Mammogenesis in Ovary-Thyro-Parathyroidectomized Rats.* (25586)

R. VON BERSWORDT-WALLRABE† AND C. W. TURNER
(With technical assistance of Mary E. Powell)
Dept. of Dairy Husbandry, College of Agriculture, University of Missouri, Columbia

Little is known concerning role of parathyroid glands in mammary gland growth. In our studies concerning the role of various hormones on mammogenesis, levels of estradiol benzoate (EB) and progesterone (P) were indicated which stimulated lobule-alveolar growth (as measured by total DNA) equal to that observed at the end of pregnancy, when given daily for 19 days to ovariectomized (OE) rats(1). The present experiment was undertaken to determine the effects of absence of parathyroid hormone upon mammogenesis.

Materials and methods. Sprague-Dawley-Rolfsmeyer rats were OE on day 1 of experiment and thyro-parathyroidectomized (TPE) on day 7. One group was injected daily with 2 μg EB plus 6 mg P, a second group received additional 3 μg l-thyroxine (T4)/100 g body weight (BW) from day 15 through day 33. Animals were sacrificed on day 34, 24 hours after 19th injection. Control animals were operated in the same way but not injected with hormones. All animals were injected with 1 μc I^{131} on day 31 or 32. Forty-eight hours later I^{131} uptake was checked in 3 regions: neck, body (abdomen) and bladder. Animals which showed a higher uptake in the neck region than in the body were excluded from the experiment under the assumption that removal of thyroid tissue was incomplete. Animals were killed with ether, pituitaries and the 6 posterior mammary glands removed rapidly. Processing of mammary tissue was conducted as previously described(1,2). Lobule-alveolar development was checked in whole mounts of glands.

Results. The OTPE group at levels of 2 μg EB plus 6 mg P showed mammary development (as measured by total DNA content of the 6 abdominal mammary glands/100 g body weight (BW)) equal to that of OE group. Due to significantly reduced amount of dry, fat-free tissue (DFFT)/100 g BW there was no further increase of total DNA when 3 μg T4/100 g BW were given to replace the thyroid gland, although DNA/mg DFFT was significantly increased.

Wet weight of pituitaries/100 g BW increased markedly under the influence of ovarian hormones. T4 reduced this hyperplasia but increase was still significant in relation to controls.

Completeness of thyroidectomy was shown by minimal I^{131} uptake at 48 hours. Completeness of parathyroidectomy was not determined.

Mammary glands of control animals showed duct development, whereas rats receiving ovarian hormones exhibited lobule-alveolar development. The fatty pads in which mammary glands grow were well developed in all groups except those given T4.

Discussion. Data presented are first quantitative evidence that complete mammogenesis can be induced experimentally with adequate levels of ovarian hormones in OTPE rats, confirming previous studies based on qualitative data(3). However, this observation was unexpected since T4 deficiency was expected to depress mammary gland growth. These data suggest the possibility of higher levels of ovarian hormones replacing thyroid and parathyroid hormone deficiencies. It was shown that 3 μg T4/100 g BW increased total DNA of mammary glands of OE rats when given in addition to same amounts of ovarian hormones (2). Furthermore, in pregnant rats, DNA was increased when 2.5 and 3.5 μg T4/100 g BW were injected daily. (Unpublished data).

In the present experiment, however, addition of 3 μg T4 did not increase total DNA of mammary glands of OTPE rats given ovarian hormones compared to OE rats. Since the

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† Research Fellow, Dept. of Animal Physiology and Animal Nutrition, Univ. of Goettingen, West Germany, and Medical Fellow of Population Council.

TABLE I. Experimental Mammogenesis in Ovary-Thyro-Parathyroidectomized Rat.

Daily treatment from Day 15-33	No. of rats	Body wt Day 1 (g)	Body wt Day 34 (g)	Gain, %	Pituitary Wet wt, 100 g BW, mg	48 hr uptake of I^{131}, neck, %	6 posterior mammary glands DFFT Total, 100 g BW, mg	DFFT Total, mg DFFT, µg DNA	DNA Total, 100 g BW, mg
Controls* OE	15	263	274				359	131	23	8.3	3.1 ±.1
OTPE	17	214	240	13.5 ±2.4	5.3 ±.21	1.3 ±.1 [4]	376	153 ± 9[7]	22 ± 1[10]	8.0	3.2 ±.1[13]
2 µg EB + 6 mg P* OE	12	270	272				593	218	37	22.1	8.1 ±.4[14]
OTPE	37	228	257	12.6 ± .8	7.7 ±.22	1.1 ±.1 [5]	589	229 ± 7[8]	36 ± 1[11]	21.0	8.1 ±.2[15]
Idem + 3 µg T4/100 g BW* OE	35	254	257				663	258	38	25.5	9.9 ±.3[16]
OTPE	33	228	254	11.0 ± .8	6.2 ±.23	.2 ±.03[6]	518	204 ± 5[9]	41 ± 1[12]	21.0	8.3 ±.2[17]

* Data from (2). BW = Body wt. DFFT = Dry, fat-free tissue. EB = Estradiol benzoate. OE = Ovariectomized. OTPE = Ovary-thyro-parathyroidectomized. P = Progesterone. T4 = Thyroxine.

Student's "t" Probability

1–2	10–11, 12	1–3	.001 < p < .005	
2–3	11–12	14–16		
4–6	<.001	8–9	.005 < p < .01	
5–6	13–15, 17	15–17	.4 < p < .2	
7–8, 9				

difference in the groups is a lack of parathyroid hormone, a need of parathormone under these conditions is indicated.

One observation is noteworthy in regard to effect of 3 µg T4, namely a reduction in DFFT /100 g BW associated with an increase in DNA µg/mg DFFT, in comparison with control animals. While this level of T4 did not affect BW adversely, it might influence mammogenesis adversely reducing DFFT. Lower levels of T4 may restore DFFT to normal.

Summary. Daily administration of 2 µg estradiol benzoate plus 6 mg progesterone to mature ovary-thyro-parathyroidectomized rats for 19 days resulted in mammary gland growth (DNA) comparable to ovariectomized rats receiving same treatment. Replacement therapy with 3 µg thyroxine/100 g BW depressed total DFFT and increased DNA concentration but failed to increase total DNA equal to that of ovariectomized rats so treated. These data suggest that higher levels of ovarian hormones may offset thyro-parathyroid hormone deficiencies. With 3 µg thyroxine/ 100 g BW total DNA of glands did not equal those of ovariectomized group. It is suggested that lack of comparable response may be due either to lack of parathormone or slight excess of thyroxine.

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