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Anatomic and Physiologic Effects of the Antithyroid Drug, Propylthiouracil, on Rats

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Abstract. Administration of the antithyroid drug, propylthiouracil (PTU), to albino male rats at the dietary level of 0.1% PTU is accompanied by a decrease in growth rate and a decrease in the oxygen consumption rate. After the initial administration of PTU, prolonged treatment with the drug did not further lower the oxygen consumption rate. The ratios of organ weight to body weight for the testes, stomach, thyroid, eyes, pituitary, and brain were found to be larger in the treated rats than in the untreated controls. The organ weight to body weight ratios of the spleen, liver, kidneys, and heart were smaller in the PTU treated rats than in the untreated controls examined.

Propylthiouracil is known to affect various aspects of metabolism such as lowering the rate of oxygen consumption and lowering the rate of increase of weight in young rats (Cook 1962).

It has also been found that PTU treatment increases the ratio of organ weight to body weight of various organs including the thyroid, eye, and testes (Fregly and Hood, 1959). PTU treatment has been found to decrease the ratio of organ weight to body weight in the case of the heart and the kidneys (Fregly and Hood, 1959).

The experiments reported here were conducted to determine whether prolonged administration of PTU resulted in a further decrease in the oxygen consumption rate, and to study the effects of PTU on the ratio of organ weight to body weight on various organs not previously studied as well as those already studied.

Methods

Two experiments were conducted using albino male rats of the Holtzman strain. All the animals were kept in separate cages in a thermoregulated room maintained at 25±2°C. and were subjected to approximately nine hours of illumination per day.

Experiment I

Thirteen rats, age 31 days at the beginning of the experiment, were used. All animals were given Purina laboratory checkers and tap water for a period of one month. The weight of each animal was recorded frequently throughout this period, and at the end of the period oxygen consumption measurements in cc/100 gms. body weight/hour were recorded for each animal. The procedure outlined in *D'Amour and Blood* (1954) was used for the oxygen consumption determinations. The animals were then separated into two groups. One group, containing six animals, remained on the same diet and a second group was subjected to the same envir-

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onmental conditions, but placed on a diet of 0.1% PTU mixed thoroughly in finely ground Purina laboratory meal as a substitute for the Purina laboratory checkers.

After 10 days oxygen consumption determinations on all animals were made and recorded in the same manner as before. Five months after the administration of PTU oxygen consumption rates were again determined on a few rats from both groups.

Experiment II

After a three month period of exposure to PTU, four rats from the normal control group were sacrificed by chloroform inhalation. The testes, adrenals, spleen, kidneys, liver, stomach (emptied of contents), thyroid, heart (drained completely of blood), eye balls, pituitary, brain, and gastrocnemius muscle of each animal were removed and carefully trimmed of fat and connective tissue. Each organ was weighted on a Roller-Smith torsion balance or an analytical balance. To establish the water content of each organ, the organs were dried at 100 C. to a constant weight and the dry weights established with an analytical balance.

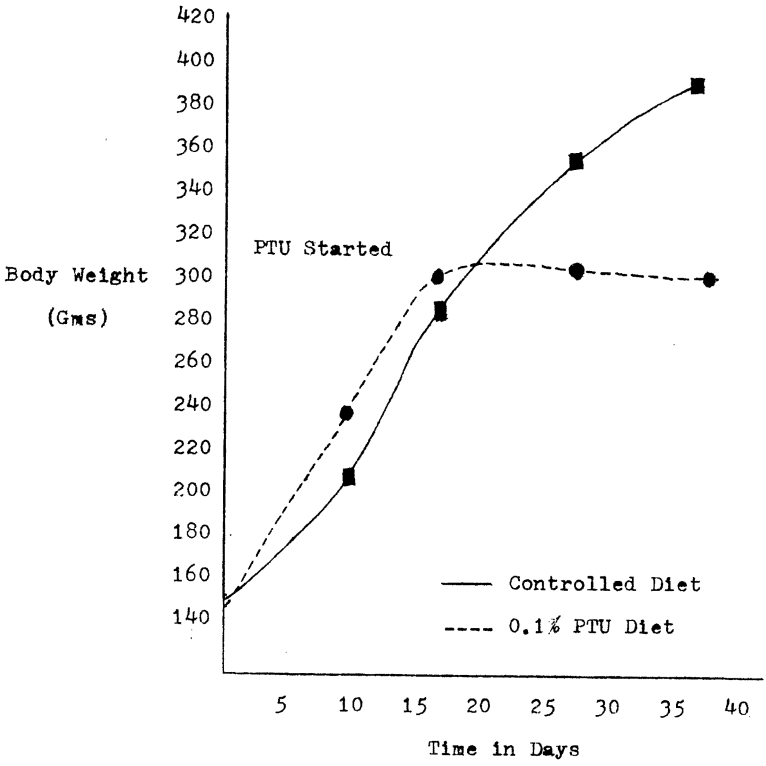

Figure 1. Effect of PTU on body weight

Results

Experiment I

The animals treated with PTU showed almost no gain in body weight while the normal animals showed a steady increase as shown in Figure 1.

After treatment with PTU for a period of 10 days, the animals showed a marked decrease in oxygen consumption rate; however, prolonged treatment with PTU caused no further decrease in the rate of oxygen consumption, but rather an increase. The normal animals of the control group showed a uniform level of oxygen consumption rate throughout the period. These data are shown in Figure 2.

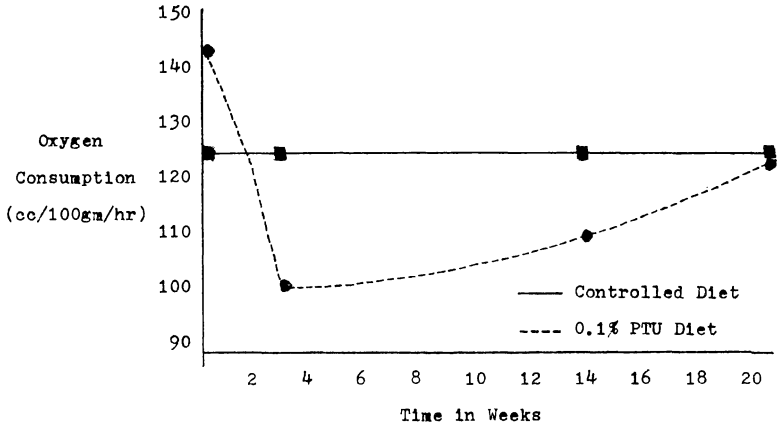

Figure 2. Effect of PTU on the rate of oxygen consumption

Experiment II

The water content of the organs examined was not affected by PTU treatment except in the case of the thyroid gland (Table I). The ratios of the organ weight to body weight for various

Table 1

Effect of PTU on the water content of various organs

	% Water					
Treatment	Testes	Spleen	Adrenals	Kidneys	Liver	Stomach
Control	85.4	77.1	55.9	78.5	74.0	74.2
PTU-treated	86.7	76.8	56.8	78.1	72.2	75.8

	% Water						
	Thyroid	Thymus	Heart	Eyes	Pituitary	Brain	Gastroc-nemius
Control	59.4	76.3	77.6	77.4	72.5	70.7	73.5
PTU-treated	81.5	75.8	77.8	74.0	78.5	78.1	75.2

Table 2

Effect of PTU on the organ weight to body weight ratio of certain organs

	organ wt./body wt. ratio (mg./100 gm.)						
Treatment	Testes	Spleen	Adrenals	Kidneys	Liver	Stomach	
Control	770	178	11	751	4140	335	
PTU-terated	1185	127	13	702	3511	523	
	organ wt./body wt. ratio (mg./100 gm.)						
	Thyroid	Thymus	Heart	Eyes	Pituitary	Brain	Gastroc-nemius
Control	4.4	37	281	59	2.8	386	488
PTU-treated	48.0	40	268	87	4.0	550	504

organs were, however, affected by PTU treatment as can be seen in Tables II and III.

Despite the higher content of water, there was considerable tissue enlargement in the case of the thyroid gland in the animals on the PTU diet. These animals also showed a significant enlargement of the testes, stomach, and brain. The spleen, the pituitary, and the adrenals also showed an increase of organ weight to body weight ratio.

The liver showed a reduction in its organ weight to body weight ratio in the PTU-treated animals. A slight decrease was indicated for the kidney weight to body weight ratio in the animals exposed to PTU.

The PTU appeared to produce no significant change in the thymus weight to body weight ratio and the gastrocnemius muscle weight to body weight ratio.

Discussion

Administration of the antithyroid drug, propylthiouracil, to young male rats retarded the increase in body weight and decreased the rate of oxygen consumption. Prolonged exposure to PTU tended to produce an increase in the lowered oxygen consumption rate; however, after an exposure period of 5 months the oxygen consumption rate was still below the rate determined for the animals before administration of PTU. This finding suggests that the enlargement of the thyroid gland may have partially compensated for the antithyroid effects of PTU. Further experiments need to be carried out to verify the results because the sample used in the present study was small.

It is believed that the hypotensive effect of PTU shown in other studies is a result of thyroid hypofunction (Fregly and Cook, 1960). The large increase in the thyroid weight ratio and the

Table 3

Organ weight to body weight ratio of certain organs of the animals tested

	CONTROL GROUP				EXPERIMENTAL GROUP			
	Rat #3	Rat #4	Rat #7	Rat #8	Rat #2	Rat #9	Rat #10	Rat #11
Testes	835	695	663	889	1175	1204	1171	1191
Adrenals	13	11	6	14	22	13	13	14
Spleen	212	163	173	163	81	128	148	123
Kidneys	777	720	773	734	671	758	677	701
Liver	4538	3779	4491	3751	3405	3731	3287	3619
Stomach	324	342	369	316	676	479	474	463
Thyroid	5.5	4.4	2.0	5.5	40	46	60	48
Thymus	43	30	40	68	154	49	43	28
Heart	298	280	242	304	250	289	271	262
Eyes	62	55	54	64	87	86	88	88
Pituitary	2.9	2.9	2.5	3.1	4.0	5.0	3.7	3.4
Brain	433	350	347	424	517	523	554	605
Gastrocnemius	636	273	320	725	522	561	584	349

All values are in mg./100 grams of body weight

pituitary weight ratio increase found to occur with administration of PTU in this experiment suggests interference with the production or use of thyroxin by PTU and compensatory enlargement.

The possibility that the decreased metabolic rate is due to hypoadrenalism must be considered. Recent studies (Fregly and Hood, 1959) and (Fregly and Cook, 1960) showed that PTU treatment increased adrenal size and that the increase in thymus weight to body weight ratio, which accompanies hypoadrenalism, didn't occur. The findings of this experiment concur with the aforementioned results supporting the idea that PTU doesn't cause hypoadrenalinism.

The increase in testes weight ratio with PTU treatment has been suggested to indicate a relationship between the thyroid and the testes (Fregly and Hood, 1959); however, the significance of this change is not known. Since the kidney weight to body weight ratio is decreased, the increase in testes size is probably not accompanied by an increase in testosterone.

A significant increase in eye weight to body weight was found to occur with PTU treatment. Upon examination of the data it was found that the eyeballs of both the control and experimental groups are about the same size. This suggests that the eyeballs grow at a normal rate despite the lower metabolic rate (Fregly and Hood, 1959).

There was found to be a significant reduction in liver weight to body weight ratio in the PTU-treated animals, which probably resulted from the lowered metabolic rate since the liver functions in connection with carbohydrate, fat, and protein metabolism. Also the effects of the lower metabolic rate on the circulatory system is shown by the decreased organ to body weight ratios in the liver and spleen which are storehouses for blood, and in the slight reduction of the ratio of heart weight to body weight in the PTU-treated animals.

It is interesting to note that although the PTU-treated animals show a decreased food intake and metabolic rate (Fregly and Hood, 1959) the ratio of stomach weight to body weight is considerably higher in the PTU-treated animals.

The study of the effects of PTU treatment upon the various organs would be enhanced greatly if the oxygen consumption rates of the vairous organs were determined. Such a determination is being planned utilizing the Warburg apparatus.

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