

1949

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Recommended Citation

Shepherd, Ralph H. (1949) "The Effect of Thiouracil on the Golgi Apparatus of the Thyroid Gland in the White Rat," *Proceedings of the Iowa Academy of Science*, 57(1), 505-510.

Available at: <https://scholarworks.uni.edu/pias/vol57/iss1/73>

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The Effect of Thiouracil on the Golgi Apparatus of the Thyroid Gland in the White Rat

By RALPH H. SHEPHERD

INTRODUCTION

Thiouracil, a heterocyclic derivative of thiourea related to pyrimidine, has been found to have certain goitrogenic effects as well as various other bodily effects on laboratory animals treated with the substance. The goitrogenic effects are inhibition of active thyroid hormone formation and a stimulation of gland growth. Inhibition of hormone formation is believed to be due to the combination of thiouracil with iodine (Miller, Roblin, and Astwood, 1945), and, as has been suggested, the drug may act as an antivitamin or antibiotic, since its toxic reactions are similar to those of sulfanilamide, another antivitamin (Laufer and Stewart, 1947). Stimulation of gland growth is a response to excessive secretion of thyrotropic hormone (Mackenzie and Mackenzie, 1943; Astwood et al., 1943). Morphological changes are hypertrophy and hyperplasia of the acinar cells, increased size and weight, loss of follicular colloid, increased height of the acinar epithelium, and marked hyperemia.

Bodily effects include basophilia, appearance of "thyroidectomy" cells in the anterior hypophysis, increased resistance to lowered barometric pressures, reduced B.M.R., inhibition of normal weight gains, slight anemia, and granulocytopenia (Gordon, Goldsmith, and Charipper, 1945). Jones, Seigar, Delfs, and Foote (1946) noted that the drug does not cause sterility in either male or female rats but that if given over a sufficiently long period will cause resorption of embryos in 100 per cent of females. Return of erythrocytes and hemoglobin to normal levels following bleeding in thiouracil treated rats was observed by Gordon, Kadow, Finklestein, and Charipper (1946); retardation both of tooth eruption and of opening of the eyelids was observed in newborn rats by Parmer (1947); involution of the adrenal cortex was found by Zarrow and Money (1949); reduced food and water consumption and increased urine output were observed by Gordon, Goldsmith, and Charipper (1946).

In a study of the effect of alloxan diabetes on the Golgi apparatus and mitochondria of the rat thyroid, Applegarth and Koneff (1946) demonstrated that the Golgi apparatus was greatly reduced and assumed a bar form rather than the normal ring-like appearance. In addition, the Golgi extensions around the cell nucleus were lost.

Mitochondria were reduced in number and were rearranged. These changes in the cytoplasmic inclusions of alloxan diabetes together with the low epithelium, small colloid-filled follicles, and reduced weight, (Bennett and Koneff, 1946), indicate hypofunction. Thiouracil, however, has the opposite effect. It increases the size of the gland and should cause a corresponding enlargement of the Golgi apparatus. The present study was undertaken to determine just how thiouracil influences the Golgi apparatus.

MATERIALS AND METHODS

Both male and female rats, 50 days old and 126.9 grams average weight, were given daily doses of a heavy aqueous suspension of thiouracil at the rate of 20 mg./100 grams of body weight. The suspension was given by mouth with a tuberculin syringe fitted with a 17 gauge needle ground to a blunt end. This method was employed, since it seemed to provide better control over the amount of thiouracil each animal received.

Twenty-six animals were used, 14 of which were experimental animals and 12 of which were control animals. They were weighed at the beginning of treatment and every second day thereafter to adjust thiouracil dosage to weight gains. After three days of thiouracil treatment, a control animal and an experimental animal were weighed and killed with ether. Every second day following this, an experimental animal was sacrificed with a control, excepting the last two rats which lacked controls. Thus, a series of animals whose period of treatment ranged from 3 to 29 days was utilized.

As soon as the animal was killed, the thyroid was removed, cleaned of connective tissue, weighed on an analytic balance, and fixed with Aoyama's fixing fluid (cadmium chloride, 1 gm.; neutral formalin, 85 cc.). Following fixation, the glands were quickly rinsed in distilled water, impregnated with 1.5 per cent silver nitrate for 10-15 hours, and transferred to the following solution:

hydroquinone	1.0 gm.
neutral formalin	15.0 cc.
distilled water	85.0 cc.
sodium sulfite	0.1 gm.

After 5-10 hours in this solution, the material was rinsed in tap water and upgraded to absolute alcohol, cleared in xylol, and embedded in paraffin under 25-30 inches vacuum. The glands were sectioned at 8 micra and affixed to slides in the usual manner. Sections were mounted in balsam and examined under 1.8 mm. oil immersion lens. Additional slides were toned in gold chloride,

according to Mohr's method (1943), stained in brazilian, and counterstained in methyl blue. However, Mohr's method was unnecessary, inasmuch as Aoyama's original technique was sufficient.

RESULTS

Up to the thirteenth day weight gains of experimental animals ranged from 1.1 gram to 10.2 grams greater than control gains. From 13 through 23 days the control animals showed 2.0 to 16.5 grams greater gain than the experimental animals. The thiouracil treated animal sacrificed at 25 days showed a gain of 44.3 grams over its control (Table 1).

Table 1
Animal Weight Gains

Group	Experimental	Control	Difference	Treatment
	grams	grams	grams	days
1	18.0	9.0	9.0	3
2	22.4	13.4	9.0	5
3	19.6	9.4	10.2	7
4	21.3	20.2	1.1	9
5	32.0	30.6	1.4	11
6	17.3	24.4	7.0	13
7	27.1	29.4	2.3	15
8	30.5	32.5	2.0	17
9	69.7	74.7	5.0	19
10	24.5	41.0	16.5	21
11	26.8	34.7	7.9	23
12	79.6	35.3	44.3	25
13	53.0	—	—	27
14	50.5	—	—	29

Thyroid weights, figured in milligrams per gram of body weight, ranged consistently higher for experimental animals throughout the investigation (Table 2). In gross appearance the thyroids of experimental animals were marked by their darker color and by increased vascularity. Histologically the glands showed the usual changes associated with thiouracil administration: namely, gradually increasing height and papillar folding of the epithelium, loss of follicular colloid, hyperemia, and hypertrophy.

In the normal rat thyroid glands, as described by Applegarth and Koneff (1946) and revealed in the thyroids of control animals in this investigation, the Golgi apparatus occupies the area between the nucleus, which lies at the base of the cell, and the lumen of the follicle. The net is a more or less elaborate ring with extensive arborizations and with delicate extensions over the nucleus.

Table 2

Group	Thyroid Weights in Mg./Gm. Body Weight			Treatment days
	Experimental mg.	Control mg.	Difference mg.	
1	.151	.109	.042	3
2	.097	.094	.003	5
3	.173	.122	.051	7
4	.115	.111	.004	9
5	.113	.122	.011	11
6	.160	.131	.029	13
7	.161	.127	.034	15
8	.220	.157	.063	17
9	.199	.128	.071	19
10	.207	.165	.042	21
11	.188	.157	.031	23
12	.192	.131	.061	25
13	.191	—	—	27
14	.108	—	—	29

Examination of approximately ninety sections from each thyroid gland revealed that in 72 hours a response of the Golgi net was apparent in the thyroids from treated animals. The net became larger and more diffuse, and the number of extensions over the nucleus increased. These changes became more pronounced with the longer administration of thiouracil.

DISCUSSION

Inasmuch as it is generally thought that the Golgi apparatus is concerned in the process of secretion, any increase in Golgi apparatus size should reflect greater secretion. Therefore, it seems logical to assume that the increase in size of the Golgi apparatus in the thyroids of thiouracil treated rats is indicative of hyperfunction, just as Applegarth and Koneff concluded that reduction in the size of the apparatus and mitochondrial changes in alloxan diabetes are indicative of hypofunction. This conclusion is supported by the work of Thomas (1944) with thiourea. He found that there was an increase in basal colloid (using the method of Bensley, 1916) following thiourea administration.

Grasso (1946), drawing from his own work and that of others, notes that there is an initial diminution of follicular colloid as a result of reabsorption, followed by an increase over normal amounts after prolonged treatment with thiourea. In his own words:

... thiourea acts on the thyroid by inhibiting the process of iodination, but it does not affect the synthesis of the protein group which is biolog-

ically inactive. The lack of thyroxine stimulates the output of thyrotropic hormone from the pituitary gland, thus inducing all the biological and cytological changes found in the thyroid. Under this action the gland is really secreting in excess but the product of secretion has less hormonal activity.

Severinghaus (1933) claims that the numbers of mitochondria are connected with alterations in the amount of hormone transported across the cell. If future work reveals that the numbers of mitochondria indicate at first a diminished amount, followed in time by an increased amount of hormone passed into the follicle, it would appear to offer some confirmation of Grasso's conclusions when coupled with the appearance of the Golgi apparatus. Briefly, then, there may be a greater amount of colloid formed in thiouracil treated thyroids than in normal glands, but the colloid lacks the thyroxin necessary to make it biologically active.

SUMMARY

Both male and female rats, 50 days old, were treated for varying lengths of time up to 29 days with thiouracil at 20 mg./100 grams of body weight. It was found that the Golgi apparatus of the thyroid glands increased in size and complexity. This was interpreted as indicating increased secretory activity of the cells.

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