Jikeikai Med J 2003 ; 50 : 93-7

Effect of Nateglinide on Early Insulin Response after Sucrose Loading in OLETF Rats

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ABSTRACT

We studied the effects of nateglinide on early insulin secretion after sucrose loading in spontaneously diabetic Otsuka Long-Evans Tokushima Fatty rats. Six 8-week-old and 6 16-week-old OLETF rats were fasted for 17 hours, then given 50 mg/kg of oral nateglinide. Rats in two age-matched control groups of 6 rats each were given 0.5% oral methylcellulose. Immediately after these administrations, all groups received an oral loading dose of of sucrose (2.5 g/kg). Nateglinide significantly increased insulin levels and decreased blood glucose levels. Insulin levels returned to near control levels at 60 and 180 minutes in 8- and 16-week-old rats, respectively. Subsequently, four groups ($n=6$) of 24-week-old OLETF rats were given the following drugs orally after a 17-hour fast : 50 mg/kg of nateglinide ; 4 mg/kg of glibenclamide ; 0.2 mg/kg of voglibose ; or 0.5% methylcellulose (control), then immediately received 2.5 g/kg loading dose of oral sucrose. Both nateglinide and voglibose significantly decreased glucose levels at 30, 60, and 120 minutes ; and glibenclamide decreased glucose levels at 120 minutes. Insulin levels after sucrose loading in 24-week-old rats did not increase in the nateglinide group, continued to increase until 360 minutes in the glibenclamide group, and were finally lower in the voglibose group. Fast-acting insulin secretagogues, such as nateglinide and α-glucosidase inhibitors, may be more appropriate than glibenclamide for patients with early type 2 diabetes who show reduced early insulin secretion and delayed hyperinsulinemia after glucose loading. (Jikeikai Med J 2003 ; 50 : 93-7)

Key words : nateglinide, early insulin response, glibenclamide, voglibose, Otsuka Long-Evans Tokushima Fatty rat

INTRODUCTION

Nateglinide is a fast-acting, short-duration postprandial hypoglycemic agent that promotes insulin secretion. Nateglinide promotes early insulin secretion with activity peaking between 15 and 45 minutes in dogs[1] and 15 minutes after sucrose loading in normal rats[2]. However, in animal models of diabetes in which insulin secretion is reduced soon after glucose loading and delayed, no reports have yet been made. In healthy persons the pancreatic β-cells immediately secrete insulin in response to a rise in blood glucose levels. In contrast, in persons with prediabetes or early type 2 diabetes mellitus, insulin secretion is decreased after glucose loading, allowing blood glucose levels to rise, and increases only much later[3,4]. Indeed, insulin level can continue to rise even as blood glucose levels begin to decrease 2 or 3 hours after

Received for publication March 8, 2003
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glucose loading. This phenomenon suggests that pancreatic β-cells in patients with type 2 diabetes mellitus take longer to recognize a rise in blood glucose level, to secrete insulin in response, and to recognize a subsequent decrease in the glucose level.

In our study, we used spontaneously diabetic Otsuka Long-Evans Tokushima Fatty (OLETF) rats[5,6] (in which early post-glucose-loading insulin secretion is decreased and insulin secretion response is delayed naturally with age) to examine whether insulin secretion immediately after sucrose loading is promoted by nateglinide and whether the secreted insulin levels fall quickly. We also compared the effects of nateglinide with those of two other hypoglycemic agents, glibenclamide and voglibose.

MATERIALS AND METHODS

Animals: Four-week-old OLETF rats were provided by the Tokushima Research Institute of Otsuka Pharmaceutical (Tokushima, Japan). They were subsequently raised at the Institute for Experimental Animals, Department of Clinical Research, National Higashi-Utsunomiya Hospital, then used for the experiments.

Experiment 1: Six 8-week-old and 6 16-week-old male OLETF rats were fasted for 17 hours, then given 50 mg/kg of oral nateglinide. Rats in two age-matched control groups of 6 rats each were given 0.5% oral methylcellulose. Immediately after these administrations, all groups received an oral loading dose of of sucrose (2.5 g/kg).

Experiment 2: Four groups ($n=6$) of 24-week-old male OLETF rats were given the following drugs orally after a 17-hour fast: 50 mg/kg of nateglinide; 4 mg/kg of glibenclamide; 0.2 mg/kg of voglibose; or 0.5% methylcellulose (control), then immediately received 2.5 g/kg loading dose of oral sucrose.

Nateglinide, glibenclamide, and voglibose were suspended in 0.5% methylcellulose at concentrations of 50 mg/10 ml, 4 mg/10 ml, and 0.2 mg/10ml, respectively. Then, 10 ml/kg of each drug was administered and the control group received 10 ml/kg of 0.5% methylcellulose by gavage with microsyringes. Blood was drawn a total of 8 times from the orbital venous plexus: before treatment, and 30, 60, 120, 180, 240, 300, and 360 minutes after treatment. Plasma glucose levels were measured with the enzyme method, and plasma insulin levels were measured with radioimmunoassay (RIA) method using rat insulin as the standard.

All numerical values are expressed as means$\pm$SD. The Student's t-test and one-way analysis of variance were used to compare differences within groups. Differences with a p value less than 0.05 were considered significant.

RESULTS

Experiment 1

Figure 1 shows the results of the sucrose tolerance testing. In the control group blood glucose levels peaked 30 minutes after sucrose loading at greater than 200 mg/dl in 8-week-old rats and greater than 350 mg/dl in 16-week-old rats. Blood glucose levels in both 8-week-old and 16-week-old rats of the nateglinide group were significantly lower ($p<0.01$) than those in the control group 30 and 60 minutes after sucrose loading (Fig. 1).

Insulin levels in 8-week-old rats of the nateglinide group were significantly higher ($p<0.05$) than those in control rats 30 minutes after sucrose loading but had decreased to control levels by 60 minutes after sucrose loading. Insulin levels in 16-week-old rats of the nateglinide group were significantly higher ($p<0.01$) than those in control rats 60 minutes after sucrose loading but had decreased to control levels by 180 minutes after sucrose loading (Fig. 1).

Experiment 2

Figure 2 shows the results of the sucrose tolerance testing. Baseline blood glucose levels were approximately 150 mg/dl in all groups and did not differ significantly. In the control group blood glucose levels peaked 60 minutes after sucrose loading at approximately 500 mg/dl then gradually decreased.

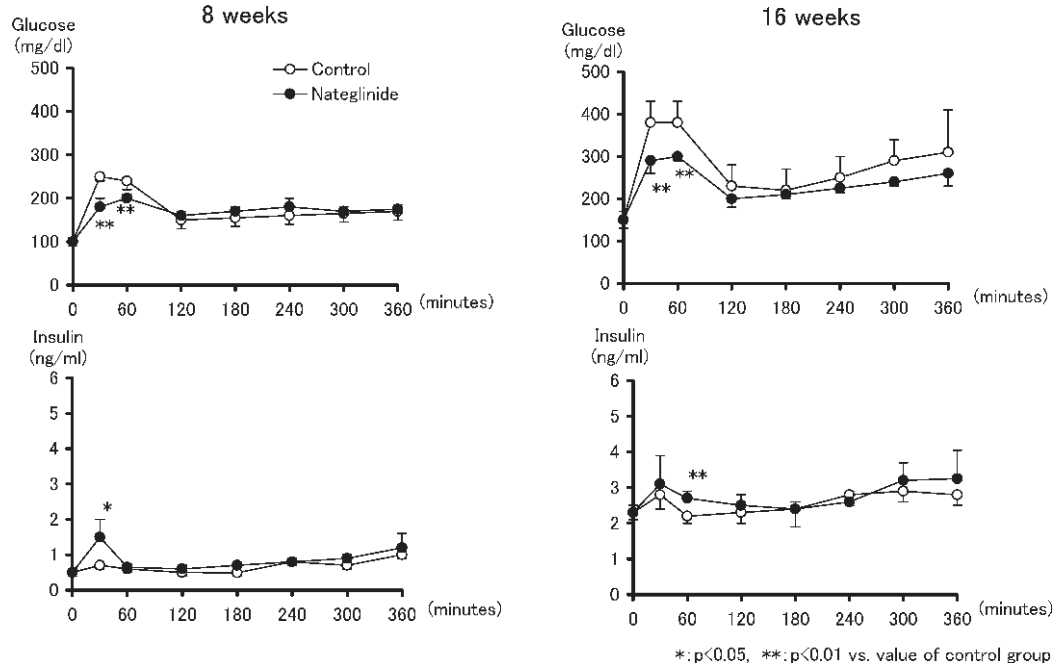

Fig. 1. Sucrose tolerance tests in OLETF rats of the nateglinide group and the control group at 8 weeks and 16 weeks.

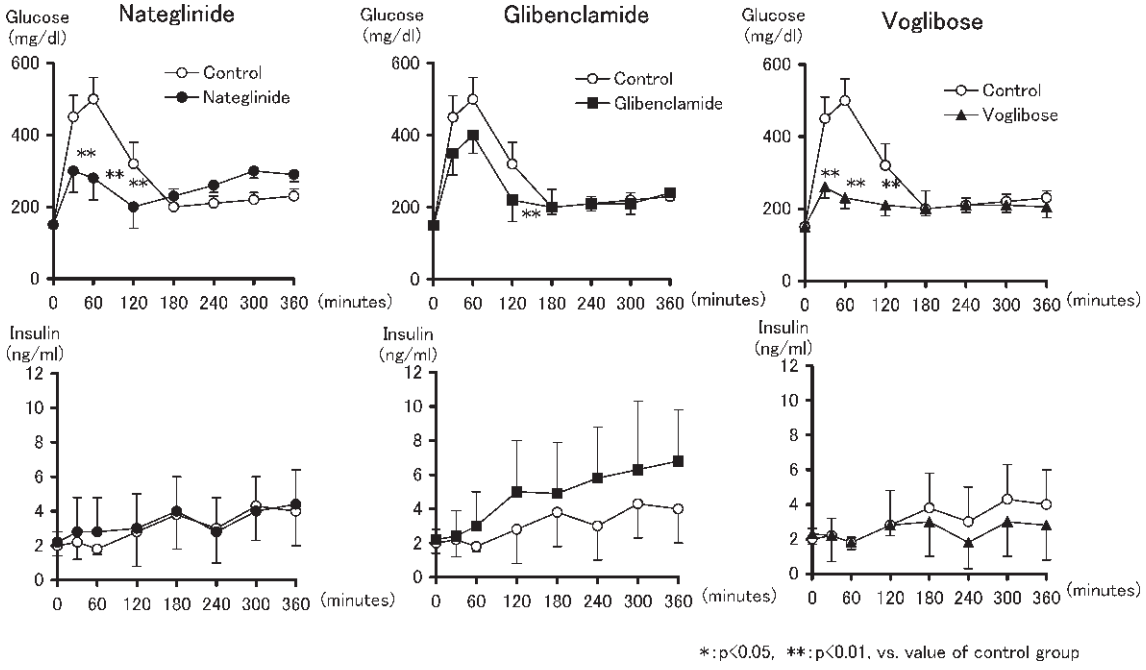

Fig. 2. Sucrose tolerance tests in OLETF rats of the nateglinide group, the glibenclamide group, and the voglibose group in comparison with the control group at 24 weeks.

Blood glucose levels were significantly lower than control in the nateglinide and voglibose groups at 30, 60, and 120 minutes after sucrose loading and in the glibenclamide group 120 minutes after sucrose loading.

Insulin levels in the control group were higher than baseline from 120 to 360 minutes after sucrose loading. The insulin levels 30 and 60 minutes after

sucrose loading in 24-week-old rats of the nateglinide group, unlike levels in 8-week-old and 16-week-old rats, were not significantly higher than control, although blood glucose levels after sucrose loading were significantly lower than control. In the glibenclamide group insulin levels after sucrose loading continued to increase until 360 minutes. In the voglibose group insulin levels after sucrose loading were slightly, but not significantly, lower than control.

DISCUSSION

Spontaneously diabetic OLETF rats are characterized by obesity (visceral fat accumulation)[7] and insulin resistance[8] and show decreased insulin secretion soon after glucose-loading and a delayed insulin secretion response with increasing age. We used these rats to investigate the effects of nateglinide on insulin secretion after sucrose loading. Our results show that the effects of nateglinide on insulin secretion dynamics after sucrose loading differ greatly depending on individual insulin secretion status. In 8-week-old and 16-week-old rats with near-normal insulin secretion, nateglinide stimulated early secretion of insulin, which peaked 30 minutes after sucrose loading, and was effective for a short time. This result agrees with the results of other experiments[2] in which nateglinide was shown to promote early insulin secretion in normal rats, with secretion peaking 15 minutes after sucrose loading. In contrast, in 24-week-old rats with advanced illness, nateglinide did not promote insulin secretion, which had increased little by 30, 60 and 120 minutes after sucrose loading, at least in the peripheral blood.

Although blood insulin levels after sucrose loading did not increase with nateglinide, blood glucose levels 30 and 60 minutes after sucrose loading were significantly lower. The reason for this lack of correlation is unknown. However, one possible explanation is that the nateglinide-induced increase in insulin levels within the portal vein inhibits hepatic glucose output and promotes hepatic glucose uptake, but at the same time insulin removal into the liver increases so that peripheral insulin levels do not rise. Thus, after nateglinide administration insulin levels in the peripheral blood are influenced by the amount of insulin secreted into the portal blood and by the amount of insulin removed into the liver. The levels of insulin in the peripheral blood thus may not accurately reflect the promotion of insulin secretion induced by nateglinide. For this reason, we believe a future study should examine how nateglinide changes insulin levels within the portal vein after sucrose loading in 24-week-old OLETF rats.

Glibenclamide continued to stimulate insulin secretion for an extended time after sucrose loading in 24-week-old OLETF rats. Even after 360 minutes, insulin levels were higher than control. Sulfonylureas, which are insulin secretagogues used for the last 30 years as oral hypoglycemic drugs, stimulate pancreatic β-cells, increase insulin secretion, and increase insulin levels in the portal vein. However, sulfonylureas cannot compensate for a lack of additional insulin secretion to correct postprandial hyperglycemia, which is a characteristic insulin response in type 2 diabetes mellitus. In other words, sulfonylureas cannot stimulate a rapid rise in insulin levels that normally occurs in response to glucose challenge. Moreover, our present results have shown that in viscerally obese rats with insulin resistance, decreased early insulin secretion, and a delayed insulin secretion response, sustained insulin secretion-stimulating drugs, such as glibenclamide, may further promote obesity and exacerbate insulin resistance.

In contrast, voglibose significantly inhibits the activity of α-glucosidases (enzymes involved in the digestion and absorption of carbohydrates) and inhibits the postprandial increase in blood glucose levels. These pharmacologic activities were also seen in our present experiments, in which voglibose was observed to suppress the rise in blood glucose after sucrose loading, concurrently suppressing the intrinsic delayed and excessive insulin secretion after sucrose loading. These experimental results show that α-glucosidase inhibitors can decrease insulin resistance and prevent the exhaustion of pancreatic β-cells and might inhibit the development of arteriosclerosis in the long term.

Our results indicate that glibenclamide is unsuitable for treatment of patients with early type 2

diabetes who have insulin resistance, reduced early insulin secretion properties after glucose loading, and delayed insulin secretion. Glibenclamide is unsuitable for such patients because it stimulates insulin secretion for extended periods of time in response to a rise in blood glucose after glucose loading. More appropriate are fast-acting, short-duration drugs that stimulate insulin-secretion, such as nateglinide, or α-glucosidase inhibitors, which suppress insulin secretion in a secondary manner. More research is needed before any conclusions can be drawn about when to use either nateglinide or α-glucosidase inhibitors for postprandial hyperglycemia. However, nateglinide, which rapidly responds to an increase in blood glucose levels by increasing insulin levels inside the portal vein, suppressing hepatic glucose output, and increasing hepatic glucose uptake, can be used to mimic normal insulin secretion dynamics.

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