THE ROLE OF THE PITUITARY HORMONES IN HYPERPLASIA OF THE MAMMARY GLANDS

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There is no doubt that pituitary hormones play a direct part in the hyperplasia of the mammary glands because administration of estrogens to hypophysectomized animals does not cause hyperplasia [10, 13, 15, and others]. According to the most widely held opinion, one of the pituitary hormones, namely prolactin, is essential for the development of hyperplasia. In fact, in rats, following removal of the pituitary, gonads, and adrenals, hyperplasia may be induced by the combined administration of estrogen, progesterone, growth hormone, and prolactin [15]. In the same experimental model, however, hyperplasia may be obtained if the prolactin (and the growth hormone) in the "tetrad" is replaced by insulin [6, 7]. Moreover, after hypophysectomy, estrogens acquire the property of stimulation of growth of the follicles in the ovaries [18, 19], and it is quite possible that in hypophysectomized animals the principles of regulation of hyperplasia of the mammary glands may be severely deranged. Finally, in the course of lactation, when the prolactin level is elevated [12], a sharp decrease is observed in the mitotic coefficient in the epithelium of the mammary glands [2], which is incompatible with their hyperplasia.

Meanwhile, in several investigations, hyperplasia of the mammary glands has occurred as a result of the administration of gonadotropic hormones [16 and others]. In pregnant animals, in which marked hyperplasia of the mammary glands is observed, the level of the gonadotropic hormones, but not of prolactin, is considerably elevated [12].

Furth and co-workers [9] consider that hyperplasia of the mammary glands is due to a specific mammotropic hormone of the pituitary. This view is not in agreement with the facts described, and has justifiably been criticized.

Hence, there is as yet no generally accepted hypothesis regarding what pituitary hormones play an essential part in the hyperplasia of the mammary glands. The present research is devoted to the study of this problem.

In this research we used an experimental model developed in our laboratory by T. G. Khaleeva [5]. According to Khaleeva, the mammary glands of rats (young immature animals) aged from 5 to 30 days, like the glands of hypophysectomized animals, do not react by hyperplasia to the action of estrogens, but neither do they react by hyperplasia to the action of a suspension of pituitary tissue alone, although the combined action of estrogens and of a pituitary suspension under identical conditions regularly causes marked hyperplasia of the mammary glands.

These findings (demonstrating that two components are essential for this reaction) made it appear likely that, by creating a constant level of estrogens and administering different pituitary hormones, we should be able to discover which pituitary hormones are concerned in producing hyperplasia.

EXPERIMENTAL METHOD AND RESULTS

Experiments were conducted on 262 female rats aged 9-10 days. In control groups (controls from the same litter) young rats received injections of either a suspension of pituitary tissue [1] (ox or rat), or of one of the following hormonal preparations: prolactin, chorionic gonadotropin, or serum from pregnant mares (PMS), possessing a gonadotropic (especially a follicle-stimulating) action. The rats in the experimental groups received daily injections of 50 μg of synestrol suspension in conjunction with one of the hormonal preparations or with pituitary suspension. Twenty days later, the animals were sacrificed, and the state of the mammary glands was studied; some of the glands were impregnated with hydrogen sulfide [4], and from others, total preparations were made. No treatment whatever was given to 19 rats from different litters. As might have been expected, their mammary glands remained in a rudimentary state throughout this period.

Reaction of the Mammary Glands of Young Female Rats to Administration of Hormonal Preparations

Preparation	Daily dose	No. of animals at end of experiment	Hyperplasia of mammary glands	Preparation	Daily dose	No. of animals at end of experiment	Hyperplasia of mammary glands
Control	–	19	–	PUPW	0.1-0.2 mg		
Synestrol	50 μg	33	–	+ synestrol	50 μg	13	+++
Ox pituitary	3-50 mg	14	–	Chorionic			
Prolactin	1-4 units	14	–	gonadotropin +	50-150 i.u.	20	+++
Ox pituitary +	3-50 mg	15	–	synestrol	50 μg		
synestrol	50 μg			PMS	36 i.u.		
				+ synestrol	50 μg	8	+++
Prolactin +	1-4 units			Hypophysis ♂♂	3 mg	9	–
synestrol	50 μg	15	–	Hypophysis ♀♀	3 mg	10	–
				Hypophysis ♂♂	3 mg		
PUPW	0.1-0.2 mg	8	–	+ synestrol	50 μg	14	+++
Chorionic				Hypophysis ♀♀	3 mg	12	±*
gonadotropin	50-150 i.u.	20	–	+ synestrol	50 μg		
PMS	36 i.u.	9	+++	Hypophysis ♀♀	15 mg		
				+ synestrol	50 μg	9	+++

*Ill defined hyperplasia (see figure, F) observed in only 5 of 12 females.

In order to elucidate the role of prolactin, in the first place we studied the possibility of producing hyperplasia of the mammary glands of young rats with synestrol in conjunction with rat's pituitary tissue [5] or with ox pituitary tissue, which is especially rich in prolactin [8]. At the same time we studied the possibility of causing hyperplasia with estrogen in conjunction with prolactin purified by the method of the All-Union Institute of Experimental Endocrinology, for this hormone was used in the experiments of Lyons and co-workers on hypophysectomized animals [13]. In this way we attempted to compare the results of our experiments with the results obtained on the other model.

Altogether in this experiment we used 106 young rats, of which 16 received synestrol, 30 received ox pituitary tissue in doses of 3-50 mg, 16 prolactin in doses of 1, 2, and 4 units, 28 a suspension of ox pituitary in conjunction with synestrol, and 16 received prolactin in conjunction with synestrol.

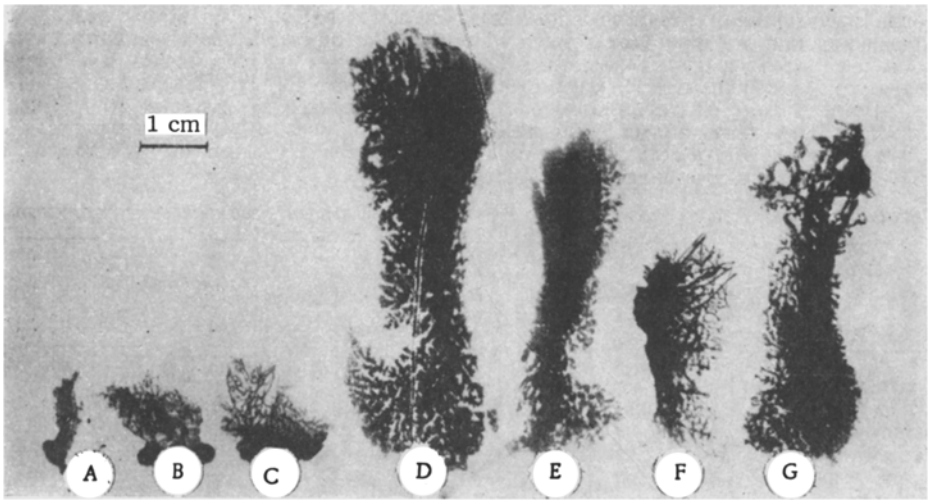
In all the animals the mammary glands remained in a rudimentary condition (see table and figure, A, B, C). Hence, in contrast to the rat's pituitary, which consistently caused hyperplasia in young female rats in a dose of as little as 3 mg, ox pituitary in doses from 3 to 50 mg did not produce hyperplasia. When large doses of a suspension of ox pituitary were injected, inflammatory granulomas appeared at the site of injection, and these may have prevented absorption of the hormones. Yet, even the administration of purified prolactin in a dose of 4 units (corresponding in activity to approximately 2400 mg of ox pituitary) in conjunction with synestrol did not cause hyperplasia. These results do not support the view that prolactin is of decisive importance in the hyperplasia of the mammary glands.

In the next experiment we studied the role of the gonadotropic hormones in hyperplasia of the mammary glands of young female rats.

This experiment was conducted on 102 females, in the same conditions. Synestrol was injected into 12 rats, chorionic gonadotropin in doses of 50-150 i.u. into 24 rats, water-soluble gonadotropic residue of the urinary proteins of pregnant women (PUPW), less purified than chorionic gonadotropin, in doses of 0.1 and 0.2 mg – 12 rats, PMS – 9 rats, and in conjunction with synestrol, chorionic gonadotropin – 23 rats, PUPW – 13, and PMS – 9 rats.

Investigation of the mammary glands showed that administration of synestrol alone, as also of chorionic gonadotropin or PUPW alone, in no case caused hyperplasia of the mammary glands, whereas the simultaneous injection of synestrol and these preparations in different doses caused marked hyperplasia (see figure, D). The administration of PMS alone caused hyperplasia, but this preparation is known to contain estrogens also [20]; consequently, it also contains the combination of estrogens and gonadotropic hormones necessary to give rise to hyperplasia.

The results of the two experiments we have described demonstrate that hyperplasia of the mammary glands in young rats is determined by a combination of the action of estrogens and gonadotropic hormones, but not of prolactin.



Inguinal mammary glands of female rats on the 30th day of life. A) From an intact female; B) after injection of 50 μg synestrol; C) after injection of 50 μg synestrol and 4 units prolactin; D) after injection of 50 μg synestrol and 100 i.u. chorionic gonadotropin; E) after injection of 50 μg synestrol and 3 mg pituitary from a male rat; F) after injection of 50 μg synestrol and 3 mg pituitary from a female rat; G) after injection of 50 μg synestrol and 15 mg pituitary from a female rat.

However, two gonadotropic hormones are known – follicle-stimulating (FSH) and luteinizing (LH) hormones. The question arises, do both these hormones play a part in the development of hyperplasia or only one of them?

The pituitary of the sexually mature male rat is known to contain approximately five times more FSH than the pituitary of the female rat [14], but much less LH [11]. If, as we have suggested, only one of these hormones is concerned in hyperplasia, then as a result of the use of equal amounts of the pituitaries from male and female rats in identical experimental conditions the degree of hyperplasia of the mammary glands must differ. A preliminary investigation showed that hyperplasia developed regularly in response to the daily administration of a suspension of 3 mg of a mixture of tissue from male and female pituitaries in equal proportions. On the basis of these results an experiment was carried out on 54 young female rats, of which 19 were given pituitary tissue from a male or a female only, while 35 received simultaneously synestrol and a suspension of different amounts of tissue from male or female pituitary.

These experiments showed that in response to the simultaneous injection of synestrol and 3 mg of male pituitary, marked hyperplasia developed regularly (see figure, E), but as a result of injection of 3 mg of female pituitary with synestrol, in 7 rats no hyperplasia developed whatever, and in 5 rats it was only slight (see figure, F).

These results were sufficient to indicate the existence of a clear correlation between hyperplasia and the concentration of FSH, but not of LH. However, a still clearer correlation was revealed by the following experiment, in which the daily dose of female pituitary tissue was increased five-fold, i.e., to 15 mg, which corresponds approximately in its content of FSH to 3 mg of male pituitary. In this experiment hyperplasia was observed in all the young rats, corresponding to the hyperplasia caused by the male pituitary (see figure, G). This demonstrates that FSH plays the decisive role in the development of hyperplasia of the mammary glands of young female rats.

These results make it easier to understand several paradoxical results of hormone therapy, and, in particular, the successful estrogen therapy of carcinoma of the breast [3]. The paradoxical nature of these results is shown by the fact that administration of estrogens leads to hyperplasia of the mammary gland tissue, and may actually cause carcinoma of the mammary glands to develop. We have shown that hyperplasia of the mammary glands is, in fact, caused by the simultaneous action of estrogens and FSH. Estrogens are known to depress the follicle-stimulating function of the pituitary. These considerations lead us to suppose that the mechanism of the anti-tumor action of estrogens is by suppression of the follicle-stimulating function of the pituitary; it is this mechanism which lies at the basis of the new possibilities of hormone therapy of carcinoma of the mammary glands.

SUMMARY

Combined administration of estrogens and prolactin did not induce any hyperplasia of the mammary glands of female suckling rats. However, combined administration of estrogens and gonadotropic hormones regularly caused a marked hyperplasia of the mammary glands. The extent of hyperplasia was connected with the amount of follicle-stimulating hormone administered, but did not depend upon the dose of the luteinizing hormone given; this points to the decisive role played by the follicle-stimulating hormone in the mammary gland hyperplasia occurring in female suckling rats.

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