PATHOGENESIS AND HORMONAL PROPHYLAXIS OF EXPERIMENTAL DYSHORMONAL DISEASES OF THE MAMMARY GLANDS

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When different methods were used to induce tumors of the mammary glands (constant illumination, administration of dimethylbenzanthracene or dihydrostilbestrol) and for the prevention of dyshormonal diseases (by the use of testosterone and castration), changes in the endocrine system were uniform in character and consisted of changes in the secretion and content of follicle-stimulating hormone and of estrogens.

The role of hormones in the pathogenesis of mammary gland carcinoma is firmly established [1-3, 5, 6], although few investigations have been reported which reveal the general features of the endocrine genesis of tumors of hormone-dependent organs, including the mammary glands, when different methods are used for their induction and prophylaxis.

The object of the investigation described below was to study the role of sex hormones in the development of neoplasms of the mammary glands.

EXPERIMENTAL METHOD

Experiments were carried out on 466 sexually mature noninbred female mice. A group of 92 mice was kept under constant illumination with 75 and 200 W electric lamps suspended over the cages at a height of 32 cm. Another 60 mice received a single injection of 1 mg dimethylbenzanthracene (DMBA) in 0.2 ml peach oil directly into the tissue of the right mammary gland. A third group of 80 animals received subcutaneous injections of dihydrostilbestrol (as a suspension in physiological saline, 0.2 ml per injection) weekly in doses of 200 μg per injection. To prevent the development of dyshormonal diseases of the mammary glands induced by the above-mentioned factors, ovariectomy was performed on 97 mice two weeks before the experiment, and 137 animals received injections of testosterone propionate in doses of 0.4 ml of 1% solution once a week from the first day of the experiment. The illumination and administration of hormones continued until the end of the experiments.

To investigate the mechanism of action of inducing and prophylactic factors on the animals, the concentrations of gonadotropins and estrogens were studied, the pituitary, ovaries, and adrenals were weighed, and the ovaries and vaginal smears were examined. To isolate estrogens from the urine, the method of extraction described in [8] was used and the hormone content was determined biologically. The content of gonadotropins was determined by preparation of an extract of the pituitary and its injection into infantile mice [4]. Activity of both estrogens and gonadotropins was determined on the basis of the increase in weight of the uterus and fallopian tubes of infantile mice after injection of the hormone.

In the course of the experiments morphological investigations were made of total preparations and of tumors of the mammary glands.

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EXPERIMENTAL RESULTS

In group 1 (191 animals) the effect of testosterone and castration on the development of dyshormonal diseases of mammary glands induced by constant illumination was studied. Dyshormonal diseases of the mammary glands (hyperplasia, tumors) developed in 83 of the 92 (90.1%) mice kept under constant illumination with electric light, and in 3.2% of these mice the tumors were of the cystadenocarcinoma and keratinizing squamous-cell carcinoma type. Following prophylactic administration of testosterone or castration, no tumors developed after constant illumination, while the incidence of hyperplasia fell to 8.6% (in four of 46 animals) when testosterone was used and to 15% (in eight of 53 mice) in the case of ovariectomy.

In group 2 (120 animals) the effect of testosterone on the development of tumors of the mammary gland induced by dimethylbenzanthracene was studied. The use of the carcinogen led to the development of hyperplasia in 70% of animals, of carcinoma (of the cystadenocarcinoma, adenocarcinoma, or squamous-cell carcinoma types) in 16.7%, and sarcoma in 11.6% of animals (altogether 60 animals were used in this experiment). Administration of testosterone in association with DMBA reduced the incidence of dyshormonal diseases to 18.3% (11 of 60 mice), prevented the development of tumors, and prolonged the survival of the mice on the average by 9 weeks.

In group 3 (155 animals) the effect of testosterone and castration on the development of dyshormonal diseases of the mammary glands induced by dihydrostilbestrol was studied. Administration of female sex hormone led to the development of hyperplasia and tumors in 95% of cases (in 76 of 80 mice), in 5% of cases the tumors being of the cystadenocarcinoma and adenocarcinoma type. When testosterone was given prophylactically or castration carried out no tumors developed, and the incidence of precancerous diseases fell to 48.3% (in 15 of 31 mice) when testosterone was used and to 45.4% (in 20 of 44 animals) in the case of preliminary castration.

All changes in the hormonal state of the animals following administration of the various inducing factors were similar in type, and consisted of an increase in the secretion of follicle-stimulating hormone (FSH) and of estrogens. Constant illumination, for instance, the effect of which was probably mediated through the hypothalamus, led to an increase in FSH secretion (the weight of the uterus of infantile mice following injection of extract of pituitary glands taken from animals with dyshormonal diseases 75.07 ± 1.11 mg, in intact mice 19.6 ± 0.11 mg) which, in turn, led to an increase in the secretion of estrogens by the ovaries and, via ACTH, by the adrenals (weight of uterus of infantile mice following injection of estrogens obtained from animals with dyshormonal diseases 74.6 ± 1.91 mg, in intact mice 14.3 ± 1.64 mg). Following administration of dihydrostilbestrol the concentration of estrogens in the body was increased (weight of uterus of infantile mice following injection of estrogens 69.9 ± 0.82 mg). The secretion of FSH was increased simultaneously (weight of uterus of infantile mice after injection of pituitary extract 81.3 ± 0.42 mg), probably on account of the effect of progesterone and luteinizing hormone [2]. In the case of DMBA, besides its local action, this carcinogen also affected pituitary function and increased the secretion of gonadotropins (weight of uterus of infantile mice following injection of pituitary extract 65.1 ± 0.17 mg), and this in turn stimulated production of estrogens by the experimental animals (weight of uterus of infantile mice after injection of extracted estrogens 58.5 ± 0.22 mg).

These results show that at a certain stage of development of the neoplasm in the mammary gland, changes in the endocrine system became identical in type, i.e., the concentration of FSH and estrogens was increased. A prolonged increase in the secretion of FSH and estrogens leads to the development of proliferative changes in the mammary glands [2, 3].

Administration of testosterone in conjunction with constant illumination, with injection of carcinogens, or with saturation of the body with female sex hormones also led to basically identical changes in the hormonal balance: secretion of FSH was sharply reduced, whereas the concentration of estrogens reached twice its usual level. The increase in concentration of estrogens following administration of testosterone to animals under constant illumination (weight of uterus of infantile mice following injection of estrogens 39 ± 0.61 mg) can be explained by the conversion of testosterone into estrogens [7]. The increase in the concentration of estrogens after administration of DMBA and testosterone (weight of uterus of infantile mice following injection of estrogens isolated from urine 37.8 ± 0.09 mg) is attributed mainly to conversion of the androgen into female sex hormone, for no characteristic changes indicating the possibility of an increase in the secretion of folliculin were present in the ovaries (large numbers of small follicles and corpora lutea of the usual size were present). Following simultaneous administration of dihydrostilbestrol and testosterone, the prophylactic effect can be explained by an increase in the concentration of estrogens (weight of uterus of infan-

tile mice after injection of estrogens 30.2 ± 0.47 mg) on account of their possible hyperproduction by the adrenals and, probably, through conversion of androgen into estrogens.

Castration, like testosterone prophylaxis, led to inhibition of FSH secretion with a simultaneous increase in the concentration of estrogens (weight of uterus of infantile mice following injection of estrogens in different groups of experiments from 29.4 ± 1.16 mg in the case of administration of dihydrostilbestrol and of ovariectomy to 35.5 ± 0.55 mg following illumination and castration). The increase in secretion of female sex hormones probably took place on account of its hyperproduction by the adrenal cortex. Evidence in support of the adrenal origin of the estrogens was given by the increase in weight of the adrenals (weight of organ increased to 9.3 ±0.92 mg following illumination and castration and to 10.6 ±0.44 mg following administration of dihydrostilbestrol and ovariectomy; weight of organ in intact animals 7 ±0.12 mg).

Consequently, following administration of testosterone and ovariectomy, the insufficiently high FSH production and the increased concentration of estrogens inhibit the development of proliferative changes in the mammary glands and they thus play a prophylactic role in the development of tumors of this organ [2, 3]. Hence, despite different methods used for the induction (constant illumination, dimethylbenzanthracene, dihydrostilbestrol) and prophylaxis (testosterone, ovariectomy) of tumors of the mammary glands, the changes in the endocrine system were similar in character and consisted of changes in the secretion and concentration of FSH and estrogens.

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