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Differences in Insulin Secretion in Portal Blood after Administration of Glimepiride and Glibenclamide : A Study in OLETF Rats

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ABSTRACT

Aims : To clarify differences in insulin-secretagogue and antihyperglycemic properties between glimepiride and glibenclamide.

Methods : Catheters were inserted into the portal veins of 12-week-old, obese, spontaneously type 2 diabetic Otsuka Long-Evans Tokushima Fatty rats and left in place. After 17-hour fasting, the rats were given either 1 mg/kg of glibenclamide, 1 mg/kg of glimepiride, or 0.5% methylcellulose (control), and then immediately given oral glucose 1 g/kg.

Results : Portal insulin levels increased after glucose loading and began to decrease 60 minutes after glucose loading in the glimepiride group, but those in the glibenclamide group were significantly higher than those in the glimepiride group and continued to increase well after 60 minutes after glucose loading. The area under the curve for insulin did not differ between the glibenclamide group (1,259±674 ng min/dL) and the glimepiride group (1,068±388 ng min/dL) for 0 to 60 minutes but was significantly lower in the glimepiride group (1,901±928 ng min/dL) than in the glibenclamide group (3,392±1,047 ng min/dL) for 60 to 270 minutes. Glucose levels in peripheral blood after glucose loading were significantly lower than control in the glibenclamide group after 120 minutes and in the glimepiride group after 60 minutes, but the area under the curve for glucose did not differ significantly between the glibenclamide group (29,213±6,449 mg min/dL) and glimepiride group (24,524±3,618 mg min/dL).

Conclusions : Glimepiride has a faster onset of action but otherwise has antihyperglycemic properties similar to those of glibenclamide. In contrast, glimepiride is a weaker, shorter-acting insulin secretagogue than is glibenclamide. (Jikeikai Med J 2003 ; 50 : 173-7)

Key words : glimepiride, glibenclamide, insulin secretion in portal blood, type 2 diabetes

INTRODUCTION

The UK Prospective Diabetes Study[1] found significant reductions in median glycosylated hemoglobin levels in patients who had received intensive therapy with sulfonylureas, insulin, or metformin for 10 years. Patients receiving insulin, glibenclamide, or chlorpropamide showed a 25% decrease in risk for diabetes-related endpoints but also gained significantly more weight than did patients receiving conven-

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tional diet-only therapy.

The strong insulin secretagogic activity of first- and second-generation sulfonylureas can easily elevate blood levels of insulin. Such an elevation can increase weight and exacerbate insulin resistance as well as producing hypoglycemia. Glimepiride, a new, recently approved third-generation sulfonylurea, has antihyperglycemic activity equivalent to that of such drugs as glibenclamide but has weaker insulin secretagogic activity[2-4]. Therefore, glimepiride would likely increase insulin sensitivity by, for example, increasing the rates of hepatic and peripheral glucose utilization[5-6].

To assess differences in insulin secretagogic and antihyperglycemic activities between a third-generation sulfonylurea (glimepiride) and a second-generation sulfonylurea (glibenclamide), we examined the acute effects of these drugs on portal blood insulin secretion dynamics and peripheral blood glucose levels in Otsuka Long-Evans Tokushima Fatty (OLETF) rats, an animal model of spontaneous type 2 diabetes with obesity.

MATERIALS AND METHODS

Animals

OLETF rats[7,8] were obtained at 4 weeks of age from the Tokushima Research Institute, (Otsuka Pharmaceutical Co., Tokushima). The rats were housed in plastic cages (320×270×175 mm) in an animal room with a controlled temperature (23±2°C) and relative humidity (55±15%) and a 12-hour light/12-hour dark cycle (lights on at 0700). They were given free access to standard rat chow (CE-2; CLEA Japan, Inc., Tokyo) and tap water until 12 weeks of age. The care and use of the animals in this study were in accordance with the guidelines of the Laboratory Animal Facilities of The Jikei University School of Medicine.

Experimental design

Indwelling catheters were placed in the portal vein of 12-week-old OLETF rats. The next day, the rats were fasted for 17 hours, then treated with oral glibenclamide 1 mg/kg ($n=7$), glimepiride 1 mg/kg ($n=7$), or 0.5% methylcellulose (vehicle control) ($n=9$). The dose of glibenclamide was determined from previous studies showing an adequate glucose-lowering effect after oral administration to fasting normal rats[9]. The same dose of glimepiride was used because the glucose-lowering effects of glimepiride are similar to those of glibenclamide[6]. Immediately after being treated with glimepiride, glibenclamide, or methylcellulose, the rats underwent oral glucose tolerance testing (OGTT) with a glucose load of 1 g/kg. Blood samples were drawn at baseline and 15, 30, 60, 120, 180, and 270 minutes after glucose loading. Samples of portal blood were taken from the catheter in the portal vein, and samples of peripheral blood were drawn from the caudal vein. The rats were not restrained and did not receive anesthesia during OGTT. Areas under the curve (AUC) were calculated for levels of insulin in the portal blood and glucose in the peripheral blood for the periods of 0 to 60 minutes, 60 to 270 minutes, and 0 to 270 minutes after glucose loading. Blood glucose levels were measured enzymatically. Plasma insulin levels were measured with enzyme immunoassay using rat insulin as the standard.

Statistical methods

All numerical values are expressed as means± standard errors of mean. We applied one-way analysis of variance, and followed up with Scheffe's method as a post-hoc test for significant differences among the groups. A level of $p<0.05$ was considered to indicate statistical significance.

RESULTS

Elevated levels of insulin in portal blood decreased within 60 minutes in the glimepiride group but persisted for more than 60 minutes in the glibenclamide group (Fig. 1). Levels of insulin in portal blood were significantly higher in the glibenclamide group than in the control group 60 and 120 minutes after treatment and were also significantly higher in the glibenclamide group than in the glimepiride group

120 minutes after treatment. The insulin AUC for 0 to 60 minutes after treatment did not differ between the glimepiride group and the glibenclamide group. However, the AUC in the glimepiride group was significantly lower than that in the glibenclamide group for 60 to 270 minutes after treatment and was also slightly but not significantly lower for 0 to 270 minutes (Table 1).

Glucose levels in peripheral blood were significantly lower than control from 120 minutes after glucose loading in the glibenclamide group and from 60 minutes after loading in the glimepiride group (Fig. 2). No significant difference in the AUC for glucose was noted between glibenclamide and glimepiride at 0 to 60 minutes, 60 to 270 minutes, or 0 to 270 minutes (Table 1).

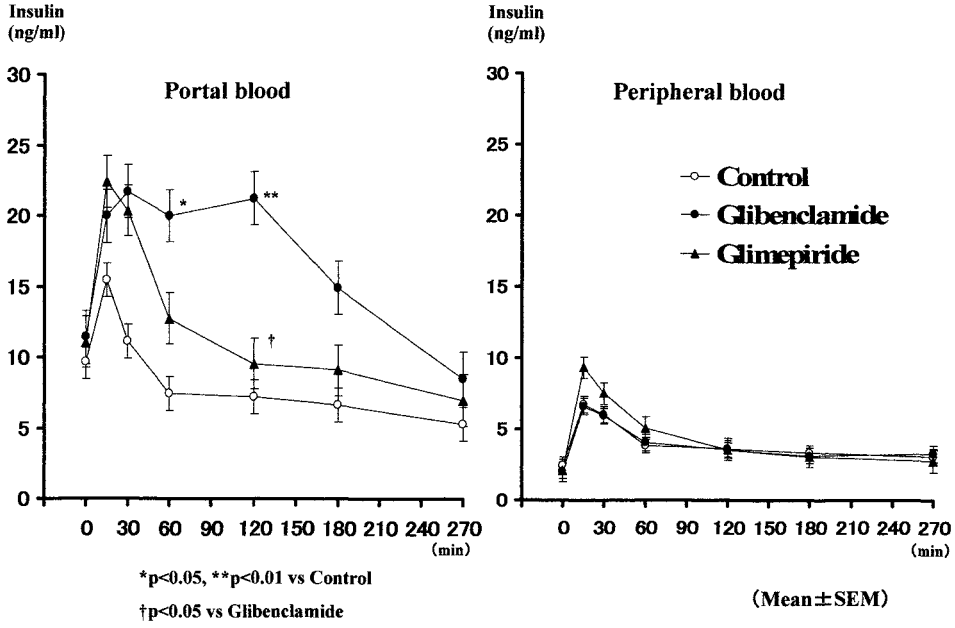

Fig. 1. Insulin levels after glucose loading in portal and peripheral blood: Comparison of acute effects of glimepiride and glibenclamide.

Table 1. Comparison of AUC for insulin and glucose

AUC for insulin (ng・hr/ml)

	Portal blood			Peripheral blood		
	Control	Glibenclamide	Glimepiride	Control	Glibenclamide	Glimepiride
0–60 min	12.9±0.4	30.0±4.6	17.8±2.4	5.2±0.7	5.1±0.8	6.7±0.5
60–270 min	26.2±3.3	56.5±7.1**	31.7±58†	11.9±1.7	11.9±2.0	12.0±0.7
0–270 min	39.1±3.6	77.5±11**	49.5±6.5	17.1±2.3	17.1±2.7	18.7±1.1

AUC for glucose (mg・hr/dl)

	Portal blood			Peripheral blood		
	Control	Glibenclamide	Glimepiride	Control	Glibenclamide	Glimepiride
0–60 min	262±13	247±22	251±10	178±10	186±18	152±7
60–270 min	388±21	264±19**	238±5**	397±26	301±26*	257±17**
0–270 min	650±26	511.2±40*	489±8*	575±33	487±44	409±23**

(Mean±SEM) *$p<0.05$, **$p<0.01$ vs Control
†$p<0.05$ vs Glibenclamide

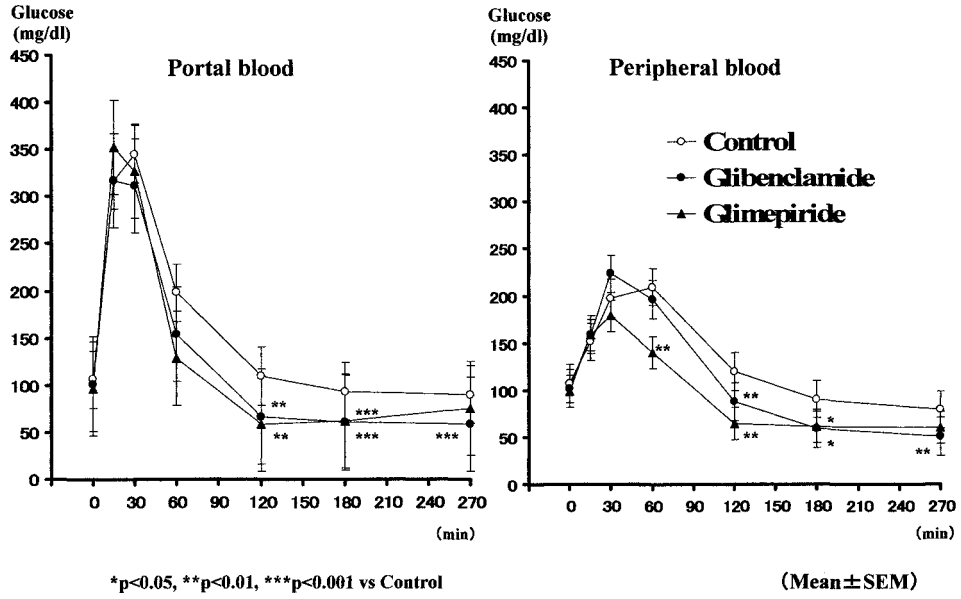

Fig. 2. Glucose levels after glucose loading in portal and peripheral blood: Comparison of acute effects of glimepiride and glibenclamide.

DISCUSSION

Glimepiride, a third-generation sulfonylurea with extrapancreatic effects[7,8], has antihyperglycemic activity equivalent to that of glibenclamide, a second-generation sulfonylurea. However, the weaker insulin secretagogic activity of glimepiride suggests that this drug is less likely to cause weight gain[6] or to exacerbate insulin resistance[2-4]. In OLETF rats undergoing long-term treatment, glibenclamide produced significantly higher levels of cellular hypertrophy than did glimepiride and significantly increased tumor necrosis factor-α mRNA expression in adipose tissue[10]. In normal dogs a single dose of glimepiride significantly increased systemic glucose uptake but did not increase the rate of hepatic glucose uptake[5]; this result suggests that the main acute effect of glimepiride is to increase glucose uptake in skeletal muscle. In the present study we found that although glimepiride elevated insulin levels in portal blood for less than 60 minutes and did not significantly decrease glucose levels in portal blood 60 minutes after treatment; glucose levels in peripheral blood were significantly reduced 60 minutes after treatment. These results suggest that glimepiride affects glucose uptake in skeletal muscle.

In the present study, although portal insulin levels were lower with glimepiride than with glibenclamide, peripheral insulin levels were similar with the two drugs. A possible explanation for this difference in insulin levels between portal and peripheral blood is that a major portion of the insulin produced is taken up by the liver before it reaches the peripheral circulation[11,12]; changes in hepatic uptake of insulin would therefore greatly affect peripheral insulin levels. Experiments with in situ perfused rat liver[13] support the hypothesis that the portal free fatty acids (FFA) produced by intra-abdominal adipose tissue interfere with hepatic uptake of insulin. The difference in portal insulin secretion dynamics between glibenclamide and glimepiride might cause portal FFA levels to differ after treatment through the antilipolytic properties of insulin[14]. This difference in portal FFA levels after treatment might cause hepatic uptake of insulin to differ between glibenclamide and glimepiride and consequently might cause peripheral insulin levels to be similar with both drugs.

Our findings show that the antihyperglycemic effects of glimepiride are equivalent to those of glibenclamide but are expressed earlier. In general, glibenclamide does not have postprandial antihyperglycemic activity, so would be clinically less effective than

would glimepiride against postprandial hyperglycemia. Our findings also clearly show that the insulin secretagogue activity of glimepiride is shorter-lasting than that of glibenclamide. This difference would make glimepiride more effective against such conditions as secondary failure resulting from pancreatic β cell exhaustion and progressive arteriosclerosis due to hyperinsulinemia.

Our findings clearly show that glibenclamide and glimepiride differ in their duration and intensity of action as insulin secretagogues and in the time until their antihyperglycemic effects appear.

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