Effect of Thyroidectomy and Food Intake on Oral and Intravenous Glucose Tolerances in Rats

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IN A PREVIOUS STUDY of the effect of thyroidectomy on oral glucose tolerance, interpretation of the findings was complicated by the marked difference in size between thyroidectomized and normal control rats (1). It was demonstrated that age had a pronounced effect on the rate of intestinal absorption of glucose, but it was not ascertained if this was a direct effect of age or secondary to its effect on body size.

The present experiments were planned so that thyroidectomized rats could be compared directly with body size controls of the same age. Body growth in normal rats was restricted by pair-feeding them to ad libitum-fed thyroidectomized rats. Other thyroidectomized rats were force-fed an increased amount of food in an attempt to maintain their body weight gain at the same rate as that in ad libitum-fed normal rats. Both oral and intravenous glucose tolerances were studied, the latter to eliminate any effect of intestinal absorption on the glucose tolerance test. Glucose tolerance in thyroidectomized rats was found to be impaired when determined by both the intravenous and oral tests. There was no effect of food intake on oral and intravenous glucose tolerances in thyroidectomized and normal rats.

EXPERIMENTAL

Female Sprague-Dawley rats were thyroparathyroidectomized or sham-operated at 21-27 days of age and were fed a complete purified-type diet (4185) (2). Completeness of thyroidectomy was determined by use of 131I radioautographs of the cervical and mediastinal tissue as described by Reinhardt (3). The thyroidectomized rats included in this report had negative radioautographs with the exception of several rats in which the image area was less than 2 mm².

Rats were divided into five groups: Group A consisted of sham-operated rats fed ad libitum; group B, thyroidectomized rats tube-fed an amount of food nearly equal to that consumed by group A; group C, thyroidectomized rats fed ad libitum; group D, sham-operated rats fed one time daily an amount equivalent to that eaten each day by litter-mates in group C; and group E, sham-operated rats fed the same amount and in the same manner as those in group B. The growth curves, food consumptions, and carcass analyses of these animals, as well as details concerning the tube-feeding technique, were reported earlier (4).

The glucose studies were carried out after the 45th postoperative day.1 Both oral and intravenous tests were made in each animal. In general, the oral test was made 7-10 days before the intravenous test. All tests were carried out on 17-hour fasted, unanesthetized rats. Blood glucose levels were determined on 0.05-ml heparinized samples of tail blood according to the method of Haslewood and Strookman (4). The oral glucose tolerance test consisted of tube feeding 300 mg of glucose (30% solution)/100 gm body weight and observing changes in blood sugar concentration. The intravenous glucose tolerance test was performed according to the procedure described by Samuels, Schott and Ball (5). Glucose, 125 mg (0.25 ml of 50% solution)/100 gm body weight, was injected quickly into the saphenous vein through a 27-gauge needle. The vein was exposed by a quick, precise incision through the overlying skin made with a sharp razor blade. While being injected, the rat was held in the hands of an assistant. Intravenous injection of water or saline solution, equivalent in volume to that used in the glucose tolerance test, had no effect on the blood glucose level in unanesthetized rats, both normal and thyroidectomized.

RESULTS

The average body weight for each group at the time of the oral glucose studies is presented in the upper right hand corner of figure 1.2

1 Because of the long postoperative period (45 days or more) before the glucose studies were made, it would seem unlikely that there would be any residual effects of the sham-operation on these studies. For this reason, sham-operated rats are referred to as normal controls.

2 Although the body weight of thyroidectomized rats was nearly doubled as the result of increased food intake (group C vs. group B), 55% of the body weight gain was fat (2). Restricted food intake in the sham-operated animals reduced the body weight gain (group A vs. group D), as would be expected, but it had only a slight effect on the proportion of the three chief chemical components in the carcass. Less than 13% of the

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The daily food intake per animal at this time averaged 11 gm in group A, 9 gm in groups B and E, and 3.5 gm in groups C and D.

The results of the oral glucose tolerance tests are presented in figure 1. With the exception of slightly lower blood glucose levels throughout the test in underfed normals (group D), there was no effect of restricted food intake on the oral test in normal rats.

The oral glucose tolerance curve for both the ad libitum and force-fed thyroidectomized rats was different from that for normals. Although the maximum level was higher in thyroidectomized than in normal rats, there was no difference in the time necessary for the blood glucose concentration to return to the pretest level. Force-feeding had no effect on the tolerance curve in thyroidectomized rats other than to increase the initial level and, consequently, the level at other times.

The intravenous studies are presented in figures 2, 3, and 4. There was no effect of restricted food intake on the intravenous glucose tolerance curve in normal rats (fig. 2). Thyroidectomy resulted in marked impairment of glucose removal from the blood following intravenous administration (fig. 3). The blood glucose level at 60 minutes in thyroidectomized rats was about twice as much as that in normal controls. During the first 60 minutes of the test, the blood glucose concentration was significantly higher in force-fed than in ad libitum-fed thyroidectomized rats.

Interpretation of the intravenous glucose tolerance data is facilitated by plotting the logarithm of the excess blood glucose (that above the pretest level) against time (fig. 4). A straight line can be drawn through all observed points for normal rats (group A) during the first 60 minutes, which would indicate that the rate of removal of excess glucose from the blood during this period was constant. In thyroidectomized rats, a nearly horizontal line can be drawn through the plotted points during the first 20 minutes, and a second line through those between 20 and 60 minutes, inclusive. The removal rate during the latter period was not only significantly different from that for the first 20 minutes ($P < .01$) but also different from that of the normal rats (table 1). Although the level of blood glucose during the first 60 minutes was higher in force-fed thyroidectomized rats, there was no difference between the two groups of thyroidectomized rats in the slope of the line during the first 20 and during the subsequent 40-minute periods.

**DISCUSSION**

Marked reduction in the rate of glucose removal from the blood was demonstrated in thyroidectomized rats when glucose was given intravenously. Crawford (6) found that hypo-
thyroid children had impaired glucose tolerance when studied with the intravenous test and that it was restored to normal by treatment with thyroid extract. Yriart (7) reported that thyroidectomy had no effect on the intravenous glucose tolerance curve in rabbits. However, since the postoperative period of 2 weeks was probably too short for the thyroid deficient state to be well established and since the degree of thyroid ablation was not ascertained, it may be that sufficient thyroid hormone was present in the operated rabbits to maintain the intravenous tolerance curve within the normal range.

The onset of removal of blood glucose during the intravenous tests was delayed in the thyroidectomized rats about 20 minutes. After this time, the blood glucose concentration began to fall but at a much slower rate than in normals. Preliminary studies, consisting of measuring urinary glucose excretion and preventing excretion by nephrectomy, strongly suggest that the fall in blood glucose in thyroidectomized rats was due primarily to urinary clearance. In normal rats, however, urinary glucose excretion during the intravenous test was negligible, amounting to less than 10% of the administered glucose.

Samuels et al. (5) have made intravenous glucose tolerance studies in hypophysectomized rats. The observed values for hypophysectomized (5 weeks postoperative) and normal rats are nearly identical with those observed in this study in thyroidectomized and normal rats, respectively. They presented evidence that impaired glucose tolerance in the hypophysectomized rats was not due to depressed adrenal activity. Since thyroid activity is also depressed, the results in the present studies suggest the possibility that impaired glucose tolerance in hypophysectomized rats might be accounted for, at least in part, by their reduced thyroid activity.

The differences between thyroidectomized

![Intravenous Glucose Tolerance](https://example.com/glucose_tolerance.png)

**Fig. 3.** Intravenous glucose tolerance in thyroidectomized and normal rats. After a 17-hour fast, each rat was injected intravenously with 125 mg glucose (0.25 ml of 50% solution)/100 gm body weight. The average fasting blood sugar level was 63 mg/100 ml in group A, 65 in group B, and 73 in group C.

**Fig. 4.** Intravenous glucose tolerance in thyroidectomized and normal rats. This is a replotting of the data presented in fig. 3. Here the logarithm of the concentration of the excess glucose in the blood (that above the pretest level) is plotted.

<table>
<thead>
<tr>
<th>No. Removal Rate, % excess glucose/min.</th>
<th>Group</th>
<th>No. Removal Rate, % excess glucose/min.</th>
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<tbody>
<tr>
<td>A. Normal (fed ad libitum) 19 4.6 ± 0.3*</td>
<td>B. Thyroidectomized (force-fed) 5 2.0 ± 0.4</td>
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<tr>
<td>C. Thyroidectomized (fed ad libitum) 7 2.2 ± 0.4</td>
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* Standard error of removal rate.
and normal rats in rate of removal of glucose from blood observed during the intravenous test cast light on the interpretation of the difference observed during the oral test. If the removal rate in the thyroidectomized rats is as much below the normal rate during the oral glucose tolerance test as it is during the intravenous test, we should, unless the absorption rates are very different, expect marked differences in the oral curves. The greater elevation of blood sugar at 30 minutes in the thyroidectomized rats was about two and a half times that of the normals. The larger fall in glucose concentration in the thyroidectomized rats after thirty minutes could then be a consequence of the higher excess glucose level at this point and is consistent with a removal rate below that of the normals. This explanation assumes that there are no important differences in intestinal absorption. The necessity of making this assumption as well as the contradictory reports concerning the effect of thyroid deficiency on this test (1, 6, 9) highlight the difficulty in interpreting the results of an oral glucose tolerance test as a measure of metabolic malfunction.

In an earlier paper (1), it was suggested that the effect of age on oral glucose tolerance in normal rats might be secondary to its effect on body size. In view of the present observation that varying body size independently of age had no effect on the glucose tolerance curves, it would seem that age was a more important factor than body size.

SUMMARY

Oral and intravenous glucose tolerance studies were made in thyroidectomized and normal rats of various sizes but of the same age. Body size of thyroidectomized rats was increased by force feeding, the result of which was marked obesity. The body size of normal rats was varied by reducing the daily food intake. There was no effect of food intake, or body size, on the oral and intravenous glucose tolerance curves in normal and thyroidectomized rats.

Intravenous studies demonstrated a marked impairment of glucose tolerance in thyroidectomized rats. The maximum blood glucose level in the thyroidectomized rats during the oral test was 50% above that of the normals, presumably because of the impaired rate of glucose removal from the blood. The blood glucose removal rate during the intravenous tests in thyroidectomized rats was much lower during the first 20 minutes than during the subsequent 100 minutes. Preliminary results suggest that the latter was primarily due to urinary excretion of glucose, the onset of which was delayed 20 minutes.

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REFERENCES