Metabolic Effect of Decreasing Nonesterified Fatty Acid Levels With Acipimox in Hyperthyroid Patients

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Glucose intolerance is often found in patients with hyperthyroidism, but the pathogenetic mechanisms are not fully understood. Since lipolysis is increased in hyperthyroidism, elevated plasma nonesterified fatty acids (NEFAs) may contribute to abnormal glucose metabolism in hyperthyroidism. The aim of this study was to investigate whether decreasing the plasma NEFA level with acipimox can affect glucose metabolism in hyperthyroidism. We performed an intravenous glucose tolerance test (IVGTT) with acipimox 250 mg or placebo in six untreated hyperthyroid men and six age- and body mass index (BMI)-matched controls. Fasting plasma NEFA levels were significantly higher in the hyperthyroid patients versus the controls (997.0 ± 303.4 *v* 290.5 ± 169.1 μmol/L, $P < .001$). Plasma NEFAs decreased rapidly with acipimox treatment in both controls and hyperthyroid patients. In the controls, the glucose disappearance constant (K_G) was not different for acipimox treatment versus placebo (2.18 ± 0.62 *v* 2.42 ± 1.00% · min^{-1}). In hyperthyroid patients, acipimox treatment increased the K_G significantly compared with placebo treatment (2.44 ± 0.84 *v* 1.58 ± 0.37% · min^{-1}, $P < .05$). Changes in K_G values with acipimox treatment were inversely correlated with changes in plasma NEFA levels ($r = -.65$, $P < .05$). Acipimox treatment increased the acute insulin response (AIR) in hyperthyroid patients (943 ± 381 *v* 698 ± 279 μU/mL · min, $P < .05$), whereas it did not change the AIR in controls. Changes in the AIR with acipimox treatment correlated significantly with changes in the K_G ($r = .70$, $P < .05$). There was a weak correlation between changes in the AIR with acipimox treatment and changes in plasma NEFA levels ($r = -.55$, $P = .06$). In summary, decreasing the plasma NEFA level with acipimox in hyperthyroid patients increases both the K_G and AIR during an IVGTT. These findings suggest that the abnormal glucose metabolism in hyperthyroidism could be attributed, at least in part, to the increase of plasma NEFA.

ABNORMALITIES OF GLUCOSE metabolism are frequently found in hyperthyroidism.[1,2] However, the mechanism of glucose intolerance in hyperthyroidism is not fully understood. In addition to abnormal glucose metabolism, lipolysis is enhanced in hyperthyroidism and plasma nonesterified fatty acids (NEFA) levels are frequently elevated in hyperthyroid patients.[3,4] It has been speculated that an increase in plasma NEFA levels in patients with obesity and type 2 diabetes may be a cause of insulin resistance via the glucose–fatty acid cycle.[5-7] Indeed, infusion of Intralipid and heparin decreases peripheral glucose utilization and increases hepatic glucose production in healthy subjects.[8] Thus, elevated plasma NEFA levels may be an explanation for the abnormal glucose metabolism in hyperthyroidism.

Acipimox is a powerful inhibitor of lipolysis that significantly decreases plasma NEFA levels.[9] Reducing plasma NEFA levels with acipimox has been shown to improve glucose tolerance and insulin action in type 2 diabetics[10] and in subjects with hepatic cirrhosis.[11] The aim of this study was to determine the effect of a decrease in plasma NEFA levels with acipimox on glucose metabolism in hyperthyroidism.

SUBJECTS AND METHODS

Subjects

Six untreated hyperthyroid men and six age- and body mass index (BMI)-matched healthy men were included in the study. Hyperthyroidism was established in all patients by clinical and laboratory findings (Table 1). The hyperthyroid patients were newly diagnosed and had diffuse goiter demonstrating uniformly increased radionuclide uptake in a ^{99m}Tc thyroid scan. The subjects did not receive any medication before or during the study. None had any disorder influencing glucose metabolism. They did not have a family history of diabetes. They were on a free diet containing at least 200 g carbohydrate for 1 week or longer prior to the study. The study was approved by the human ethics committee of Seoul National University Hospital. All subjects provided written informed consent before participating in the study.

Intravenous Glucose Tolerance Test

For each subject, an intravenous glucose tolerance test (IVGTT) was performed twice, with acipimox or placebo. The order of the two tests was randomized, and they were performed with an interval of 5 to 7 days.

The subjects fasted overnight and ingested either acipimox 250 mg or placebo at 7 AM. Two hours later, 25 g glucose (50 mL in 50% glucose solution) was injected into an antecubital vein within 1 minute. Blood samples were collected from the other antecubital vein at −120, 0, 2, 3.5, 5, 7, 9, 12, 17, 22, 30, 40, 50, and 60 minutes. Blood samples for measurement of glucose were collected in tubes containing NaF, samples for insulin were collected in plain tubes, and samples for free fatty acid were collected in tubes containing paroxon (diethyl *p*-nitrophenyl phosphate; Sigma Chemical, St Louis, MO).

Calculations

Using the plasma glucose concentration at 12, 17, 22, 30, and 40 minutes after the intravenous glucose load, the glucose disappearance constant (K_G) was calculated as follows: $K_G = (0.693/t_{1/2}) \times 100$. The acute insulin response (AIR) and late insulin response (LIR) were calculated as the incremental insulin area from 0 to 9 minutes and 9 to 60 minutes of the IVGTT, respectively.

Analytical Procedures

The blood glucose level was measured by the glucose oxidase method using a YSI glucose analyzer (Yellow Springs Instruments, Yellow Springs, OH). Plasma insulin was determined using a commer-

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Table 1. Clinical Characteristics of the Hyperthyroid Patients and Control Subjects (mean ± SD)

Characteristic	Hyperthyroid	Control
Age (yr)	25.8 ± 1.3	26.3 ± 1.0
Sex ratio (male:female)	6:0	6:0
BMI (kg/m²)	20.2 ± 1.5	22.0 ± 1.9
Triiodothyronine (ng/dL)	481 ± 190	78 ± 12
Thyroxine (μg/dL)	20.0 ± 1.9	6.5 ± 1.3
Triiodothyronine bead uptake (%)	51.6 ± 6.7	26.2 ± 3.2
Thyrotropin (μIU/mL)	<0.01	0.81 ± 0.25

cial radioimmunoassay kit (Diagnostic Products, Los Angeles, CA). The plasma NEFA level was measured by enzymatic assay.[12]

Statistical Analysis

The data are expressed as the mean ± SD. Statistical comparisons were made using Student's *t* test for paired and unpaired data.

RESULTS

Plasma Glucose, Insulin, and NEFA During the IVGTT

There were no differences in fasting plasma glucose and insulin levels between hyperthyroid patients and controls. However, fasting plasma NEFA levels were higher in the patients versus the controls (997.0 ± 303.4 *v* 290.5 ± 169.1 μmol/L, $P < .001$) (Fig 1).

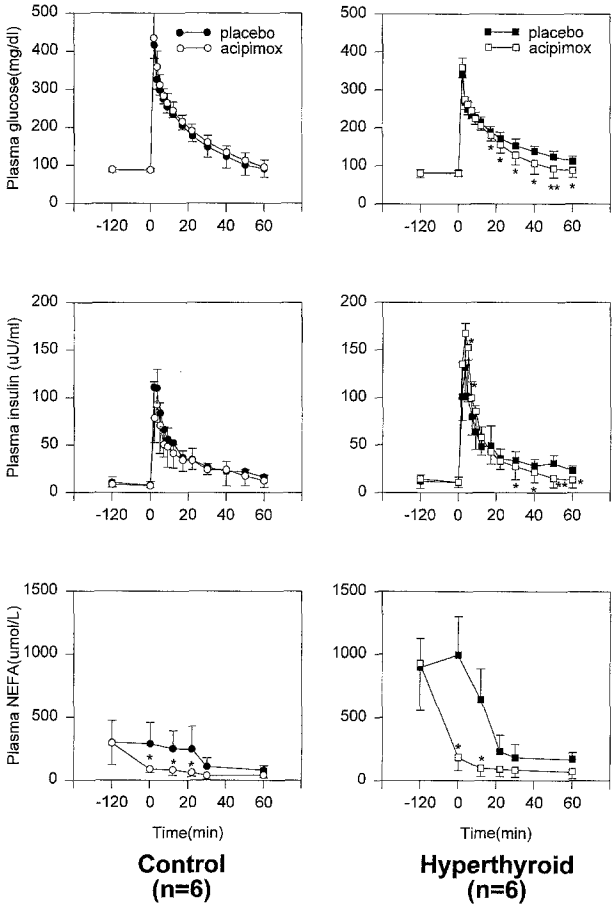

Fig 1. Plasma glucose, insulin, and NEFA levels during the IVGTT. *$P < .05$ *v* placebo. **$P < .01$ *v* placebo.

There were no differences in plasma glucose and insulin levels between acipimox and placebo treatment in controls. In contrast, in hyperthyroid patients, plasma glucose was significantly lower with acipimox treatment versus the placebo at 17 minutes and thereafter. Plasma insulin was higher with acipimox ingestion at 5 and 7 minutes after the glucose load and lower at 30 minutes and thereafter versus the plasma insulin level with placebo ingestion in hyperthyroid patients. Plasma NEFAs decreased to 10% to 20% of the basal value after acipimox ingestion in both controls and hyperthyroid patients (Fig 1).

Glucose Disappearance Constant

In controls, the K_G value was not significantly different for acipimox treatment versus placebo (2.18 ± 0.62 *v* 2.42 ± 1.00% · min^{-1}). In hyperthyroid patients, the K_G was significantly higher with acipimox treatment versus placebo treatment (2.44 ± 0.84 *v* 1.58 ± 0.37% · min^{-1}, $P < .05$; Fig 2). K_G values were inversely correlated with fasting plasma NEFA concentrations in placebo treatment ($r = -.58$, $P < .05$; Fig 3A), and changes in the K_G value with acipimox treatment were inversely correlated with the changes in plasma NEFA levels ($r = -.65$, $P < .05$; Fig 3B).

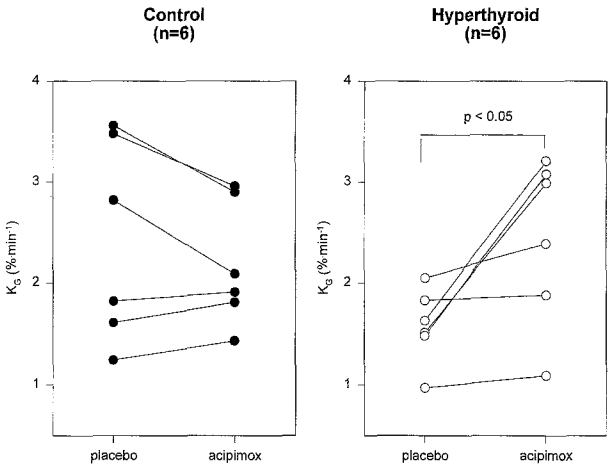

Fig 2. K_G for hyperthyroid patients and control subjects.

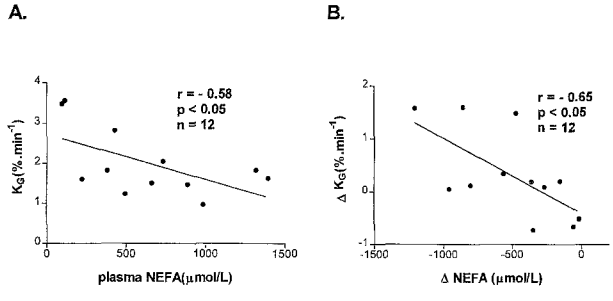

Fig 3. (A) Correlation between plasma NEFA level and K_G in 6 hyperthyroid patients and 6 control subjects. (B) Correlation between the change in plasma NEFA (ΔNEFA) and change in K_G (ΔK_G) in 6 hyperthyroid patients and 6 control subjects.

Acute and Late Insulin Secretion

Acipimox treatment increased the AIR in hyperthyroid patients (943 ± 381 *v* 698 ± 279 μU/mL · min, $P < .05$), whereas it did not change the AIR in controls (Table 2). The LIR tended to decrease with acipimox treatment in hyperthyroid patients, but it was not statistically significant. Changes in the AIR with acipimox treatment correlated significantly with changes in the K_G ($r = .70$, $P < .05$). There was a weak correlation between changes in the AIR and changes in plasma NEFAs ($r = -.55$, $P = .06$).

Table 2. AIR and LIR During the IVGTT (μU/mL · min, mean ± SD)

Group	AIR (0-9 min)	LIR (9-60 min)
Control		
Placebo	872 ± 379	1,347 ± 359
Acipimox	656 ± 249	1,244 ± 506
Hyperthyroid		
Placebo	698 ± 279	1,595 ± 999
Acipimox	943 ± 381*	794 ± 327

*$P < .05$ *v* AIR in placebo treatment of hyperthyroid patients.

DISCUSSION

In the present study, plasma NEFAs were increased in hyperthyroid patients, and a reduction of plasma NEFA levels with acipimox significantly increased the K_G and AIR during the IVGTT as compared with placebo treatment in hyperthyroid patients.

The role of elevated NEFA in glucose metabolism was first proposed by Randle et al.[7] Thereafter, there are many reports showing that elevated NEFA levels lead to insulin resistance.[8,13,14] Thyrotoxic patients with elevated plasma NEFAs had significant impairment of glucose tolerance with normal insulin concentrations.[1] In this study, we also demonstrate that hyperthyroid patients had higher plasma NEFA levels than controls and plasma NEFA correlated with the K_G, a measure of intravenous glucose tolerance.

A reduction in plasma NEFA levels with acipimox caused an increase in the K_G in hyperthyroid patients. There was also a significant correlation between changes in plasma NEFA and changes in the K_G. These findings are consistent with the finding in type 2 diabetics that decreasing plasma NEFA levels with acipimox improves glucose tolerance,[10] and also with the report that the inhibition of lipolysis by propranolol improves glucose tolerance in hyperthyroidism.[15,16]

Interestingly, we also found that acipimox treatment in hyperthyroid patients increased the AIR significantly compared with placebo treatment. The relation between NEFA and insulin secretion is still debated.[17-19] However, there is accumulating evidence that a prolonged elevation of plasma NEFA may inhibit glucose-induced insulin secretion.[17,18,20-22] It is suggested that the accumulation of triglyceride and activation of the Randle cycle in the islet might hamper glucose-induced insulin secretion.[20,21] Our finding that reducing fatty acid levels with acipimox increases the AIR in hyperthyroid patients provides further evidence of an inhibitory effect of NEFA on glucose-induced insulin secretion. This observation is in agreement with recent data showing that decreasing fatty acids with acipimox potentiates the AIR in first-degree relatives of type 2 diabetics.[23] Since our study is based on a relatively small number of nondiabetic hyperthyroid patients and there was only a weak correlation between changes in NEFA levels and changes in the AIR in this study, further investigation is needed to elucidate the relation between NEFA and insulin secretion in hyperthyroidism.

In summary, our study shows that decreasing plasma NEFAs with acipimox is associated with an increase in the AIR and K_G during an IVGTT in hyperthyroid patients. These results suggest that the abnormal glucose metabolism in hyperthyroidism could be attributed, at least in part, to the increase of plasma NEFA.

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