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The Hypoglycemic Effects of Acarviosine-Glucose Modulate Hepatic and Intestinal Glucose Transporters *In vivo*

Mi Ja Chung, Young-Soo Lee[1], Byoung-Chul Kim, Soo-Bok Lee[2], Tae-Hwa Moon[1], Sung-Joon Lee*, and Kwan-Hwa Park[1]

Division of Food Science, College of Life Sciences and Biotechnology, Institute of Biomedical Sciences and Safety, Korea University, Seoul 136-713, Korea

[1]Center for Agricultural Biomaterials, Department of Food Science and Technology, School of Agricultural Biotechnology, Seoul National University, Seoul 151-921, Korea

[2]Research Institute of Food and Nutritional Sciences and Department of Food and Nutrition, Yonsei University, Seoul 120-749, Korea

Abstract Acarviosine-glucose (AcvGlc) is an α-glucosidase inhibitor and has similar inhibitory activity to acarbose *in vitro*. We synthesized AcvGlc by treating acarbose with *Bacillus stearothermophilus* maltogenic amylase and fed C57BL/6J and *db/db* mice with diets containing purified AcvGlc and acarbose for 1 week. AcvGlc (50 and 100 mg/100 g diet) significantly reduced plasma glucose and triglyceride levels in *db/db* mice by 42 and 51%, respectively ($p<0.0001$). The hypoglycemic and hypotriglyceridemic effects of AcvGlc were slightly, but significantly, greater than those seen with acarbose treatment ($p<0.0001$) in C57BL/6J mice. In an oral glucose tolerance test, glucose tolerance was significantly improved at all time points ($p<0.01$). The expression of two novel glucose transporters (GLUTs), GLUT10 and GLUT12, were examined by Western blot analysis. GLUT10 was markedly increased in the *db/db* livers. After AcvGlc treatment, the expression of hepatic GLUT10 was decreased whereas intestinal GLUT12 was significantly increased in both strains of mice. Our results show that AcvGlc improves plasma lipid and glucose metabolism slightly more than acarbose. Regulation of hepatic GLUT10 and intestinal GLUT12 may be important in controlling blood glucose levels.

Keywords: α-glucosidase inhibitor, acarviosine-glucose, diabetes mellitus, *in vivo*, glucose transporter-10, glucose transporter-12

Introduction

Alpha-glucosidase inhibitors block brush border enzymes such as maltase, sucrase, and α-amylase, thus reducing the production of glucose from starch-based foods and improving hyperglycemia in diabetic patients (1, 2). Acarbose, one of the α-glucosidase inhibitor drugs, is efficient for both the treatment and prevention of hyperglycemia (3, 4), and could lower the risk of coronary heart disease among diabetic patients (5, 6). Some adverse effects of acarbose include flatulence and abdominal distension associated with the fermentation of unabsorbed carbohydrates or delayed carbohydrate digestion.

Acarviosine-glucose (AcvGlc) shows similar levels of α-glucosidase inhibitor activity *in vitro* (7-9) compared with acarbose and is relatively resistant to intestinal fermentation due to the lack of a fermentable glucose moiety from the non-reducing end of acarbose (10). This characteristic of AcvGlc may help diminish the adverse effects associated with conventional α-glucosidase inhibitor treatments. AcvGlc can be produced from acarbose following its incubation with *Bacillus stearothermophilus* maltogenic amylase (BSMA) (11-13).

Controlling hyperglycemia by α-glucosidase inhibitor treatment could beneficially affect cellular glucose uptake mediated by glucose transporters (GLUTs). The GLUT family is subdivided into three different classes (Class I, II, and III) according to sequence homology. GLUTs mediate facilitative and energy independent transport of glucose across the cell membranes in various tissues. Some GLUTs are insulin sensitive and are thought to be associated with diabetes due to the chromosomal locations of the corresponding genes. GLUT4 is a well-characterized insulin sensitive GLUT that is abundant in muscle. The translocation of GLUT4 from intracellular stores to the plasma membrane in response to insulin is enhanced by exercise and improved hyperglycemia. Two Class II GLUTs, GLUT10 and 12, are highly expressed in the liver and the small intestine, respectively, and both are presumed to be associated with diabetes. This is because the GLUT 10 gene is located in the Type II diabetes-linked region of human chromosome 20, and GLUT 12 is specifically expressed in insulin-sensitive tissues and can be translocated from the cytosol to the cell membrane in response to insulin, as is GLUT4. However, the expression of GLUT10 and GLUT12 as a consequence of improved hyperglycemia is not well understood.

In this report we studied the hypoglycemic effects of AcvGlc in a mouse model of monogenic diabetes (*db/db*) and in C57BL/6J control mice. After a 1-week treatment, AcvGlc compounds effectively improved diabetic hyperglycemia. The expression of hepatic GLUT10 and intestinal GLUT12 was markedly elevated in *db/db* mice compared with C57BL/6J mice. After AcvGlc treatment, hepatic GLUT10 was significantly reduced whereas intestinal GLUT12 expression was increased. Our results indicate that short-term treatment with AcvGlc improves diabetic hyperglycemia in mice and modulates GLUT expression in the liver and small intestine.

*Corresponding author: Tel: 82-2-3290-3029; Fax: 82-2-3290-3029
E-mail: junelee@korea.ac.kr
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Materials and Methods

Preparation of acarbose and AcvGlc Acarbose was generously provided by Bayer Korea (Seoul, Korea). The culture and purification of *B. stearothermophilus* maltogenic amylase (BSMA) was described previously (11). AcvGlc was produced enzymatically from acarbose by incubation with BSMA as described previously (8, 9). Acarbose and AcvGlc were analyzed using high-performance ionic chromatography (HPIC). Filtered samples were applied to a CarboPac PA1 column (0.45×25 cm, Dionex, Sunnyvale, CA, USA) equipped with an electrochemical detector (ED40; Dionex). The sample was eluted with a linear gradient ranging from 100% eluent A (150 mM NaOH in double distilled water) to 40% eluent B (150 mM NaOH + 600 mM sodium acetate) over 40 min. The flow rate of the mobile phase was maintained at 1.0 mL/min.

Animals and feeding studies The *db/db* mice (BKS.Cg-m+/+*Lepr*^{db}/J) provide a monogenic mouse model of type II diabetes due to leptin receptor deficiency, and C57BL/6J mice serve as the control. The control mice have an identical genetic background to the *db/db* mice. The mice were purchased from Jackson Laboratory (Bar Harbor, ME, USA) and were maintained in the animal facilities at Hae-Eun Biotech (Seoul, Korea). The animals were kept in a specific-pathogen-free room at 21-25°C with a 12-hr day/night cycle, and water and standard chow were provided *ad libitum*. All experiments were performed using protocols approved by the Committee on Animal Experimentation of the Hae-Eun Biotech Research Committee. Ten to 12 weeks old mice were fed normal chow or chow containing purified α-glucosidase inhibitors (acarbose or AcvGlc) for one week. Two different amounts of the two α-glucosidase inhibitors were used, 50 mg/100 g chow (Acarbose 50 and AcvGlc 50) and 100 mg/100 g chow (Acarbose 100 and AcvGlc 100). After feeding, the mice were fasted overnight (16-19 hr) and then blood samples were collected retro-orbitally in purple-topped EDTA tubes for further analysis.

Measurements Blood plasma was separated by centrifugation, and then glucose, total cholesterol, total triglyceride, and free fatty acid levels were measured enzymatically (Shin-Yang Chemical, Seoul, Korea). Protein concentration was determined using a Bio-Rad protein kit (Bio-Rad, Hercules, CA, USA) with bovine serum albumin (Sigma Chemical Co., St. Louis, MO, USA) as a standard.

Oral glucose tolerance test (OGTT) Four age-matched male and female mice from each genotype were raised on the AcvGlc 100 diet. After one week on the AcvGlc 100 diet, mice were fasted for 18 hr, then anesthetized and given glucose (1.0 g/kg of 20% D-glucose, injected orally) for the OGTT. The test was performed based on previously reported methods with minor modifications (14, 15). Blood samples were obtained retro-orbitally at 0, 15, 30, 34, 60, and 120 min after glucose administration. Glucose elimination was quantified as the K_G (*i.e.*, the glucose elimination constant), which is defined as the reduction in circulating glucose between 1 and 20 min after the intravenous administration of glucose and is calculated after the logarithmic transformation of the individual plasma glucose values. K_G is expressed as the percent elimination of glucose per min. For the OGTT, the K_G was calculated based on the glucose elimination rate between 15 and 60 min.

Western blot analysis Liver membrane preparations were made as previously described (16). The anti-mouse low density lipoprotein (LDL) receptor and LDL receptor related protein (LRP) antibodies were gifts from Dr. Allen Cooper (Stanford School of Medicine). Anti-mouse apoE antibody was purchased from Academy Biomedical (Houston, TX, USA). Anti-GLUT5, -GLUT10, and -GLUT12 antibodies were purchased from Alpha Diagnostics International (San Antonio, TX, USA). Horseradish peroxidase (HRP)-conjugated secondary antibody was purchased from Merck-Korea (Seoul, Korea). Western blots were performed by standard procedures and bands were visualized using the ECL method (Amersham-Pharmacia Korea, Seoul, Korea). The density of each band was quantified using Sigmagel software (Jandel Scientific, San Rafael, CA, USA).

Data analysis The data were expressed as the mean ± SE, unless otherwise indicated. Student's *t*-test was performed for two-group comparisons. Values were considered statistically significant at $p<0.05$.

Results and Discussion

Animal feeding studies, baseline glucose, and lipid concentrations The purity of the AcvGlc used in the feeding studies was approximately 96% (Fig. 1). One week of feeding with diets containing acarbose or AcvGlc reduced the fasting glucose and triglyceride levels in both strains of mice (Table 1). The body weight and food intake of each strain was unchanged during feeding (Table 1). Overall, the hypoglycemic and hypolipidemic effects of AcvGlc were similar to those of acarbose. However, in C57BL/6 mice, AcvGlc 100 reduced plasma glucose and triglyceride slightly more efficiently than acarbose (Table 1). The reduction in free fatty acids was significant with the AcvGlc 100 diet (154±8, baseline; 118±8 μeq, AcvGlc100, $p<0.01$), but not with the Acarbose 100 diet. In *db/db* mice, the effects of acarbose and AcvGlc on blood glucose and triglyceride levels were similar (Table 1).

Oral glucose tolerance test Glucose tolerance was examined after 1 week on the AcvGlc 100 diet (Fig. 2A and 2B). The administration of AcvGlc improved glucose tolerance significantly in both hyperglyceridemic *db/db* and C57BL/6 mice ($p<0.0001$). In C57BL/6J, the plasma glucose level reached a maximum at 30 min after glucose challenge. Thereafter, glucose elimination persisted until 120 min when the original plasma glucose level was restored. AcvGlc treatment lowered the maximum glucose level at 30 min to the fasting glucose concentration (Fig. 2B). By contrast, there was little glucose elimination between 15 and 60 min in *db/db* mice, which suggests severe glucose intolerance (Fig. 2A). In both animals, the

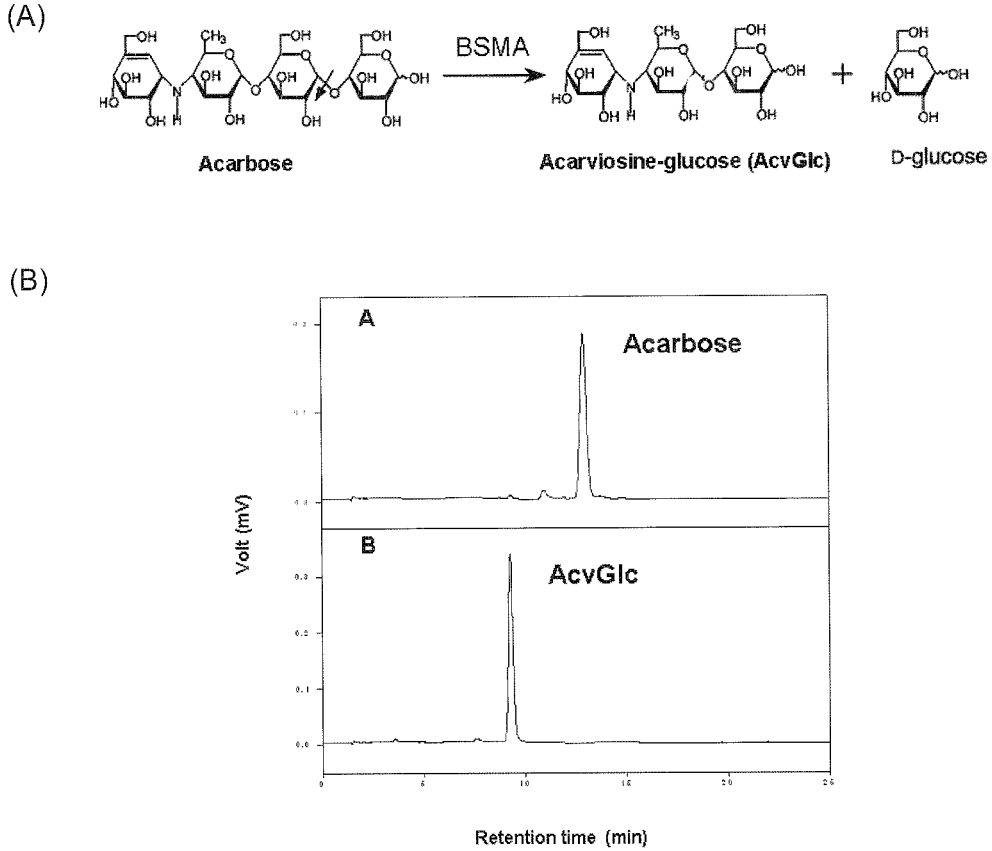

Fig. 1. A. Enzymatic production of acarviosine-glucose from acarbose by *Bacillus stearothermophilus* maltogenic amylase (BSMA). B. HPIC analyses of acarbose and purified AcvGlc. (a) Acarbose before treatment with BSMA, (b) AcvGlc purified after treatment with BSMA. The purities of acarbose and AcvGlc are 92 and 96%, respectively.

Table 1. Plasma concentrations of glucose, triglycerides (TG), and cholesterol in control (C57BL/6J) and diabetic (*db/db*) mice[1)]

	Body weight (g)	Food intake (g/day)	Glucose (mg/dL)	TG (mg/dL)	Cholesterol (mg/dL)
C57					
Baseline	21.1±0.6	2.8±0.2	130.0±18.0	79.9±19.4	94.4±14.7
Acarbose 50	21.2±0.7	2.7±0.1	123.0±13.0	78.3±14.6	98.3±12.6
Acarbose 100	21.1±0.5	2.7±0.2	106.9±8.5[2,3)]	72.9±11.3	83.8±20.0
AcvGlc 50	20.5±0.4	2.8±0.1	119.4±19.3	55.9±3.3[4)]	91.2±6.5
AcvGlc 100	21.0±0.5	2.8±0.3	59.0±4.8[2,3,4)]	55.6±4.7[4)]	85.1±13.3
DB					
Baseline	41.5±1.7	7.3±0.2	479.9±12.8	125.3±7.4	113.5±5.1
Acarbose 50	40.9±1.6	7.3±0.1	365.6±24.0[2)]	107.9±8.6	112.5±7.5
Acarbose 100	41.1±2.0	7.4±0.2	281.4±18.9[2,3)]	64.3±4.4[2,3)]	97.3±4.3[2)]
AcvGlc 50	41.8±1.4	7.4±0.1	348.0±28.0[2)]	102.6±5.2[2)]	118.0±7.5
AcvGlc 100	40.5±0.8	7.6±0.4	277.9±12.0[2,3)]	61.7±4.2[1,3)]	100.1±9.0
Baseline	41.5±1.7	7.3±0.2	479.9±12.8	125.3±7.4	113.5±5.1

[1)]Data are the mean (mg/dL)±SE. Acarbose 50 and 100 are 1-week interventions with 50 and 100 mg acarbose/100 g diets, respectively. AcvGlc 50 and 100 are 1-week interventions with 50 and 100 mg AcvGlc/100 g diets, respectively, C57, C57BL/6 mice; DB, *db/db* mice. [2)]$p<0.05$ compared with baseline; [3)]$p<0.05$ compared with the 50 mg/100 g diet treatment; [4)]$p<0.05$ compared with acarbose treatment.

glucose removal rate was significantly improved after AcvGlc treatment, and this result was dramatic in *db/db* mice. The K_G between 30 and 60 min was 3.9%/min in vehicle-treated *db/db* mice, and glucose elimination was significantly improved after AcvGlc treatment (11.4%/min). This effect was blunted in control mice, but still remained significant (7.0%/min with AcvGlc vs. 3.9%/min with vehicle). Similar findings were observed in *db/db* mice.

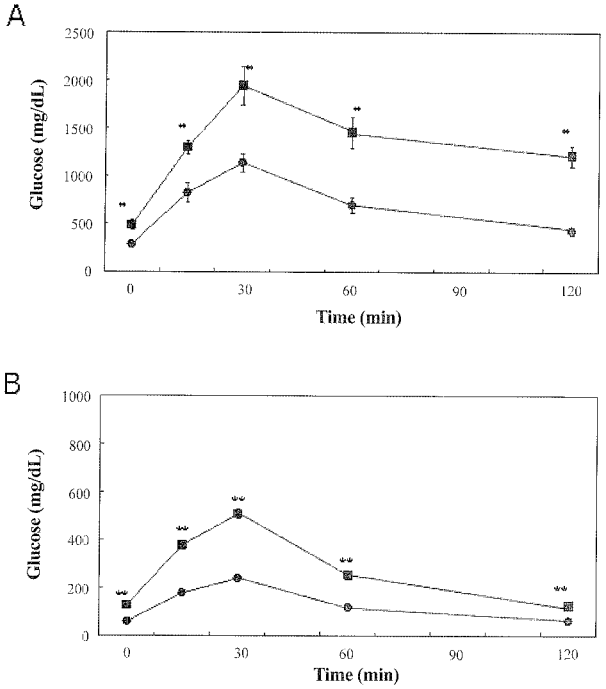

Fig. 2. Plasma levels of glucose during the OGTT in *db/db* (A) and C57BL/6J mice (B) given normal (■) and AcvGlc-containing (100 mg/100 g, ●) diets for 1 week. Data are means±SD. $^{**}p<0.001$ between ■ and ●. N = 4 per group.

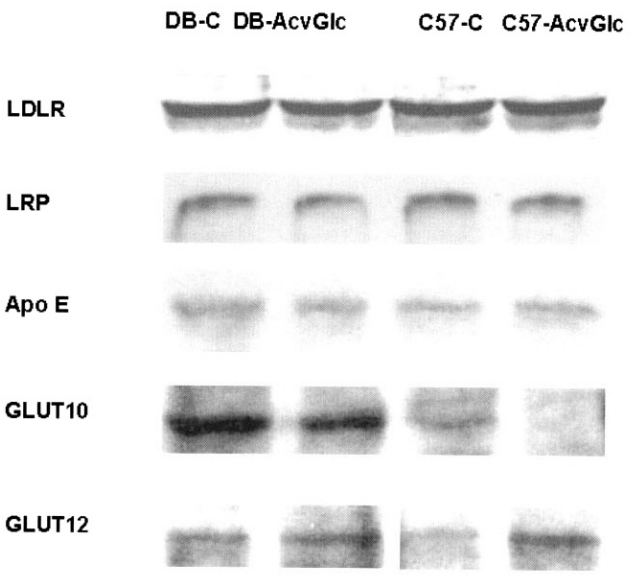

Fig. 3. Western blot analysis of lipid and glucose transport proteins. All experiments were performed using liver samples except those involving GLUT12 (small intestine). LDLR, LDL receptor; LRP, LDL receptor protein; apoE, apolipoprotein E; GLUT10, glucose transporter-10; GLUT12, glucose transporter-12. DB and C57 indicate *db/db* and C57BL/6J mice, respectively. C and AcvGlc indicate the control and AcvGlc-containing (100 mg/100 g) diets, respectively.

Effect of AcvGlc on the expression of GLUTs in the liver and small intestine GLUT expression was examined since the hypoglycemic effects of AcvGlc could alter cellular glucose uptake in the liver and the small intestine. GLUT10, which is abundant in the liver, was initially identified in a survey of expressed sequences in the Type II diabetes-linked region of human chromosome 20q12-13.1 (17) and is the highest-affinity transporter identified in the GLUT family with a K_m of approximately 0.3 mM (18). Under a normal diet, GLUT10 levels were markedly increased in diabetic mouse livers compared with controls. After the AcvGlc 100 diet, GLUT10 levels decreased in both mice (18% reduction, $p<0.01$ in *db/db*; 51% reduction, $p<0.01$ in C57BL6J). In C57BL/6J mice, GLUT10 was nearly undetectable.

GLUT12 is specifically expressed in insulin-sensitive tissues and is abundant in the small intestine (19). Its expression was induced after AcvGlc treatment in both strains of mice (Fig. 3). Similar results were observed for the expression of GLUT5, especially in *db/db* mice, which is a fructose transporter highly expressed in the small intestine (data not shown). These results suggest that AcvGlc administration may induce monosaccharide transporters in the small intestine, probably to ensure the sufficient uptake of monosaccharide energy sources.

Effect of AcvGlc on the expression of molecules involved in lipid transport in the liver The LDL receptor and LDL receptor related protein (LRP) are two major receptors for the removal of apoB-containing lipoproteins, including triglyceride-rich chylomicron remnants and very-low-density lipoprotein (VLDL) (20). The hepatic secretion of apoE facilitates triglyceride-rich lipoprotein removal (21), thus its expression after triglyceride lowering by AcvGlc was examined. The levels of the LDL receptor, LRP, and apoE were not altered by AcvGlc treatment in either the control or the *db/db* mice after AcvGlc treatment.

This is one of the few studies to investigate the expression of GLUTs after treatment with α-glucosidase inhibitor. We examined the expression of two novel glucose transporter proteins that may be associated with diabetes, GLUT10 and GLUT12, both of which have physiological roles and regulation that are not well understood *in vivo*.

GLUT10 was identified in a survey of expressed sequences in the Type II diabetes-linked region of human chromosome 20q12-13.1 (17), and is the highest-affinity transporter in the GLUT family with a K_m of approximately 0.3 mM (18). GLUT12 is an insulin-sensitive glucose transporter protein in the small intestine, as is GLUT4 in adipocytes and muscle (19). We found that both hepatic GLUT10 and intestinal GLUT12 were markedly increased in diabetic mice and our data clearly showed that the overexpression of these two GLUTs was indeed associated with diabetes status, at least in mice. The etiological implications and the mechanism of the overexpression of these two GLUTs in diabetes should be studied further. It will be also interesting to examine GLUT10 and GLUT12 expression in human tissue samples, if possible.

In the intestine, we showed that GLUT12 is induced in both *db/db* and control animals after feeding an AcvGlc containing diet. Paive *et al.* (22) previously reported that acute treatment with acarbose induced intestinal GLUT1, but did not change the levels of intestinal Na^+-glucose cotransporter-1 (SGLT-1) and GLUT2. Total glucose uptake

in the intestine was not altered in the study. Since GLUT2 is a low affinity but high capacity glucose transporter, it is probably a major shuttle system for intestinal glucose uptake with SGLT-1. Other intestinal GLUTs including GLUT1 and GLUT12 may participate in the fine tuning of glucose uptake. Therefore, it may be possible that the upregulation of GLUT12 as well as GLUT1 may help to preserve the total glucose absorption capacity of the small intestine in the presence of α-glucosidase inhibitor.

In the liver, we found that GLUT10 expression was dramatically repressed in *db*/*db* livers treated with AcvGlc. GLUT10 was nearly undetectable after feeding the AcvGlc diet. GLUT2 is also abundant in the liver as well as in the small intestine; however, it cannot be the major hepatic GLUT for glucose homeostasis due to its high Km (15-20 mM). Since the increased rates of gluconeogenesis and glycogenolysis in diabetic patients (24) are normalized in response to improved glucose tolerance, we speculate that the down-regulation of GLUT10 after AcvGlc treatment may be associated with improved glucose tolerance.

Additionally, we investigated the expression of receptors for triglyceride-rich lipoproteins. The LDL receptor and LRP are two major receptors for triglyceride rich lipoproteins and remove more than 90% of chylomicron remnants in a single-pass liver perfusion experiment (23, 24). Apolipoprotein E is a major ligand of the LDL receptor and LRP regarding the transport of triglyceride rich lipoproteins and is produced by the liver (21). We found that LDL receptor, LRP and apoE expression were not altered after AcvGlc treatment, thus the triglyceride lowering effects of AcvGlc may operate via mechanisms other than those enhancing receptor-mediated lipoprotein uptake.

In conclusion, our results show that AcvGlc improved plasma triglyceride and glucose metabolism as effectively as acarbose. GLUT10 was markedly increased in diabetic mice. AcvGlc treatment reduced hepatic GLUT10 and induced intestinal GLUT12 expression. These data suggest that the regulation of GLUT10 and GLUT12 may be important in the improvement of plasma glucose metabolism.

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