Thyroid dysfunction modulates gluco-regulatory mechanism in rat

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The role of the thyroid gland in glucose homeostasis remains incompletely understood. To get a better insight hypothyroid and hyperthyroid conditions were experimentally induced in rat and found severe defects in glucose homeostasis. While blood glucose level returned to normal level after 2.5 hr of oral glucose challenge in control rats the blood glucose level remained high even after 24 hr of glucose load in both hypo- and hyperthyroid rats. These experimentally manipulated rats displayed higher levels of liver glycogen (10.45-22.8-fold) and serum glutamic pyruvic transaminase (1.48-9.8-fold). Liver histology of hyperthyroid treated rats revealed hepatotoxicity. From the results it can be concluded that thyroid gland plays an important role in glucose homeostasis.

Keywords: Blood glucose, Glycogen, Hyperthyroid, Hypothyroid Liver

Thyroid hormones [(primarily 3,5,3’5’-l-tetraiodothyronine (T4), and to a lesser extent 3,5,3’-l-triiodothyronine (T3)] regulate a variety of biochemical reactions in virtually all tissues. These hormones are known as important factors in gene regulation in tissues such as brain, liver, muscles and adipose tissue. They are involved in the control of resting metabolism. Thyroid hormone status is also important for glucose homeostasis. In thyrotoxic subjects, glucose turnover and oxidation rates are increased, whereas non-oxidative glucose turnover is unchanged, decreased or increased. In contrast, glucose production is decreased in hypothyroidism. Impaired glucose tolerance is a frequent complication of hyperthyroidism. This alteration changes both insulin secretion and degradation in humans. Impairment in the insulin-induced suppression of glucose production in hyperthyroid patients has been reported. At low insulin levels, insulin-stimulated glucose disposal is usually unaffected, whereas it has been reported to be decreased, unchanged or even increased at high insulin levels. In addition, thyroid hormones also blunt the insulin-induced increases in the total distribution volume of the exchanging pool of glucose, possibly by accelerating intracellular glucose degradation.

However, the role of thyroid gland in glucose homeostasis has remained elusive. Therefore, to uncover this complex interaction an attempt has been made by generating hypothyroidism (by treatment with methimazole) and hyperthyroidism (by treatment with thyroxine) in rats to study the effects on glucose levels during oral glucose tolerance test and changes in serum glutamic pyruvic transaminase (SGPT) have been examined. In addition, morphological and biochemical changes in liver have been observed. Higher glucose levels were noted in both hypo- and hyperthyroid rats in response to oral glucose tolerance test, higher liver glycogen content, and elevated levels of SGPT. In addition, profound alteration in liver histology were observed. These findings may help to better understand the complex relationship between thyroid dysfunction and glucose homeostasis.

Materials and Methods

Young adult rats, Rattus rattus (8-10 weeks: 70-80 g) were housed in polypropylene cages and were acclimatized in the laboratory condition for a week with standard food and water in natural light and dark schedules. Rats were divided into following 4 groups: group I (for hypothyroid studies), group II (for hyperthyroid studies) and their respective control groups. While Group I animals were treated with Methimazole (20 mg/kg body weight in 1 ml water / day) for 14 days, Group II animals received thyroxine (600 μg/kg body weight in 1 ml of water/day) for 14 days. Control rats received 1 ml of water only. Rats were anesthetized with chloroform and blood was collected directly from the heart for serum T3 and T4 hormone level. T3 or T4 concentra-
tions in rat serum were determined by radioimmunoassay (RIA). $^{125}$I-labeled thyroid hormone (either T3 or T4) competes with thyroid hormone in the serum sample and for antibody sites on the tube, in the presence of blocking agents for thyroid hormone binding proteins. Thyroid gland and liver were dissected out, fixed in Bouin’s fixative, and processed for routine histology. Liver glycogen was determined by the colorimetric method by digesting 1 g fresh liver in 30% KOH and treatment with the anthrone reagent. Serum SGPT was measured colorimetrically using the method of Reitman. For oral glucose tolerance test (OGTT) blood was collected first from the tail veins of control and treated (hypo- and hyperthyroid) rats after 18 hr of fasting followed by challenge with glucose (25 mg glucose/100 g body weight) and at the following time point after oral glucose infusion: 0.5, 2.5 and 24 hr. Blood glucose was measured estimated using a blood glucose monitoring system (ACON Laboratories, Inc. San Diego, USA).

Results

T3 and T4 levels, body weight and liver glycogen—Rats with hypothyroidism showed lower levels of thyroid hormones T3 and T4 and with higher levels in hyperthyroid rats as compared to control rats (Fig. 1). Rats with hypothyroidism also showed increase in body weight (~18%) while those with hyperthyroidism exhibited a decrease in body weight (~18%). Liver glycogen increased dramatically in both hypothyroid (by ~22.8-fold) and hyperthyroid (by ~10.45-fold) (Fig. 2).

Oral glucose tolerance test—While hypothyroid rats displayed low glucose level (by 18%) no change in glucose level was seen for hyperthyroid rats (Fig. 3). In the control rats the blood glucose level returned to the normal level after 2.5 hr of glucose feeding. Like control rats, in hypothyroid rats glucose level increased by 90% after 0.5 hr of glucose challenge but the elevated glucose didn’t return to control level even after 24 hr of glucose challenge (Fig. 3). Unlike control and hypothyroid rats, the increments in glucose level after 0.5 hr of glucose challenge was modest (by ~22%) in hyperthyroid rats. However, like hypothyroid rats, the glucose remained elevated even after 24 hr of glucose feeding (Fig. 3).

Serum SGPT—Hyperthyroid rats showed dramatic increments in SGPT level (by ~9.8-fold) as compared to a modest (by ~0.5 fold) increase in hypothyroid rats (Fig. 4).

Liver histology—Hyperthyroid rats exhibited marked changes in the general cytomorphology of

![Fig. 1—Plasma concentrations (ng/dL) of T3 (A) and T4 (B) in hypothyroid and hyperthyroid rats. Values are expressed as mean ± SE from 6 rats. P values: *<0.001; **<0.01](image1.png)

![Fig. 2—Liver glycogen content (mg/g wet tissue) in hypothyroid and hyperthyroid rats. Values are expressed as mean ± SE from 6 rats. P values: *<0.001; **<0.01](image2.png)
Discussion

The T3 and T4 levels are low in hypothyroid and high in hyperthyroid rats (Fig. 1). A complex relationship exists between thyroid disease, body weight and metabolism. It is well known that hyperthyroidism causes extensive weight loss despite normal or increased calorie intake\(^{19,20}\). The weight loss is related to the severity of the overactive thyroid. In congruence with these findings 18% loss of body weight was observed in hyperthyroid rats. Weight loss reflects not only a depletion of body adipose tissue stores but also a loss of muscle mass caused by accelerated catabolism and heat elimination. Because of low BMR hypothyroidism is generally associated with some weight gain\(^{20}\). There was an 18% increase in body weight in the present experimental hypothyroid which is in line with reported observation.

Hypothyroidism is associated with decreased gluconeogenesis and glycogenolysis resulting in increment in glycogen in liver. In addition, hypothyroidism lowers the glycogen phosphorylase hepatocytes as evidenced by the enlargement of central terminal hepatic venule and disorientation of the nuclei and the loss of the individual boundary. Small numbers of hepatocytes were found to be picnotic. Few uniform sized cell bodies stained in eosin were found in the periphery of central terminal hepatic venule (Fig. 5). No discernible change in liver histology was detected in hypothyroid rats (data not shown).
activity in the liver. Consistent with these findings, profound increments in liver glycogen in hypothyroid rats were observed. In contrast, the hyperthyroid state is associated with low hepatic glycogen levels, but paradoxically with a high activity of glycogen synthase and low activity of glycogen phosphorylase. In hyperthyroidism, insulin-stimulated rates of glucose utilization in muscle to form lactate are increased mainly because of a decrease in glycogen synthesis. In the present study, elevated glycogen content in the liver of hyperthyroid rats is paradoxical and may be due to the high activity of glycogen synthase.

In hyperthyroid humans as well as in experimental thyrotoxicosis in animals, glucose turnover and hepatic glucose production are increased due to increased metabolic rate and peripheral glucose utilization. Experimental as well as spontaneous hyperthyroidism in humans cause increased glucose production and impaired suppression of glucose production by insulin. Consistent with these previous reports increments in blood glucose levels were observed after OGT and the hyperglycemia persisted even 24 h after glucose load. It is believed that insulin response to a glucose load is relatively decreased in hyperthyroidism, and that an inability to increase their insulin response further impairs glucose tolerance in low β-cell responder. It is possible that T4 causes deleterious effects on β-cell function thereby impairing insulin secretion after an oral glucose load. In line with this thought, Lenzen reported that injections of T4 (50-2000 μg/kg/day for 5 days) dose-dependently inhibited glucose-induced insulin secretion in the isolated pancreas. It has also been reported that hyperthyroid patients with younger age (<30 years) showed an increased secretion of insulin to compensate hyperglycemia after glucose load, but older patients (>31 years), who may have a low β-cell reserve, showed a blunted response of insulin. In addition, insulin sensitivity is altered in hyperthyroid patients. In the present study, the reason behind impaired glucose tolerance in response to glucose overload in hypothyroid rats is not known and further experiments needs to be performed.

Liver maintains a stable blood glucose level by taking up and storing glucose as glycogen, breaking this down to glucose when needed and forming glucose from non-carbohydrate sources such as amino acids. Because of the impairment of glucose tolerance in both hypo- and hyperthyroid rats we found dramatic changes in SGPT enzyme levels in these rats. It is believed that abnormal liver enzyme levels may cause liver damage. Profound alteration in liver histology in hyperthyroid rats is a reflection of changes in SGPT level in the liver an observation that is unique to this study.

References

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