin secretion by haloperidol.

Pargyline and haloperidol are believed to influence prolactin release by altering catecholamine activity in the hypothalamus, thereby increasing or decreasing release of prolactin release inhibiting factor (PIF) into the hypothalamo–pituitary portal vessels (10, 11). Pargyline is a monoamine oxidase inhibitor and therefore inhibits metabolism of catecholamines (12), increases hypothalamic PIF levels and reduces serum prolactin concentration (10). Haloperidol is a butyrophenone that blocks the actions of catechol-



FIGS. 1 and 2. Effects of pargyline, LSD, and haloperidol on growth of DMBA-induced mammary tumors in female rats: [1, (left)] av % change in tumor diameter; [2 (right)] av % change in tumor number.

amines, reduces hypothalamic PIF levels and raises serum prolactin values (11). LSD is an ergot drug that reduces serum prolactin concentration (9). Ergot drugs such as ergocornine have been found to act on the hypothalamus to increase PIF levels, and also act directly on the pituitary to inhibit prolactin release (14, 15). Many drugs now are available to increase or decrease prolactin release and thereby alter mammary tumor growth.

Summary. Daily injections into rats of 2.5 mg pargyline or 2 μg LSD/100 g body weight completely inhibited growth of DMBA-induced mammary adenocarcinomas, whereas daily treatment with haloperidol resulted in rapid stimulation of tumor growth as evidenced by a severalfold increase in tumor size and number compared to the controls. On termination of treatment with the 3 drugs, there was a complete reversal of the tumor growth patterns observed during treatment. A rapid increase in tumor size and number occurred in the groups previously given pargyline and LSD, but a marked retardation of tumor growth was observed in the rats previously given haloperidol. These effects of pargyline, LSD and haloperidol on mammary tumor growth are believed to reflect the changes produced by these drugs on pituitary prolactin release. Pargyline and LSD decrease serum prolactin levels whereas haloperidol increases serum prolactin values. The present study provides further evidence that prolactin is essential for growth of DMBA-induced mammary cancers in rats.

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