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Rare sugar D-psicose improves insulin sensitivity and glucose tolerance in type 2 diabetes Otsuka Long-Evans Tokushima Fatty (OLETF) rats

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ABSTRACT

A rare sugar, D-psicose has progressively been evaluated as a unique metabolic regulator of glucose and lipid metabolism, and thus represents a promising compound for the treatment of type 2 diabetes mellitus (T2DM). The present study was undertaken to examine the underlying effector organs of D-psicose in lowering blood glucose and abdominal fat by exploiting a T2DM rat model, Otsuka Long-Evans Tokushima Fatty (OLETF) rats. Rats were fed 5% D-psicose or 5% D-glucose supplemented in drinking water, and only water in the control for 13 weeks and the protective effects were compared. A non-diabetic Long-Evans Tokushima Otsuka (LETO), fed with water served as a counter control of OLETF. After 13 weeks feeding, D-psicose treatment significantly reduced the increase in body weight and abdominal fat mass. Oral glucose tolerance test (OGTT) showed the reduced blood glucose and insulin levels suggesting the improvement of insulin resistance in OLETF rats. Oil-red-O staining elucidated that D-psicose significantly reduced lipid accumulation in the liver. Immunohistochemical analysis showed D-psicose induced glucokinase translocation from nucleus to cytoplasm of the liver which enhances glucokinase activity and subsequent synthesis of glycogen in the liver. D-psicose also protected the pathological change of the β-cells of pancreatic islets. These data demonstrate that D-psicose controls blood glucose levels by reducing lipotoxicity in liver and by preserving pancreatic β-cell function.

1. Introduction

Obesity has emerged as the single most prevalent life-style-related health problem all over the world, and is associated with many complications [1,2]. Obese humans and experimental animals characteristically manifest hyperinsulinemia, insulin resistance, and hyperlipidemia which predispose them to glucose intolerance and type 2 diabetes mellitus (T2DM) [1]. Type 2 diabetes is a disorder that is characterized by high blood glucose in the context of insulin resistance and relative insulin deficiency [3], where sugar transportation into the cells is deregulated, and hyperglycemia results from both a decrease in glucose utilization by the liver and peripheral tissues along with an increase in hepatic glucose production [4]. The incidence of diabetes has been increasing rapidly, and the cost of managing chronic complications is also becoming an enormous problem. Therefore, it would be important to identify the high risk patients in pre-diabetic stage and focus on the effective therapeutic interventions for the prevention and treatment of diabetes and its complications [5]. Under these circumstances, the use of alternative medicines including traditional herbal medicines has also increasingly become the focus of attention [6,7]. In the liver, glucokinase has been proposed to regulate both glucose uptake and glucose output [5]. Study has shown that the lowered activity of hepatic glucokinase contributes to the pathogenesis of hyperglycemia in diabetes mellitus [8]. And thus glucokinase is considered a strong candidate target for antihyperglycemic drugs for T2DM [9]. Miwa et al. suggested that the translocation of glucokinase between the nucleus and the cytoplasm plays a role in the regulation of hepatic glucose metabolism

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[10]. Hyperglycemia is also associated with progressive pancreatic β-cell failure leading to glucose intolerance, which is followed by T2DM [11].

D-psicose, a C-3 epimer of D-fructose and is defined one of the rare sugars since it is rarely found in nature. Rare sugars are monosaccharides, present in small quantities in commercial mixtures of D-glucose and D-fructose obtained from hydrolysis of sucrose or isomerization of D-glucose [12]. Because of the scarcity of D-psicose in natural products, Izumori group has developed a new method to produce D-psicose enzymatically on a large scale [13,14], making it possible to conduct studies of bioactivity and applications in food and medicine.

Recently, various physiological activities of D-psicose have been revealed. Of those, its glucose suppressive effect has been proven by both animal [15,16] and clinical studies [17,18]. Focusing the effects on glucose and lipid metabolisms, Matsuo et al. clarified the mechanism of glucose suppression in animal experiments caused by the inhibition of α-glycosidase and presumed that D-psicose had similar behavior to D-fructose in its glucose uptake from liver [15]. They also suggested that D-psicose suppressed hepatic lipogenic enzyme activity and reduced intraabdominal fat accumulation. Research group of Matsutani Chemical Industry Co., Ltd. showed that D-psicose significantly suppressed the blood glucose elevation in glucose loading study on healthy adults [17,18]. It was also suggested that supplemental D-psicose in the diet reduced postprandial glycemic response and might have anti-diabetic effects. And thus the present study was conducted to investigate the effect of D-psicose on blood glucose level for the first time in T2DM model, OLETF rats, which is a good animal model for examining obese T2DM.

The OLETF rat is a distinctive strain that develops a syndrome with multiple metabolic and hormonal disorders that shares many features with human obesity. OLETF rats have hyperphagia because they lack receptors for cholecystokinin, and become obese, developing hyperlipidemia, fatty liver, and T2DM [19].

2. Materials and methods

2.1. Animal protocol

Four-week-old male OLETF rats and their age-matched control LETO, were provided by the Tokushima Research Institute (Otsuka Pharmaceutical, Tokushima, Japan). Rats were handled in compliance with the Guide for Experimental Animal Research. After a 1-week adaptation OLETF rats were divided into 3 groups (n = 15 each): control was given drinking water, psicose 5% D-psicose and glucose 5% D-glucose, in drinking water. Control LETO was given drinking water only.

2.2. Measurement of blood glucose, and OGTT glucose and insulin levels

Glucose was measured instantly using a freestyle glucose meter and blood was drawn from the tail at 0, 3, 7, 11, 13 and 14 weeks of treatment. Plasma was stored at −30 °C until further assay. An OGTT was performed 14 weeks after treatment by feeding glucose 2.0 g/kg body weight through gavages. Glucose concentrations were measured followed by sampling at 0, 30, 60 and 90 min for insulin measurement using an ACTIVE Insulin ELISA kit (Diagnostic System Laboratories, Webster, USA).

2.3. Liver and pancreas histology

Liver and pancreas tissues were fixed in 10% formalin. Tissues were processed, embedded in paraffin, sectioned and stained with Hematoxylin-Eosin (HE) for morphological evaluation.

2.4. Immunofluorescence staining for glucokinase

Liver block was made after alternate perfusion with ice-cold normal saline and 4% paraformaldehyde (PF), fixed in 4% PF overnight followed by a further fixation in 30% sucrose solution for 24 h at 4 °C. Blocks were embedded in OCT compound, sections were prepared, and subjected to immunostaining using anti-glucokinase antibody according to the method of Miwa [8,10].

2.5. Statistical analysis

Data are presented as means ± SD. Statistical comparison of the means among the groups was made using one-way ANOVA. Differences between the means of individual groups were analyzed by the post hoc Hoechberg's for equal and Games–Howell for unequal variances using SPSS software (version 10.01).

3. Results

3.1. Effect of D-psicose on body weight, food intake and abdominal fat content

At 13 weeks study period, all OLETF groups became markedly heavier compared with LETO group (Fig. 1A). Among the OLETF groups, D-psicose reduced body weight gain significantly compared with control (615.91 ± 45.14 vs 494.99 ± 31.20) and D-glucose (599.64 ± 21.38 vs 494.99 ± 31.20) groups. Body weight gain reduction was apparent at week 4 of treatment and persisted till study end point and was manifested by less food intake and a reduction in abdominal fat content. Before treatment the average food intake in OLETF groups was similar although it was significantly higher ($p < 0.001$) than LETO group (Fig. 1C, week0). From week 2 D-psicose-treated group apparently showed a significantly reduced amount of food consumption which persisted till the end of study when it was also significant compared to control (10.00 ± 0.70 vs 8.50 ± 1.30) and D-glucose (9.40 ± 1.20 vs 8.50 ± 1.30) groups. D-psicose reduced abdominal fat significantly than those of both control (4.12 ± 0.20 vs 2.68 ± 0.21) and D-glucose (4.05 ± 0.18 vs 2.68 ± 0.21) groups at the end of 13 weeks study period (Fig. 1B). Serum TG level in D-psicose group reduced significantly than D-glucose group (124.46 ± 42.12 vs 82.75 ± 39.83, $p < 0.01$) and non-significantly than control (94.40 ± 37.23 vs 82.75 ± 39.83, $p = 0.91$) group although no significant variation was observed in blood cholesterol levels (Fig. 1D).

3.2. Effect of D-psicose on glucose homeostasis

3.2.1. Blood glucose level

Before treatment blood glucose level was comparable in OLETF groups as compared with LETO (Fig. 2A, 0 week). From the beginning of treatment glucose levels elevated gradually in the control group and markedly in D-glucose group whereas remained static in D-psicose and LETO groups. However, at week 3 the levels were significantly higher in the control (131.75 ± 7.61 vs 99.63 ± 9.49), D-glucose (129.50 ± 23.13 vs 99.63 ± 9.49) and D-psicose (121.88 ± 13.62 vs 99.63 ± 9.49, $p < 0.001$) groups than that of LETO group. Hyperglycemia persisted with glucose levels elevated severely from week 3 to week 14 in D-glucose group (129.50 ± 23.13 to 173.88 ± 28.86), and moderately in control group (131.75 ± 7.61 to 156.75 ± 15.56), whereas, remained unchanged or decreased in both D-psicose (121.88 ± 13.62 to 107.00 ± 12.25) and LETO (99.63 ± 9.49 to 91.99 ± 4.85) groups. At the end of treatment the value in D-psicose was significantly lower than those of control (156.75 ± 15.56 vs 107.00 ± 12.25)

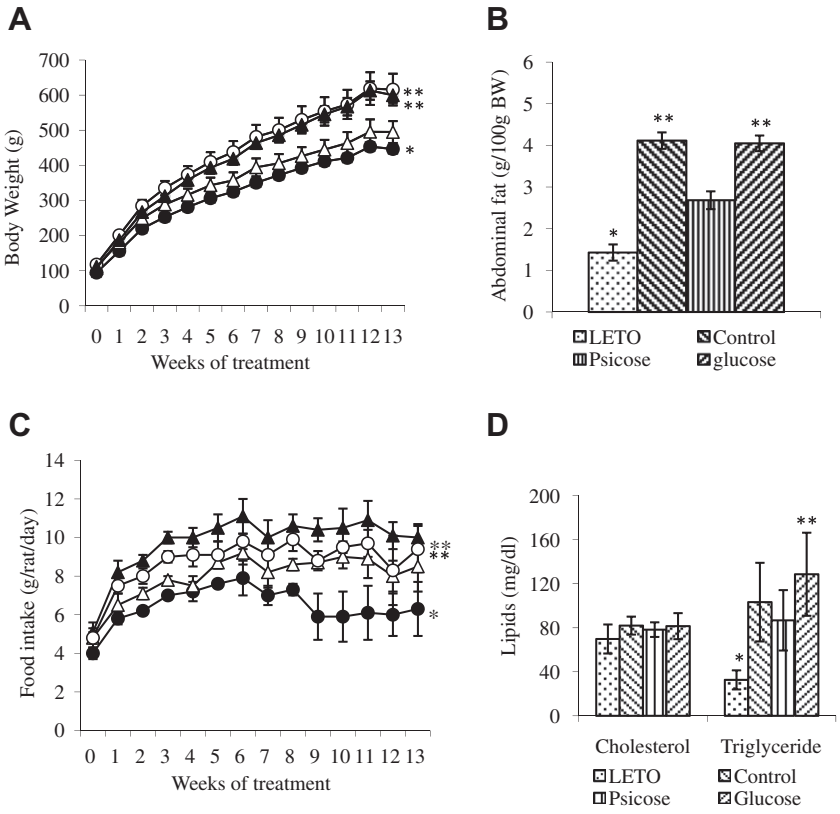

Fig. 1. Effect of D-psicose drink on body weight, total abdominal fat content, food intake, and plasma concentrations of cholesterol and triglyceride levels in type 2 diabetes model OLETF and their non-diabetic counter control LETO rats. Body weight (A), total abdominal fat content (B), average food intake (C), and plasma lipid concentrations (D). LETO (black circles); Control (white circles); D-psicose (white triangles);D-glucose (black triangles). Results are expressed as means ± SD, $n = 10$ (LETO), 15 (OLETF per group). $*p < 0.001$ vs. OLETF; $**p < 0.01$ vs. D-psicose.

and D-glucose (173.88 ± 28.86 vs 107.00 ± 12.25) groups. The mean $AUC_{glucose}$ value was also significantly lower in D-psicose group ($p < 0.01$) than both control and D-glucose groups (Fig. 2B).

3.2.2. OGTT

Blood glucose levels in OLETF rats elevated markedly in all time points with peaked at 30 min in the control group and 60 min in D-glucose group after glucose loading and then decreased until 90 min whereas the levels in LETO rats were slightly elevated with peaked at 60 min and returned close to base line at 90 min (75.00 ± 12.58 to 104.00 ± 5.66) (Fig. 2C). Among OLETF groups, D-psicose significantly suppressed the increment of blood glucose compared with control group at 60 min (423.14 ± 88.05 vs 240.20 ± 7.30) and 90 min (310.33 ± 69.04 vs 150.00 ± 46.67), as well as with the glucose group at 60 min (411.57 ± 48.06 vs 240.20 ± 70.30) and 90 min (244.00 ± 32.05 vs 150.00 ± 46.67). The mean value of the $AUC_{glucose}$ was significantly ($p < 0.01$) lower in D-psicose group than both control and D-glucose groups but no difference was detected between control and glucose groups (Fig. 2D).

Plasma insulin level in D-psicose group was significantly lower than both control (5.38 ± 0.70 vs 2.68 ± 0.79) and D-glucose (4.08 ± 0.60 vs 2.30 ± 0.45) groups at 60 min. Similarly, lower than control (4.76 ± 0.54 vs 2.30 ± 0.45) and D-glucose (4.08 ± 0.60 vs 2.30) groups at 90 min (Fig. 2E). D-psicose treatment improved glucose intolerance, as indicated by the decreased $AUC_{insulin}$ after the OGTT (Fig. 2F). The AUC of insulin during the OGTT was significantly lower in the D-psicose group than both the control ($p < 0.05$) and D-glucose ($p < 0.05$) groups.

3.3. D-psicose reverses impaired glucokinase translocation from nucleus to cytoplasm

We investigated the translocation of GK in the hepatocytes by immunofluorescence staining after 15 h fast followed by glucose load. Before glucose load GK was predominantly present in the nuclei of hepatocytes in all groups (Fig. 3A–D). Intensity of nuclear immunofluorescence was markedly decreased at 30 min after oral glucose load in LETO, D-psicose and D-glucose groups (Fig. 3E,G,H); conversely, the cytoplasmic immunofluorescence was increased. In contrast, the extent of glucokinase translocation was less marked in control than other groups.

At 90 min, intensity of the nuclear region was further decreased with increment in cytoplasmic region in D-psicose group (Fig. 3K) compared with control (Fig. 3J) and D-glucose (Fig. 3L) groups.

3.4. Effect of D-psicose on hepatic steatosis and tissue lipid contents

Liver sections (Fig. 4A–D) showed extensive micro- and macrovesicular hepatocyte vacuolization in OLETF-control group (Fig. 4B) and microvesicular vacuolization in D-glucose group (Fig. 4D), reflecting intrahepatic fat accumulation, which was confirmed with oil-red-O staining (Fig. 4F,H). In contrast, both hepatocellular vacuolization and oil-red-O-stained lipid droplets were very few in D-psicose-treated group (Fig. 4C,G).

3.5. Effect of D-psicose on pancreas morphology and islet preservation

Light microscopic findings of pancreas are shown in Fig. 4I–L. Islets of control and D-glucose-fed groups were disorganized and enlarged with expanded into the adjacent exocrine tissue suggestive

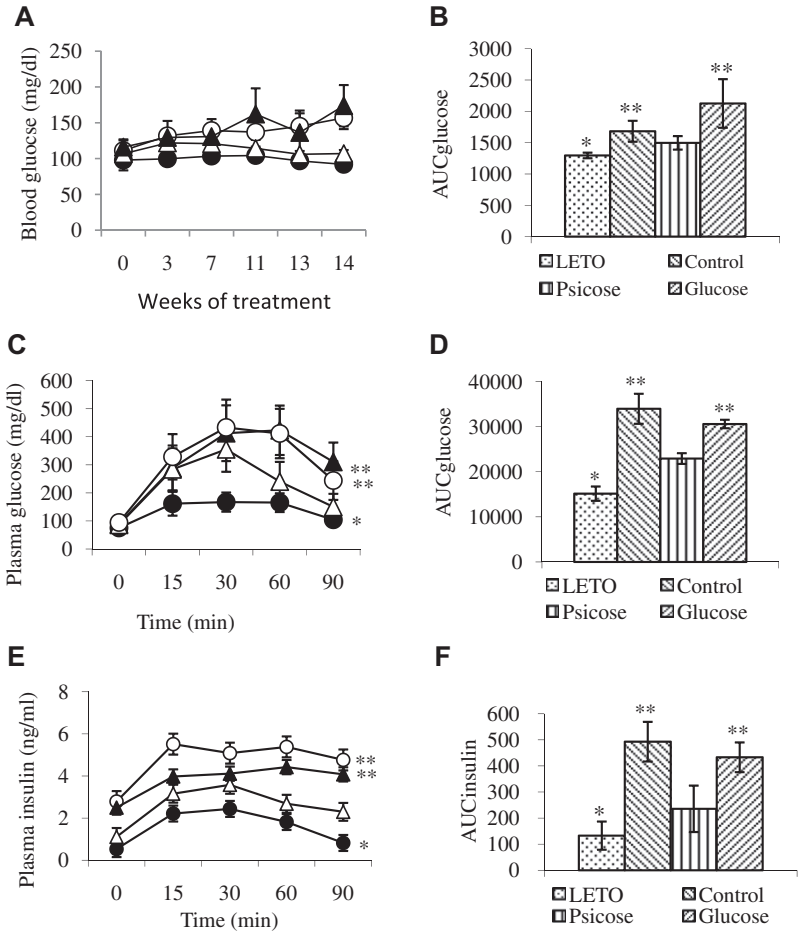

Fig. 2. Effect of D-psicose drink on blood glucose concentration in type 2 diabetes model OLETF and their non-diabetic counter control LETO rats. Blood glucose level (A) and area under curve glucose ($AUC_{glucose}$; B) measured periodically. Blood glucose level (C), area under curve glucose ($AUC_{glucose}$; D) plasma insulin level (E), and area under curve insulin ($AUC_{insulin}$; F) at oral glucose tolerance test (OGTT) during sacrifice after 13 weeks treatment. LETO (black circles); Control (white circles); D-psicose (white triangles);D-glucose (black triangles). Results are expressed as means ± SD, $n = 10$ (LETO), 15 (OLETF per group). $*p < 0.001$ vs. OLETF; $**p < 0.01$ vs. D-psicose.

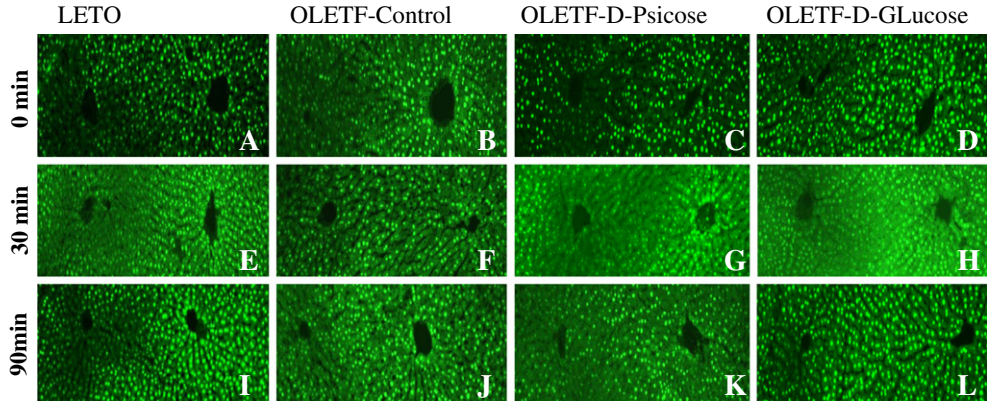

Fig. 3. Effect of D-psicose drink on glucokinase translocation in liver tissue of type 2 diabetes model OLETF and their non-diabetic counter control LETO rats. Immunofluorescence staining shows glucokinase translocation and distribution in liver tissues at 19 weeks of age from non-diabetic LETO (LETO) and diabetic OLETF (OLETF-Control, OLETF-D-Psicose, OLETF-D-Glucose) rats.

of islet hypertrophy. The islets were separated into clusters and extensive fibrosis and fatty deposition were noted, mainly in the control (Fig. 4J, arrows) and less in the D-glucose group. In contrast, D-psicose-fed islets were smaller than other OLETF rats with large number of normal, round or oval islets with almost no fibrosis (Fig. 4K). A similar overall pattern was observed in LETO rats (Fig. 4I), but structural changes of the pancreatic islets were much less prominent and islet architecture was relatively well preserved.

4. Discussion

D-psicose prevented glucose elevation and abdominal fat deposition in T2DM. T2DM is a syndrome characterized by defective insulin secretion and insulin resistance [20] where the pancreatic β-cells are forced to secrete more insulin to overcome a loss of insulin sensitivity, inducing in hyperinsulinemia. Therefore, insulin resistance is thought to exert hyperinsulinemia. D-psicose

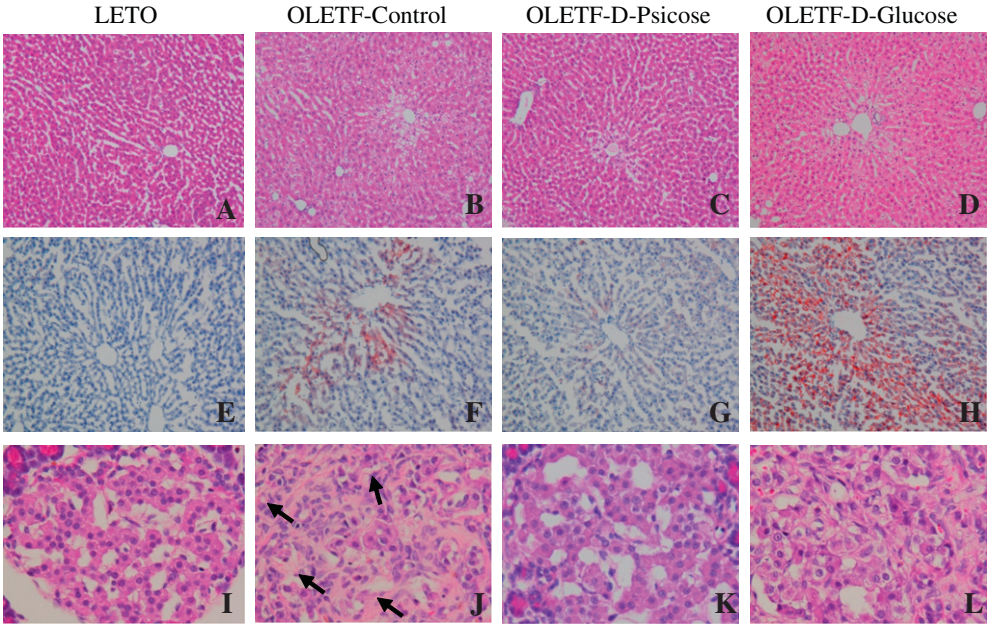

Fig. 4. Effect of D-psicose drink on the morphology of liver and pancreas tissue in type 2 diabetes model OLETF and their non-diabetic counter control LETO rats. Morphological changes of liver tissues (A–H) and pancreas islets (I–L) at 19 weeks of age from non-diabetic LETO (LETO) and diabetic OLETF (OLETF-Control, OLETF-D-Psicose, OLETF-D-Glucose) rats, stained with Hematoxylin–Eosin, x200 (A–D, liver), oil-red-O, ×200 (E–H, liver) and ×400 (I–L, pancreas).

decreased the serum insulin concentration (Fig. 2E,F) compared to the control and thought to have improved the insulin resistance, which may be one of the possible mechanisms for suppressing the blood glucose level and improving glucose tolerance. Suppressive effect of D-psicose on postprandial blood glucose elevation was also recognized in normal rats [21]. Human studies also observed the postprandial glucose suppression in normal healthy individuals and remarkable suppression in borderline diabetes individuals [17,18]. These results obviously revealed that D-psicose had glucose suppressing effect. Among the possible mechanisms D-psicose reduced or delayed glucose absorption in the intestines by the inhibition of α-glucosidase [15] since a delay or inhibition of carbohydrate digestion could be helpful for avoiding postprandial hyperglycemia in diabetic patients [22]. In the present study, D-psicose effectively suppressed the enhancement of blood glucose concentration, whereas, blood glucose level and food intake increased with time fed on the control and glucose drinks. It was thus elucidated that D-psicose had potent antihyperglycemic activity.

In the immunofluorescence study we have showed the translocation of GK from nucleus to cytoplasm of hepatocytes followed by OGTT. Torres et al. showed that GK expression in liver was progressively reduced with the development of hyperglycemia in Zucker diabetes fatty rats. And when liver GK expression was normalized it restored plasma glucose to nearly normal levels by improving the responsiveness of hepatic glucose metabolism to alterations in blood glucose during the latter phase of diabetes development [23]. In our study, immonufluorescence of GK was present predominantly in the nuclei in both strains before glucose load (Fig. 3A–D). The nuclear immunofluorescence was markedly decreased at 30 min in LETO, D-psicose and D-glucose groups (Fig. 3E,G,H); conversely, cytoplasmic immunofluorescence was increased. In contrast, cytoplasmic immunofluorescence was not increased and nuclear immunofluorescence was still evident in the control group (Fig. 3F). In 90 min the nuclear immunofluorescence was still decreased with increment of cytoplasmic intensity in D-psicose group (Fig. 3K) compared with control (Fig. 3J) and D-glucose (Fig. 3L) groups. This result indicates that glucose-induced GK translocation is impaired in hepatocytes of diabetic rats which suggests that impaired GK translocation is involved in the accelerated hepatic glucose uptake in diabetic rats and thereby, contributing to hyperglycemia. Miwa [10] at first and then Toyoda et al. [24] showed that GK was located predominantly in the nucleus under static metabolic conditions but increased condition caused translocation from the nucleus to the cytoplasm which plays an important role in the regulation of hepatic glucose metabolism. Immunostaining has shown that glucokinase is predominant in the nucleus than in the cytoplasm if hepatocytes are incubated in medium containing 5 mM glucose [24,25] and also in the liver of rats [26]. Consistently, our results using 5% D-psicose in drinking water indicated the enhanced translocation of GK from hepatic nucleus to cytoplasm and thus maintained the blood glucose level.

We measured OGTT glucose level after 13 weeks of treatment since one of the main risk factors for the progression of T2DM is blood glucose level following oral glucose load. D-psicose treatment resulted in significant improvement of glucose tolerance (Fig. 2C). On the other hand, D-psicose did not affect fasting serum glucose or insulin (Fig. 2C, 0 min). Abnormalities of lipid metabolism are also frequently complicated with T2DM [27]. Widen et al. reported that insulin-mediated glucose disposal was reduced in T2DM patients with hyperglyceridemia compared with normoglyceridemic patients [28]. Our lipid profiles proved the hypolipidemic properties of D-psicose in the attenuation of impaired glucose metabolism and insulin resistance. D-psicose significantly reduced serum triglyceride level although total cholesterol was non-significantly low (Fig. 1D). Similarly, Nakagawa et al. mentioned that a traditional Japanese herbal formulation, keishibukuryogan ameliorated serum TG and TC in OLETF rats [6]. From the consequent reports and our present study on the effect of lipids we presume that D-psicose exerts a hypolipidemic effect in the diabetic body, and this effect contributes to the amelioration of the insensitivity of peripheral tissues to insulin and glucose disposal, resulting in a reduction in glucose levels after oral glucose load.

Pancreas islet dysfunction is a key characteristic of patients with T2DM that results in hyperglycemia. In general, when the pancreas is forced to compensate insulin demand in obesity-induced insulin resistant condition islet dysfunction is accelerated

[29]. D-psicose protected pancreatic islet destruction caused by chronic hyperglycemia. Here we observed striking morphological differences among the groups. D-psicose islets showed small but somewhat irregular islets with normal cell architecture, whereas, D-glucose and control islets were enlarged and irregular with disrupted cell architecture with extensive fibrosis and fatty deposition additionally in the control rats (Fig. 4J, arrows), which was not observed in D-psicose rats (Fig. 4K). Finegood et al. presented sequence of events associated with the progressive deterioration of β-cell function in type 2 Zucker diabetic fatty rats. In untreated rats, plasma glucose level increased, the β-cell continued to expand in respond to the high demand for insulin necessitated by the developing obesity and associated insulin resistance [30].

Treatment of OLETF rats with D-psicose before the onset of significant hyperglycemia prevented the development of diabetes. Periodical plasma glucose remained relatively constant throughout the experimental period in the D-psicose-treated rats compared with the control although periodical insulin content and the β-cell mass have not been checked in the present study. However, we have mentioned the glucose and insulin contents on OGTT during sacrifice. Although the specific mechanism of action of D-psicose in preventing the development of diabetes in OLETF rats cannot be determined from the present study, the effects on plasma glucose and insulin and the effects on β-cell architecture could all be the possible results of D-psicose's action in enhancing insulin sensitivity.

In conclusion, because of the effects of D-psicose on lowering blood glucose and the availability of mass production it is expected to be approved for commercial use, which could provide an alternative to the presently dominant sweeteners due to its lack of calories, and thus be useful in the food industry as an aid to a large number of people suffering from obesity and diabetes.

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