Gluconeogenesis from Glycerol and Alanine in Thyrotoxicosis

TOKUTARO SATO, SHINTARO SAITO, MASARU KOKUBUN, TSUYOSHI SAITO, MASAaki ITO, MAKIKO YAMAMOTO, KAZUO KAISE and NOBUKO KAISE

The Second Department of Internal Medicine, Tohoku University School of Medicine, Sendai 980

Gluconeogenesis in thyrotoxicosis was studied by oral glycerol-loading test and alanine-loading test performed on 5 normal subjects and 5 cases of thyrotoxicosis. The blood glucose levels in thyrotoxicosis rose after the administration of glycerol despite elevation of the plasma levels of insulin. After the administration of alanine, the levels of IRI, pyruvate and lactate elevated in thyrotoxicosis. In normal subjects, the plasma levels of glucose, IRI, pyruvate, or lactate did not change significantly after glycerol or alanine load.

In thyrotoxicosis, oxidation and removal of glucose are increased (Lamberg 1965), and muscle wasting is common with increased excretion of urinary nitrogen (Boothby and Sandiford 1923; Kyle et al. 1966). Cori-cycle is enhanced and gluconeogenesis from glycerol is also increased in thyrotoxicosis (Svednry 1966; Freedland and Krebs 1967), but enhancement of gluconeogenesis from amino acids has not been proved (Freedland and Krebs 1967). Alanine and glycerol are physiologically important substrate for gluconeogenesis which occurs in the liver, especially during prolonged fasting (Cahill 1970; Exton 1972). The alanine-loading test and glycerol-loading test have been done to study changes of hepatic gluconeogenesis in some pathological conditions (Pagliara et al. 1972; Genuth 1973). This report presents data about effects of oral administration of alanine and glycerol on carbohydrate metabolism in thyrotoxicosis.

SUBJECTS AND METHODS

The subjects for this study were composed of 5 cases of thyrotoxicosis and 5 normal subjects; mean ages were 41 and 25 years, respectively. Habitus was normal in all of them. Mean values of BMR, plasma \( T_3 \) and \( T_4 \) of control subjects were normal.

Following an overnight fast, the subjects consumed alanine or glycerol in amount of 1 g per kg of body weight as 20% aqueous solution. Blood samples were taken from an antecubital vein making no venous stasis at 0, 30, 60, 90 and 120 min after the administration of alanine or glycerol. The levels of blood lactate and pyruvate were measured by

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enzymatic assay using Boeringer-Mannheim kit, blood glucose by an Auto-Analyzer, and plasma insulin by a double antibody radioimmunoassay method using Daiichi Isotope kit.

RESULTS

Results of the glycerol-loading test are shown in Figs. 1 and 2. The mean fasting blood glucose levels in both groups of control and thyrotoxicosis were 66.5 and 71.5 mg/100 ml, respectively. After the glycerol load, the mean blood glucose levels in the control group did not change, but those in the thyrotoxicosis group rose to 83.3 mg/100 ml at 30 min and decreased gradually to 80 mg/100 ml at 120 min. The blood glucose levels in the thyrotoxicosis group were thus higher than the control group after the glycerol load, and the differences between the two groups were statistically significant at 30, 60, 90 and 120 min (p<0.05). The mean of the sum of blood glucose changes during the test was 6.0 mg/100 ml in control group, 41.4 mg/100 ml in the thyrotoxicosis group, and the difference between the groups was statistically significant (p<0.01).

The mean plasma insulin level before the test was significantly higher in the thyrotoxicosis group than in the control group. After the glycerol load, the plasma insulin levels appeared to rise and the levels at 30, 60, 90, and 120 min were higher in the thyrotoxicosis group than in the control group. The sum of the changes of the plasma insulin after the glycerol load was also significantly higher in the thyrotoxicosis group than in the control group.

The blood lactate level before the glycerol load was 8.2±3.3 mg/100 ml in the control group and 7.3±1.6 mg/100 ml in the thyrotoxicosis group, and no significant difference was detected between the groups. After the glycerol load, no significant changes of the blood lactate levels were detected in either group.

As shown in Fig. 3, the blood glucose level during the alanine-loading test slightly decreased in the control group and slightly increased in the thyrotoxicosis group. Statistically significant difference of the mean blood glucose level between

Fig. 1. The effect of oral glycerol load on the levels of blood glucose and plasma IRI. ●● and T, thyrotoxicosis; ○○ and C, control. *p<0.05; †p<0.01.

The blood lactate level before the glycerol load was 8.2±3.3 mg/100 ml in the control group and 7.3±1.6 mg/100 ml in the thyrotoxicosis group, and no significant difference was detected between the groups. After the glycerol load, no significant changes of the blood lactate levels were detected in either group.

As shown in Fig. 3, the blood glucose level during the alanine-loading test slightly decreased in the control group and slightly increased in the thyrotoxicosis group. Statistically significant difference of the mean blood glucose level between
the two groups was detected at 120 min. The mean of the sum of blood glucose changes during the test was $+10.4 \pm 19.5$ mg/100 ml in the thyrotoxicosis group, $-15.8 \pm 18.2$ mg/100 ml in the control group; no significant difference was noted between them. The mean plasma insulin level of the thyrotoxicosis group was significantly higher than that of the control group before the test and at 30 min after the alanine load. No significant differences were noted in the mean of the sum of the plasma insulin changes during the test between the two groups.

The mean fasting blood lactate level was lower and the mean fasting pyruvate level was higher in the thyrotoxicosis group than in the control group, but no significant differences were noted between the two groups. Both of the blood lactate and pyruvate levels elevated significantly after administration of alanine in the thyrotoxicosis group, but neither of them did change in the control group.
as shown in Fig. 4. In the thyrotoxicosis group, the blood lactate levels at 90 and 120 min after alanine load were significantly higher than the initial level, and the blood pyruvate levels at 30 and 90 min were also significantly higher than the initial level. The pyruvate level at 120 min after alanine administration was significantly higher in the thyrotoxicosis group than in the control. The sum of the changes in the blood lactate and pyruvate was higher in the thyrotoxicosis group than in the control group, and the statistically significant difference between the groups was noted in the case of blood pyruvate.

![Fig. 4. The effect of oral alanine load on the levels of blood lactate and pyruvate.](image)

DISCUSSION

Hypermetabolism in thyrotoxicosis is accompanied with increased glucose oxidation and gluconeogenesis (Lamberg 1965; Svednry 1966; Freedland and Krebs 1967). In thyrotoxicosis, excess of thyroid hormones increases availability of glycerol as a result of the activated lipolysis (Genuth 1973), and augmented gluconeogenesis from glycerol was demonstrated by Freedland and Krebs (1967) using perfused liver from thyrotoxic rat. Studies of lactate turnover by Svednry (1966) suggested that Cori cycle, hepatic recycling of lactate to glucose, is also increased in T₃-treated humans. In this study, oral administration of glycerol elevated the blood glucose level despite the greater plasma IRI response, which suggests that gluconeogenesis from glycerol is enhanced in thyrotoxicosis.

In thyrotoxicosis, muscle wasting is rather common and excretion of urinary nitrogen is increased (Boothby and Sandiford 1923). In our study, a diet of 30 kcal per kg of ideal body weight was not sufficient for inpatients of thyrotoxicosis to maintain the body weight and the nitrogen balance; these were improved on diet of 60 kcal per kg of ideal body weight (Sato et al. unpublished data). These results suggest that in thyrotoxicosis, gluconeogenesis from protein as well as from glycerol or lactate, is increased, although Freedland and Krebs (1967) could not demonstrate increased production of glucose from serine in the perfused rat liver that was treated with thyroxine.

There is much evidence that alanine is the major amino acid involved in gluconeogenesis, and it is used to study on gluconeogenesis in pathological conditions
Gluconeogenesis in Thyrotoxicosis (Fisher and Ball 1967; Pagliara et al. 1972). In this study, oral administration of alanine increased the levels of blood lactate and pyruvate only in the thyrotoxic group, and the changes were more marked in the pyruvate level than in the lactate level. These results suggest that deamination of alanine is increased and the alanine-cycle is more active in thyrotoxicosis. However, compared with the changes of blood lactate and pyruvate, those of the blood glucose levels were small, and the blood glucose level in the thyrotoxicosis was significantly higher than the control group only at 120 min after alanine load. This discrepancy may be due to enhanced removal of glucose by elevation of the plasma IRI or increased oxidation of pyruvate in TCA-cycle.

References