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Effect of Graded Levels of Parathyroid Extract and
Calciferol Upon Thyroid Hormone Secretion Rate (TSR)
in Normal Female Rats

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In a previous study in this laboratory, it was reported that a parathyroid extract (PTE) at a level of 30 U.S.P. units/100 g. b.w./day increased thyroid hormone secretion rate (TSR) a significant 21% associated with a slight increase in body weight (1). In the same experiment calciferol at a level of 0.2 ug/100 g. b.w. increased TSR 48% but was accompanied by a dramatic decrease in body weight from 203 to 175 g.

In order to further confirm the evidence of a stimulating effect of these two preparations upon TSR, graded levels were administered.

Materials and Methods

Eighty-eight female rats of the Sprague-Dawley Rolfsmeyer strain were maintained at a temperature of $78 \pm 1^{\circ}\text{F}$ with uniform lighting conditions and fed Purina Lab Chow ad libitum. The first 44 rats were divided into three random groups and their individual TSR's were determined at a weight of about 174 grams. The second 44 rats were also divided into three random groups and their individual TSR's were determined at a weight of about 251 grams.

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Thyroid hormone secretion rate (TSR) was determined by the method described previously by Grosvenor and Turner (2) for each group. The TSR, as estimated by this procedure, will be slightly higher than the actual TSR of the animals, because the final level of thyroxine which blocks the release of thyroidal I^{131} must be in slight excess of the animal's own secretion of the thyroid hormone. Secondly, as the level of thyroxine is increased by 0.25 ug/100 g. b.w. every 48 hours and the dose previous to the final one does not completely block the release of thyroidal I^{131} , the error must be less than 0.25 ug/100 g. b.w. Carrier-free I^{131} was obtained from Nuclear Consultant Corporation, St. Louis, Missouri, and was diluted in distilled water to contain 10 uc/0.2 ml., and administered to rats intraperitoneally. Thyroxine ($L-T_4$) was administered daily; the first administration was 48 hours after that of I^{131} in increments of 0.25 ug/100 g. b.w. The dose of $L-T_4$ which prevented further thyroidal I^{131} output, that is 95 to 100% of the previous count, was estimated as the TSR of the animals. Correction was made for the radioactive decay and background. Twenty-one days after the TSR was determined, the groups (I, II, III) were treated with graded doses of parathyroid extract (PTE) i.e. 20, 30 and 40 U.S.P./100 g. b.w., respectively, and the other groups (IV, V; VI) were treated with graded doses of calciferol i.e. 0.1 mg, 0.15 mg and 0.2 mg/100 g. b.w., respectively. This treatment was started two weeks (14 days) before the start of TSR estimation and continued until the TSR of the animals was estimated. The difference between the TSR of the first and second determination in the same animal was used as an indication of the effects

of these materials (PTE* and calciferol⁺) upon the functional activity of the thyroid gland. When TSR estimations were completed the rats of group IV and VI were then sacrificed and the following glands were removed and weighed: ovaries, uteri, adrenals, thymus, and thyroids. The balance was sensitive to 0.01 mg.

Results

Administration of 20, 30, and 40 U.S.P. units of PTE/100 g. b.w./day for 14 days caused significant ($P < .025$) increases in TSR of 25.4, 35.6, and 54.1%, respectively, over their own controls (Table I). The body weights were increased. Administration of calciferol (Vit. D₂) in doses of 0.1, 0.15 and 0.2 mg/100 g. b.w. caused a nonsignificant reduction in TSR in the first two groups but a significant ($P < .05$) 26.7% increase in TSR and 14.2% decrease in b.w. from their own control in the VI group which was treated with 0.2 mg calciferol/100 g. b.w. A nonsignificant increase in weight of the ovaries, uteri and decrease of thymus glands weight was noticed in the group treated with 0.2 mg calciferol/100 g. b.w. as compared to the 0.1 mg calciferol/100 g. b.w. treated group (Table II). There was a significant increase in thyroid weights ($P < .001$) and adrenal weights ($P < .01$).

Discussion

A definite relationship between Vitamin D and the thyroid gland was reported by Lands and Stoland (3), Nitzesco and Bratiano (4) and Uotila (5). A prolonged and chronic stimulation of thyroid

*Kindly supplied by Eli Lilly and Co., Indianapolis, Indiana

⁺Kindly supplied by Sterling Winthrop Research Institute

glands may produce a condition of hyperthyroxinogenesis. In this condition food utilization and energy liberation are increased. A severe hyperthyroidism is generally characterized by nervousness, increased cardiac output and velocity of the blood flow. Hyperthyroidism can also be induced by administration of an excess dose of thyroxine (6). A relationship between vitamin D and thyroid gland function was reported in the 1930's. Histological studies showed that administration of vitamin D caused hyperplasia of the thyroid gland of the dog (7). Vitamin D and parathyroid hormone are known to have similar action on bone absorption, gastrointestinal transport of calcium (8, 9). Deutsch *et al.* (10) concluded that the calorogenic effect exhibited by the vitamin was via the thyroid gland. Administration of vitamin D to rachitic rat was reported to increase the basal metabolic rate (11). On the other hand, a calorogenic effect was observed when a parathyroid extract was given to dogs (12). It was also reported that parathyroid given to rabbits increased the conversion of glucose and organic acids to CO_2 in bone slices (13). Although no functional relationship between the parathyroid and thyroid glands has been reported, the investigation cited suggest the possible participation of parathyroid extract in the regulation of certain metabolic pathways. When PTE was injected at levels of 20, 30 and 40 U.S.P. units/100 g. b.w. for 14 days, it increased TSR of rats 25, 35 and 54% as compared to their own previous TSR before treatment. When calciferol was injected for 14 days at levels of 0.1, 0.15 and 0.2 mg, TSR was significantly ($P < .05$) increased only in the group which was injected with 0.2 mg calciferol/100 g. b.w. However, decreases in body were

observed. It is expected that the most likely mode of action would involve the increased secretion and discharge of the thyrotropic hormone. However, it is not impossible that these substances may act directly upon the thyroid gland to increase the responsiveness of the glands to a given level of thyrotrophin.

Summary

The effect of graded doses of parathyroid extract and calciferol upon thyroxine secretion rate (TSR) of normal female rats was studied with the aid of radioactive iodine I^{131} . Administration of 20, 30 and 40 U.S.P. units of PTE/100 g. b.w./day for 14 days induced a significant ($P < .025$) increase in TSR of 25.4, 35.6 and 54.1%, respectively, over their own controls associated with slight increase in body weight. Administration of calciferol (Vit. D₂) in doses of 0.1, 0.15 and 0.2 mg/100 g. b.w. induced a nonsignificant reduction in TSR of the first two groups (groups IV & V) but a significant 26.7% ($P < .05$) increase in TSR above their own control in group VI associated with loss of body weight of 14.2% when 0.2 mg calciferol/100 g. b.w. was given daily for the same period. A non-significant increase in weight of ovaries, uteri and a decrease of thymus glands with significant increase in thyroid and adrenal weights was noticed in the group treated with 0.2 mg calciferol/100 g. b.w. as compared to 0.1 mg calciferol/100 g. b.w.

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TABLE I

EFFECT OF GRADED LEVEL OF PARATHYROID EXTRACT AND CALCIFEROL UPON TSR IN INTACT FEMALE RATS

Groups	No. of Rats	Before Treatment		Treatment	After Treatment			
		Body Weight (g)	Mean TSR ⁺ (ug/100 gbw)		Body Weight (g)	Mean TSR ⁺ (ug/100 gbw)	Change in Percent	Probability*
I	21	178	0.67 $\pm$.06	PTE 20 USP Units/100 gbw	212	0.84 $\pm$.05	28.4	<.025
II	14	169	0.59 $\pm$.02	PTE 30 USP Units/100 gbw	188	0.80 $\pm$.08	35.6	<.025
III	9	174	0.61 $\pm$.06	PTE 40 USP Units/100 gbw	197	0.94 $\pm$.12	54.1	<.025
IV	15	244	1.03 $\pm$.07	Calciferol 0.1 mg/100 gbw	240	0.98 $\pm$.02	-4.9	N.S.
V	15	247	1.05 $\pm$.08	Calciferol 0.15 mg/100 gbw	237	1.03 $\pm$.09	-1.9	N.S.
VI	14	261	1.95 $\pm$.07	Calciferol 0.2 mg/100 gbw	224	1.33 $\pm$.15	26.7	<.05

PTE = Parathyroid Extract

TSR = Thyroid Secretion Rate

* = Student "t" test, level of significance of TSR before and after treatment of the same animals

+ = Mean $\pm$ SE

N.S. = Nonsignificant

TABLE II

EFFECT OF CALCIFEROL ON ENDOCRINE GLANDS IN FEMALE RATS

	Calciferol 0.1 mg/100 gbw	Calciferol 0.2 mg/100 gbw	Change %
Number of Rats	15	14	
Mean Body Weight (g)	240	224	
Mean Ovary Weight (mg) +SE	58.20±55.90	60.10± 6.3	3.28
Mean Ovary Weight (mg) Per 100 gbw+SE	24.20± 2.40	26.80± 2.8	10.60
Mean Uterus Weight (mg) +SE	531.00±53.20	687.50±150.0	29.50
Mean Uterus Weight (mg) Per 100 gbw+SE	221.20±22.20	306.90± 70.5	38.70
Mean Adrenal Weight (mg) +SE	51.00± 1.50	56.30± 2.9	10.40
Mean Adrenal Weight (mg) Per 100 gbw+SE	21.30± 0.56	25.10± 1.3	18.20 P< .01
Mean Thymus Weight (mg) +SE	242.10±31.90	211.70± 19.5	-13.60
Mean Thymus Weight (mg) Per 100 gbw+SE	100.20±18.90	93.90± 10.7	- 6.20
Mean Thyroid Weight (mg) +SE	7.91± 0.90	12.97± 0.9	64.00 P< .001
Mean Thyroid Weight (mg) Per 100 gbw+SE	3.29± 0.40	5.80± 0.4	75.60 P< .001

gbw = grams body weight

SE = Standard Error

P = Student "t" test, level of significance