Increased Incidence of Spontaneous Mammary Tumors in Female Rats with Induced Hypothalamic Lesions

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SUMMARY

Forty-four multiparous, mammary tumor-free, Sprague-Dawley rats, 10 months old, were divided into two groups as follows: Group 1, sham-operated controls; and Group 2, bilateral electrolytic lesions placed in the median eminence area of the hypothalamus. After 25 weeks, the animals were killed, and the number of palpable mammary tumors was determined, and blood was withdrawn for prolactin analysis by radioimmunoassay. Mammary tumor incidence and blood prolactin levels were significantly increased in median eminence-lesioned rats (12/23, 52%; 179.8 ± 23.9 μg/ml) in contrast to the controls (4/21, 19%; 50.9 ± 9.6 μg/ml). These results demonstrate that disruption of the final common pathway from the hypothalamus to the anterior pituitary can significantly enhance spontaneous mammary tumorigenesis in the female rat. The increased blood levels of prolactin observed in the median eminence-lesioned rats provide further evidence that this is the principal hormonal factor in mammary tumorigenesis in the rat.

INTRODUCTION

It has been known for many years that the CNS influences tumorigenesis in man (5) and laboratory animals (4). Lacassagne and Duplan (4) were among the first to demonstrate that tranquilizers such as reserpine hasten the development of mammary tumors in mice, an observation recently confirmed in rats by Welsch and Meites (12). Studies in our laboratories have sought to determine which specific sites in the CNS significantly influence mammary tumorigenesis in rats. We have demonstrated that electrolytic lesions placed in the median eminence area of the hypothalamus significantly hasten the growth of carcinogen-induced rat mammary tumors (10). These results have been confirmed recently by Klaiber et al. (3). Lesions in the median eminence produce an increased release of pituitary prolactin (6), believed to be an essential hormone for stimulating development and growth of mammary tumors (2).

RESULTS AND DISCUSSION

It is well established that the hypothalamus has a significant regulatory influence on anterior pituitary secretion (6). It is conceivable, therefore, that certain endocrine-related tumors may arise from disorders of the CNS. The results presented in this report support this hypothesis. We have found that, when female rats are lesioned in the arcuate nucleus-median eminence area of the hypothalamus, there is a significant increase in spontaneous mammary tumor incidence.

MATERIALS AND METHODS

All animals used in this investigation were mature, multiparous, female Sprague-Dawley rats, obtained from Spartan Animal Farms, Inc., Haslett, Mich. They were housed in a temperature-controlled (75 ± 2°F) and light-controlled (14 hr/day) room and were given a diet of Wayne Lab Blox (Allied Mills, Chicago, Ill.) and water ad libitum.

At the time of lesion placement (approximately 295 days of age), all rats were free of palpable mammary tumors and their mean body weight was 325 g. Lesions were placed in the median eminence-arcuate nucleus area of the hypothalamus by passing 3 ma/10 sec of direct current through an electrode as described previously (10). Sham lesions were placed in rats by making bilateral lesions (3 ma/10 sec) on the skull. All rats were lesioned on the day of estrus.

Twenty-five weeks after placement of lesions, all rats were sacrificed. Blood was withdrawn and assayed for prolactin by the radioimmunoassay method of Niswender et al. (7). Mammary tumors and ovaries were excised for histological evaluation. Inguinal mammary glands were removed and prepared for whole-mount evaluation as described previously (10). The significance of differences between the mean final body weight, serum prolactin levels, and mammary gland ratings was calculated by Student’s t test. Significance of differences between number of rats with mammary tumors and total number of mammary tumors in each group was determined by χ² analysis (9).

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3The abbreviation used is: CNS, central nervous system.

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Hypothalamic Lesions and Mammary Tumorigenesis

Effects of median eminence lesions on development of normal and neoplastic mammary tissue and serum prolactin levels in female rats

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Total no. of rats</th>
<th>Final body weight (g)</th>
<th>Serum prolactin levels (μg/ml)</th>
<th>Average mammary gland ratings</th>
<th>No. and % of rats with tumors</th>
<th>Total no. of tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls, sham lesion</td>
<td>21</td>
<td>360 ± 7b</td>
<td>50.9 ± 9.6b</td>
<td>3.1 ± 0.1b</td>
<td>4 (19%)b</td>
<td>4b</td>
</tr>
<tr>
<td>Median eminence lesions</td>
<td>23</td>
<td>451 ± 19c</td>
<td>179.8 ± 23.9c</td>
<td>4.2 ± 0.2c</td>
<td>12 (52%)c</td>
<td>20c</td>
</tr>
</tbody>
</table>

*All rats were sacrificed 25 weeks after placement of median eminence or sham lesions. Final body weight, serum prolactin levels, and average mammary gland ratings are represented as the mean value ± S.E.*

Proportions of prolactin levels. Lesions in this area disrupt the final common pathway to the pituitary and have been reported to reduce the secretion of all pituitary hormones except prolactin, which is increased (6). Elevated serum prolactin levels, observed in this study, are in accord with this concept, and in addition, provide further evidence of the importance of this hormone for mammary tumorigenesis. Welsch et al. (11) recently reported an increased incidence of spontaneous mammary tumors in rats grafted with multiple pituitary homografts. It has been demonstrated that such grafts, free from direct hypothalamic influence, secrete increased amounts of prolactin (13).

Histological examination of the mammary tumors revealed an adenomatous type of tumor in the median eminence-lesioned rats (Fig. 1), in contrast to a relatively fibrous type tumor, containing considerably fewer glandular elements, in the sham-lesioned controls (Fig. 2). Fifteen of the 20 mammary tumors in the median eminence-lesioned group were highly differentiated glandular neoplasms, 4 were glandular neoplasms containing an abundance of connective tissue, and 1 was entirely a fibrous tumor. Carcinomatous type tumors were not observed in animals of either group. The majority of the mammary tumors in the median eminence-lesioned rats were quite large, in excess of 4 cm in diameter. No evidence of metastases or invasiveness of tumors in either group was observed. Despite the observation that the tumors developed rapidly, the differentiated histological appearance and lack of metastases and invasiveness indicate an absence of cancer. It is clear from the results of numerous studies that greater than 90% of the spontaneous mammary tumors in the rat are benign (8). Numerous large corpora lutea were observed in the ovaries of both groups, and there was a noticeable lack of follicular tissue in the ovaries of the median eminence-lesioned rats. The mammary glands of the median eminence-lesioned rats showed considerable more alveolar development (Fig. 3) than the sham-lesioned controls (Fig. 4). Many rats in this group had lobuloalveolar development comparable to that seen in rats in advanced pregnancy. Some of the rats with lesions in the median eminence area were extremely obese, an observation previously reported on rats lesioned in this area (10). However, there was no correlation between tumor incidence and the degree of obesity. The tumor incidence in the control group is in accord with control groups of rats of similar age in a previous study (11). Sprague-Dawley rats older than those used in the present study have been shown to develop a greater incidence of spontaneous mammary tumors. Mammary tumor incidence in Sprague-Dawley rats has been reported as high as 54% in 760-day-old rats (8) and 75% in 900-day-old rats (1). The age of the rats used in this study, 25 weeks after placement of lesions, was approximately 470 days.

Previous investigations in our laboratories have demonstrated that rats bearing mammary tumors induced by DMBA responded with significantly enhanced tumor growth (10) when lesioned in the median eminence-arcuate nucleus area of the hypothalamus. The increased incidence of spontaneous mammary tumors and elevated blood prolactin levels in the rats in the present study provide additional evidence that prolactin promotes murine mammary tumorigenesis. This work also supports our concept that some hormone-related tumors may arise from specific anomalies in the CNS.

REFERENCES

Figs. 1 and 2. Representative histological sections of mammary tumors from (Fig. 1) median eminence-lesioned rat and (Fig. 2) sham-lesioned control rat. × 200.

Figs. 3 and 4. Whole mounts of mammary glands from (Fig. 3) median eminence-lesioned rat and (Fig. 4) sham-lesioned control rat. × 8.
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