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Effects of the Antithyroid Drug, Propylthiouracil, on Organ Weights, NaCl Intake, and Blood Glucose Levels of Adrenolectomized White Rats

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Effects of the Antithyroid Drug, Propylthiouracil, on Organ Weights, NaCl Intake, and Blood Glucose Levels of Adrenalectomized White Rats[1]

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Abstract. The antithyroid drug, propylthiouracil, results in anatomical changes and increase in NaCl solution intake within one week of treatment. These changes are independent of the adrenal gland. The blood glucose levels are not changed greatly with propylthiouracil treatment.

A recent report indicates that rats treated with a dietary level of 0.1% of the antithyroid drug, propylthiouracil (PTU)[3], prefer 0.15M NaCl to water when a free choice is offered between these solutions (Fregly et al., 1961). It was concluded that the preference for the NaCl was independent of the adrenal glands since animals treated with PTU prior to adrenalectomy exhibited a greater salt intake than those adrenalectomized without PTU treatment. The drug was administered prior to adrenalectomy because if initiated immediately after the operations the animals died within one week. The purpose of the present study was to compare anatomical changes, body growth, food, NaCl and water intakes, and blood glucose levels of animals treated with PTU started prior to adrenalectomy and those treated with PTU initiated at adrenalecomy with animals adrenalectomized but not given PTU at any time.

METHODS

The study was conducted in two parts. In the first experiment 32 male rats of the Holtzmann strain, age 54 days at the beginning of the experiment were used. Animals were kept in individual metabolism cages in a thermoregulated room maintained at 25± 1°C and illuminated from 8:00 AM to 5:00 PM daily. The animals were divided into four groups. The first group of eight animals was fed finely ground Purina Laboratory meal for 14 days, sham-adrenalectomized on the 15th day and continued on the meal diet. The second group of eight animals was fed the laboratory meal for two weeks, adrenalectomized, and kept on the

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Table 1. The effects of propylthiouracil on organ/weight to body/weight ratio of certain organs in Experiment I.

[3] 6-n-propyl-2-thiouracil, Nutritional Biochemical Co., Cleveland, Ohio.

meal. The third group of eight animals was fed 0.1% PTU mixed thoroughly in the ground meal for 14 days, adrenalectomized, and kept on the PTU diet. The fourth group of eight animals was fed regular meal for 14 days, adrenalectomized, and placed on the 0.1% PTU diet. Adrenalectomy was performed by the dorsal approach with ether or a dosage of 50 mg/kilogram of Nembutal as the anesthetic. All animals were given free choice between 0.15M NaCl solutions and distilled water. Habit formation in selection of drinking fluid was avoided by changing the positions of the bottles daily. The types of fluid containers and spill-proof food containers used have been described previously. Daily body weights, food, NaCl, and water fluid intakes were measured individually for all animals. Within a week after the sham or actual adrenalectomy all animals were sacrificed by ether inhalation and autopsied. Testes, heart (drained of blood), kidneys, thymus, thyroid, eyes, brain and pituitary were carefully trimmed of excess fat and connective tissue and weighed on a torsion balance. Livers were blotted and weighed on an analytical balance. Because of evaporation some difficulty was experienced in getting a constant weight. Also blood clots produced variations in weights of the liver. The organ-weight to body-weight ratio of each of the organs was calculated. At autopsy a search was made for evidence of adrenal tissue. None was found except, of course, in the sham-operated rats.

In the second experiment, 28 male rats of the Holtzmann strain, age 54 days at the beginning of the experiment were used. Daily body weights, food, NaCl, and water fluid intakes were measured as in the first experiment. The experimental groups also consisted of the same four as in the first experiment, with the only difference being in the number of animals within the groups. Blood samples were taken, by the use of a calibrated sedimentation tube, from two rats in Group 2, from seven rats in Group 3, and from seven rats in Group 4 on the seventh day before adrenalectomy, and on the fourth day after sham-adrenalectomy from seven animals from Group 1. and on the fourth and sixth days after adrenalectomy from all animals of the other groups with the exception of Group 2. Only two animals were used for blood samples on the sixth day in this group. Animals were deprived of food for 24 hours prior to the taking of the blood sample. Glucose-level measurements were made on a Coleman 14 spectrophotometer, following the technique of Folin and Malmors (1929). Analysis of the blood samples for glucose content was confined to the first week after the operation because of the anticipated death of the animals of Group 4 in which adrenalectomy was not preceded by PTU treatment. However, just one animal of this group died on the seventh day.

Animals were continued on their respective post-operative diets for five days. During this time no additional deaths occurred. At the end of this period NaCl solution was withdrawn from all animals to ascertain the completeness of the adrenalectomy. Completely adrenalectomized animals maintained on Purina laboratory chow do not survive beyond 15 days without supplementary NaCl (Dorfman et al., 1946), (Tosteson et al., 1951). All animals except the sham-operated group, three animals in Group 2 which had an extended period of NaCl intake, and two animals in Group 4 died within five days with the exception of one which died on the ninth day. Severe weight loss was exhibited by all animals prior to death. Data from two animals of Group 4 were discarded due to incomplete adrenalectomy.

Results

Body weights at the beginning of the experiments, just prior to adrenalectomy or sham operation and four days after the operation, are shown in Figure 1.

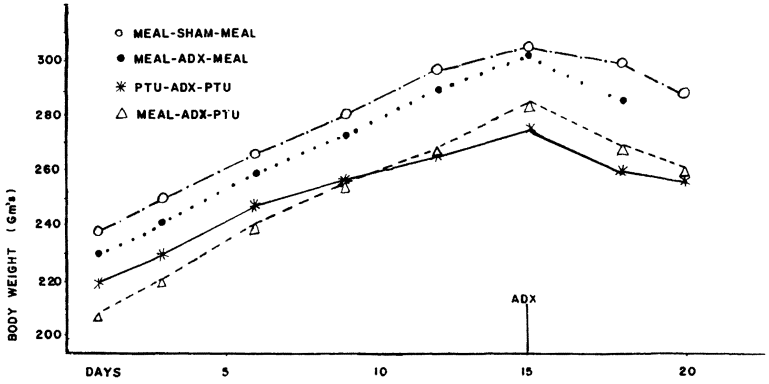

Figure 1. Effect of propylthiouracil (0.1% in diet) on body weight in sham-operated and adrenalectomized rats.

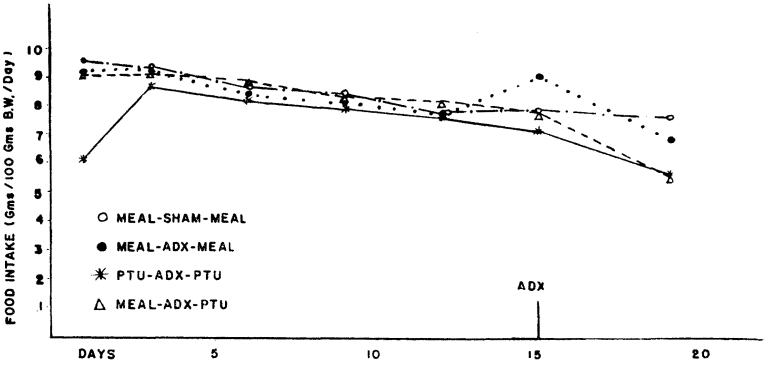

Figure 2. Effect of propylthiouracil (0.1% in diet) on food intake in sham-operated and adrenalectomized rats.

The PTU treatment caused a retardation in the growth rate.

Food consumed / 100 grams of body weight is shown in Figure 2.

The level of food consumption was similar in all groups up until the time of the operation. After the operation Group 1 soon regained its normal level of food consumption with Group 2 slightly below it. The two groups which had been on PTU or had it administered after adrenalectomy showed a much steeper drop in the ratio of food consumed and a decreased intake after the operation.

The organ weight to body weight ratio data is presented in Table 1.

Experimental Group	No. of Rats	Organ Weight to Body Weight (Mg/100 G's Body Weight) Tests	Thyroid	Pituitary	Brain	Eyes
Meal Sham Meal (1)	8	1054.2	7.1	3.4	604.0	73.9
Meal ADX Meal (2)	8	1053.4	7.4	3.1	614.2	79.7
PTU ADX PTU (3)	8	1253.0	21.5	3.9	699.6	91.3
Meal ADX PTU (4)	8	1182.3	10.4	2.9	752.5	90.9

		Kidneys	Heart	Thymus	Liver
1	8	991.4	341.3	162.8	4484.7
2	8	932.8	335.8	209.1	4378.2
3	8	851.1	298.5	135.4	4274.1
4	8	866.3	316.9	185.9	4010.2

Adrenalectomy alone (Group 2) did not result in any significant difference when compared to sham-operated Group 1 except in the case of the thymus gland where adrenalectomy resulted in higher organ-weight to body-weight ratio. Therefore, other comparisons are made in terms of Groups 3 and 4, PTU treated before and after adrenalectomy, and after adrenalectomy only, respectively, to the adrenalectomy alone group and to each other. Propylthiouracil treatment (Groups 3 and 4) decreased the heart, liver, kidney, and thymus organ-weight to body-weight ratio below those of animals without PTU treatment (Group 2) and increased the testes, brain, thyroid, and eye organ-weight to body-weight ratios. In respect to the pituitary data, Group 3 had a higher organ-weight to body-weight ratio than either Group 2 or 4. Group 3, which was treated with PTU three weeks in all, when compared to Group 4 which had but one week of treatment, had a higher increase in testes, thyroid, pituitary and eye organ-weight to body-weight data and lower values for the kidneys, heart, and thymus. Thus, the overall effect of PTU treatment on these seven organs appeared to correlate with the length of administration. Treatment for the longer period with PTU increased the liver weight. This was not in agreement with the overall effect of PTU on the liver which was to decrease its weight. Likewise, brain-weight data revealed that the longer the period of treatment with PTU, the closer the organ-weight to body-weight ratio was to normal.

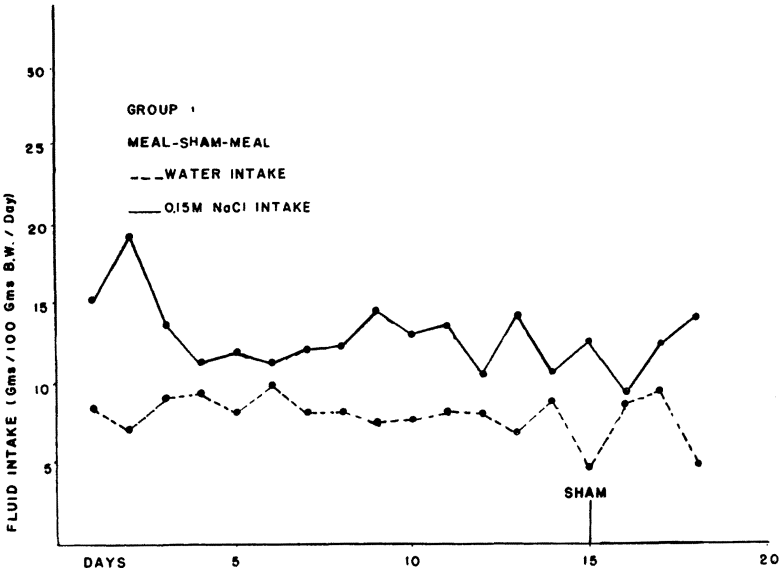

Figure 3. Mean intakes of water and 0.15M NaCl solution for sham-adrenalectomized rats.

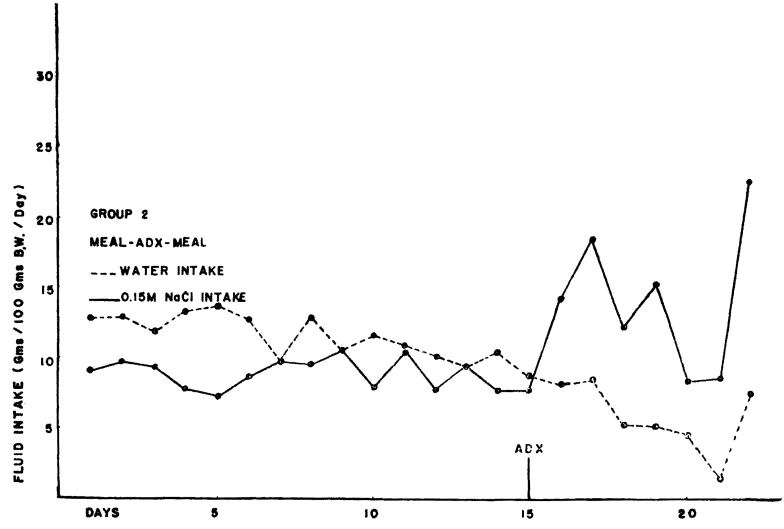

Figure. 4. Mean intakes of water and 0.15M NaCl solution for adrenalectomized rats.

Data for NaCl and water intakes are shown in Figures 3-6.

As indicated in Figure 3 sham operations do not result in any change of NaCl and water intakes. Figure 4 shows that in the plain adrenalectomized group, a salt appetite develops soon after the operation. When PTU is administered for two weeks prior to adrenalectomy, there is a gradual increase in salt intake

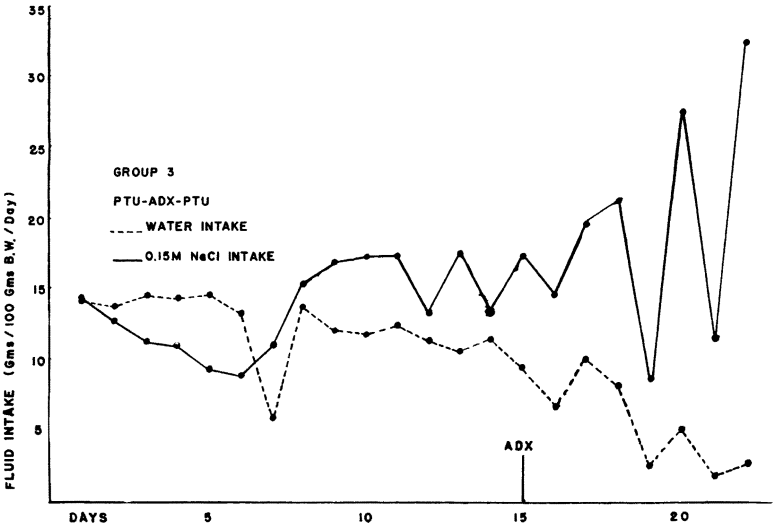

Figure 5. Mean intake of water and 0.15M NaCl solution for rats treated with 0.1% PTU before and after adrenalectomy.

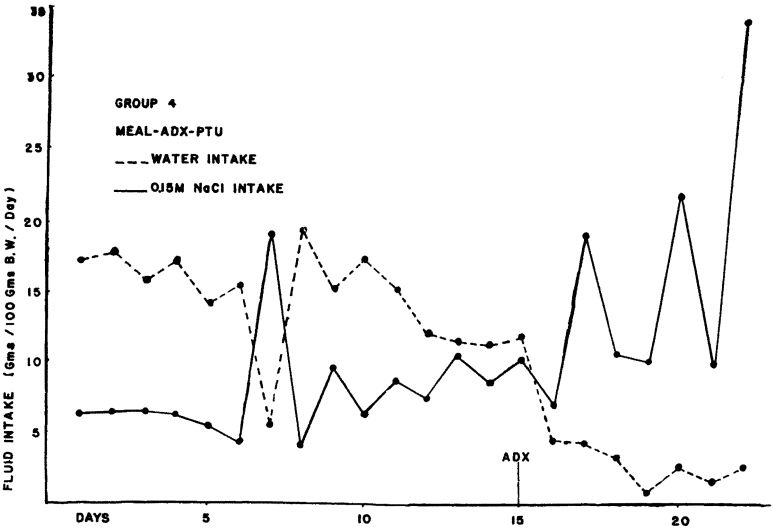

Figure 6. Mean intakes of water and 0.15M NaCl solution for rats treated with 0.1% PTU after adrenalectomy alone.

starting on the seventh day. Following adrenalectomy there is a rapid rise in NaCl intake as is represented in Figure 5. Figure 6 indicates the low NaCl intake prior to adrenalectomy and the rapid increase of NaCl intake with the initiation of PTU following the adrenalectomy.

Blood glucose levels are shown in Figure 7.

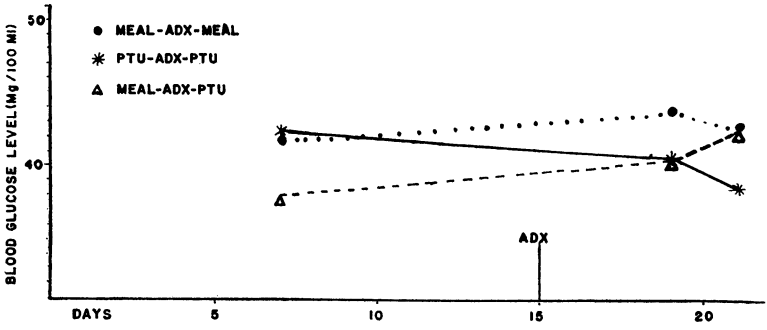

Figure 7. Effect of propylthiouracil (0.1% in diet) on blood glucose levels in adrenalectomized rats.

All considerations of blood glucose levels are made on Groups 2, 3 and 4 since samples were not taken from Group 1 on the seventh day preceding adrenalectomy or the sixth day following the adrenalectomy. Adrenalectomy alone (Group 2) did not produce any appreciable change in the blood glucose level prior to or following the adrenalectomy. Therefore, comparisons will be made of Groups 3 and 4, PTU treatment before and after adrenalectomy and after adrenalectomy respectively. The second group serves as a control for these comparisons. The blood samples taken on the seventh day following administration of the respective diets are not in agreement for Groups 2 and 4, an unexpected result since the blood glucose levels should be approximately the same. The group fed PTU prior to adrenalectomy had approximately the same level of glucose as Group 2. Following the adrenalectomy the blood samples from Groups 3 and 4 were at the same level but were below that of Group 2. On the sixth day following adrenalectomy, Groups 3 and 4, PTU before and after adrenalectomy, and PTU after adrenalectomy showed the widest divergence of blood glucose level. Group 4 increased its blood sugar level up to the blood glucose level of Group 2, which was fed meal throughout the experiment. Treatment with PTU throughout produced an inverse ratio with Group 4, PTU afer adrenalectomy. The overall effect seems to be a slight depression of the blood glucose levels with the longer administration of propylthiouracil as compared to PTU administration immediately following adrenalectomy in Group 4.

Discussion

The manifestations of the effects of PTU administration on body growth and food intakes within one week after the onset of treatment are typical of results obtained by others (Fregly and Hood, 1959; Cook, 1960). They are attributed to the hypothyroid state created by the drug. The increase in NaCl intake,

its onset within one week after initiation of administration of the drug, and its independence of the adrenal gland as is evidenced by greater intake of NaCl solution by PTU-treated, adrenalectomized rats than by adrenalectomized alone is in agreement with a recent report (Fregly et al., 1961). These authors speculate that the PTU acts at the level of the kidney tubules to decrease sodium reabsorption and increase sodium loss, thereby stimulating salt appetite. Adrenalectomized animals have an excess urinary loss of sodium and characteristically exhibit a NaCl appetite (Richter, 1936). The significance of the steeper rise in NaCl intake associated with initiation of PTU treatment at adrenalectomy as shown in Group 4 is not understood since treatment with PTU before adrenalectomy (Group 3) did not result in an immediate increase in NaCl intake.

The organ-weight to body-weight ratio data are in general agreement with those obtained by others (Fregley and Hood, 1959; Fregley and Cook, 1960). The present study is important because it represents short term treatment (one or three weeks) with the drug; whereas, others were for longer exposures (7-19 weeks) manifest themselves after only one week of treatment. Furthermore, adrenalectomy does not appear to affect the typical trend of organ-weight to body-weight data obtained with PTU treatment. Thus, the PTU mediates salt appetite, and in the time development of anatomical changes propythiouracil effects appear to be independent of the adrenal gland.

According to Spector (1956), the range of blood glucose levels in the rat is 56.5 - 76-5 mg/100 ml of blood. The results obtained in the investigation show a considerably lower level of blood glucose for all groups. The blood samples were obtained from veins in the tail and probably had a lower glucose level than arterial blood. But other than this, the reason for the consistently lower values is not clear. The results of the blood glucose work indicate that the range of the glucose levels is restricted to a difference of approximately 4.5 mg/100ml between Groups 3 and 4, which show the greatest variations. With these small differences it is difficult to determine if the variation is an actual fluctuation in the blood glucose levels or result from the close proximity of the last two days on which samples were taken.

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The Influence of the Antithyroid Drug, Propylthiouracil, on Gestation and Lactation in Rats[1]

KENNETH M. COOK[2]

Abstract. The anti-thyroid drug, propylthiouracil (PTU), when fed to female rats at the dietary level of 0.1% has a slight effect on the average number of young per litter if administered during the preconception period or gestation but if administered continuously during these periods results in a much lower litter size. PTU treatment of mothers during lactation results in cretin-like young and poor survival rates during lactation and after weaning. Ratios of thyroid weight to body weight indicate transfer of PTU to young during gestation and lactation.

The role of the thyroid gland in reproduction is incompletely understood. A recent report (Cook, 1960) indicated that the ability of white rats to produce viable sperm and to conceive is unaffected by administration of the anti-thyroid drug, propylthiouracil (PTU) during a 10-week preconception period. The administration of the PTU until mating failed to influence the duration of the gestation period, the number of offspring per litter, average weight of offspring, growth rate, and survival. The drug was also without effect on the regularity and length of the estrus cycle in female rates. However, propylthiouracil did have an anti-thyroid effect since oxygen consumption, colonic temperature, food intake, and body weight measurements of experimental animals were significantly lower than those of con-

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