Antidiabetic Activity of White Skinned Sweet Potato (Ipomoea batatas L.) in Obese Zucker Fatty Rats

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Received June 25, 1999; accepted September 30, 1999

Antidiabetic effects of white skinned sweet potato (Ipomoea batatas L.) (WSSP) and troglitazone, an insulin sensitizer, were investigated. Hyperinsulinemia in Zucker fatty rats was reduced by 23%, 26%, 60% and 50%, respectively, 3, 4, 6 and 8 weeks after starting the oral administration of WSSP. Similar results were obtained with troglitazone. In the glucose tolerance test after 7 weeks of treatment, increases in blood glucose levels after glucose loading were inhibited by the administration of WSSP. Glucose tolerance was also improved. Blood triacylglyceride (TG) and free fatty acid (FFA) lactate levels were lowered by the oral administration of WSSP. Similar effects on blood insulin, lipid and lactate levels were observed after the administration of troglitazone. Body weight gain increased in the troglitazone group, but not in the WSSP group, compared to the control group. In histological examinations of the pancreas of Zucker fatty rats, remarkable regranulation of pancreatic islet β-cells was observed in the WSSP and troglitazone groups after 8 weeks of treatment. These results suggest that WSSP shows remarkable antidiabetic activity and improves the abnormality of glucose and lipid metabolism by reducing insulin resistance.

Key words sweet potato; antidiabetic; hyperinsulinemia; glucose tolerance; Zucker fatty; troglitazone

Diabetes mellitus is a common metabolic disorder associated with various diseases such as arteriosclerosis, nephritis and hypertension. Non-insulin dependent diabetes mellitus (NIDDM) is the most common type of diabetes mellitus. It is widespread and is one of the most common chronic diseases, being present in about 5% of the Japanese population. Extensive investigations of the pathogenesis of NIDDM have identified two defects in endocrine function: insulin resistance and insulin deficiency. At present, the oral therapy of NIDDM relies upon sulfonylurea drugs such as tolbutamide, glibenclamide, and the insulin sensitizer troglitazone.

For many years, the search for antidiabetic products has focused on plants and other natural resources. Recently, investigators found that several plant products showed unique hypoglycemic activities in diabetic model animals.

Animal models of diabetes mellitus are divided into two groups: 1) an experimental diabetic model such as streptozotocin (STZ)-induced insulin deficiency diabetic model and 2) a genetic insulin resistant diabetic model such as yellow kk mice, db/db mice and Zucker fatty rats.

WSSP has been used in Shikoku, Japan as a folk medicine for the treatment of diabetes and other diseases. However, no pharmacological studies have been undertaken to confirm its effects. In our previous study, we reported that WSSP improved glucose tolerance in STZ diabetic rats, genetically diabetic mice, yellow KK mice, and db/db mice.

Zucker fatty rats, a genetic obesity model, are known to show obesity and marked hyperinsulinemia and are used as an animal model for insulin-resistance.

In the present study, the effects of WSSP on blood glucose, insulin, triacylglyceride (TG), free fatty acid (FFA) and lactate levels were evaluated in Zucker fatty rats and compared with those of troglitazone.

MATERIALS AND METHODS

Plant Material WSSP (Ipomoea Batatas L.) was purchased from Kagawa Prefectural Asa Agricultural Cooperative. The cortex (thickness: 1—2 mm) of WSSP was obtained using a peeler and extracted with 10 volumes of distilled water using a homogenizer. The water extract was dialyzed and the internal solution lyophilized. The powder obtained was kept at 4°C before use.

Animals and Experimental Procedures Male Zucker fatty rats weighing 300 to 350 g (7—8 weeks of age) were used. They were housed in an air-conditioned room at 22±2°C with a 12 h light/dark cycle. They were maintained on a standard laboratory diet (Oriental Yeast Co., Ltd.: MF) and given free access to water for a one-week acclimatization period.

The animals were divided into 3 groups (control, WSSP and troglitazone (Sankyo Co., Ltd.)) and orally administered 100 mg/kg/d of WSSP or 50 mg/kg/d of troglitazone using a stomach tube every day for 8 weeks. Each test material was dissolved in saline containing 0.5% Tween 20. The control group was given saline containing 0.5% Tween 20.

After 3, 4, 6 and 8 weeks, blood samples were collected from the tail vein of each animal and serum samples were obtained by centrifuging a blood sample at 2500rpm for 20min. The serum samples were analyzed with respect to insulin, glucose, lipid and lactate levels. After 7 weeks, the glucose tolerance test was carried out by orally loading glucose at 2 g/kg. Blood samples were collected before and at 60 and 120 min after glucose administration and blood glucose concentrations were measured.

Analytical Methods Blood glucose and insulin levels were determined using a glucose oxidase kit and by the insulin-EIA test (Wako Pure Chemical Ind., Osaka, Japan), respectively. Blood TG, total cholesterol and free fatty acid (FFA) levels were also measured using commercial kits (Wako). Concentrations of blood lactate were measured.

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using a lactate oxidase kit (Kyowa Medex, Tokyo, Japan).

**Histology** After 8 weeks, the rats were killed and the pancreas was removed and fixed in 10% neutral buffered formalin. The insulin secretory granules of Langerhans' islet β-cells were stained with aldehyde fuchsin.

**Statistical Analysis** Statistical analysis was performed by ANOVA followed by the Dunnett's test. Data were shown as means±standard deviations (S.D.).

**RESULTS**

**Effects of WSSP on Body Weight Gain and Blood Glucose, Insulin, Lipid and Lactate Levels in Zucker Fatty Rats** Changes in body weight gain in Zucker fatty rats are shown in Fig. 1. Body weight gain increased with age in both WSSP and control groups and no significant difference was detected between the two groups, whereas in the troglitazone group, body weight gain increased significantly compared with the control group from 10 d after administration began.

Changes in blood glucose and insulin levels are shown in Fig. 2. Slight hypoglycemic effects of WSSP (\(p<0.05\)) were seen after administration for 6 and 8 weeks. In the troglitazone group, no difference was seen compared to the control group. Blood insulin levels significantly decreased after 3 to 8 weeks in the WSSP group. After administration for 6 and 8 weeks, these levels were markedly lower than in the control group. In the troglitazone group, markedly low blood insulin levels were detected from 3 to 8 weeks after administration began. Blood insulin levels in the control, WSSP and troglitazone groups after treatment for 8 weeks were 753±214, 384±97 and 394±94 μU/ml, respectively.

Changes in blood lipid levels in Zucker fatty rats are shown in Fig. 3. Blood TG levels in both WSSP and troglitazone groups decreased significantly throughout the experimental period. Blood FFA levels in the WSSP group decreased significantly throughout the experimental period. In the troglitazone group, decreases in blood FFA levels were observed after administration for 4, 6 and 8 weeks. No remarkable differences in total cholesterol levels were found between the control, WSSP and troglitazone groups.

Effects of WSSP on blood lactate levels are shown in Fig. 4. Blood lactate levels in the WSSP group decreased significantly throughout the experimental period.

**Glucose Tolerance Test** Blood glucose levels in Zucker fatty rats after glucose loading are shown in Fig. 5. In both WSSP and troglitazone groups, increases in blood glucose levels 60 min after glucose loading were significantly inhib-
Fig. 4. Effects of WSSP and Troglitazone on Changes in Blood Lactate Levels in Zucker Fatty Rats

Each point represents mean±S.D. (n=7). Blood samples were collected from non-fasting rats, ○, control; ●, WSSP 100 mg/kg/d, p.o.; ▲, troglitazone 50 mg/kg/d, p.o. Significantly different from the control at the same location, * p<0.05, ** p<0.01.

Fig. 5. Effects of WSSP and Troglitazone Administered for 7 Weeks on Blood Glucose (A) and Insulin (B) Levels in Glucose Loaded Zucker Fatty Rats

Each point represents mean±S.D. (n=7). Glucose was loaded at 2 g/kg after fasting animals for 18 h. ○, control; ●, WSSP 100 mg/kg/d, p.o.; ▲, troglitazone 50 mg/kg/d, p.o. Significantly different from the control at the same location, ** p<0.01.

Fig. 6. Typical Light Micrographs of Langerhans’ Islet β-Cells in Zucker Fatty Rats in the Control (A), WSSP Administered (B) and Troglitazone (C) Groups
β-cells were stained by aldehyde fuchsin. Magnification: 100×.

Although genetic factors are highly likely to have a role in this disease, increases in insulin resistance play an important role in its pathogenesis and development. The principal action of insulin is to stimulate the transport of glucose into adipose and muscular tissues.

The most important finding of the present study is that WSSP improved hyperinsulinemia and hyperlipidemia in Zucker fatty rats. Zucker fatty rats are obese and diabetic rats which show marked hyperinsulinemia and abnormality of lipid metabolism from a low age. Although hyperinsulinemia and abnormality of lipid metabolism further progress with age, but age-related increases in blood glucose levels are slight or actually less. The control group used in the present study reproduced this general pattern. In the WSSP group, hyperinsulinemia was markedly improved compared to the control, from 3 weeks after treatment began and onward. TG and FFA levels also decreased significantly. These effects of WSSP on blood glucose, insulin and lipid levels in Zucker fatty rats were in close agreement with those observed in the troglitazone group. Therefore, WSSP is likely to improve the abnormal glucose and lipid metabolism in obese patients with insulin-resistant diabetes mellitus.

We have already reported that WSSP shows hypoglycemic activity in STZ-induced insulin deficiency diabetic rats, and
it increases blood insulin levels similarly to tolbutamide. In yellow KK and db/db mice, genetically diabetic mice, WSSP showed hypoglycemic activity and decreased high insulin levels and improved glucose intolerance, unlike tolbut-
amide. Sulfonlureas including tolbutamide, now used in
the oral therapy for NIDDM, seem to act generally as in-
sulin secretagogues from the pancreas, while thiazolidine-
diones, including pioglitazone, and troglita-
tazone improve insulin responses in peripheral tissues. 
Therefore, thiazolidinediones may act as insulin sensitizers. 
Coupled with these findings, our results suggest that WSSP has unique properties such as stimulating an increase in in-
sulin secretion and improving insulin resistance.

In the WSSP group, no change was seen in body weight gain compared to the control group throughout the experi-
mental period, whereas in the troglitazone group, significant increases were observed from 10 d after administration. The exact cause of this increase was not clear, but troglitazone was reported to cause significant increases in body weight gain in some diabetic patients, and to reduce blood leptin concentrations in Zucker fatty rats resulting in excessive food intake.

In both WSSP and troglitazone groups, blood TG and FFA levels were lower than in the control group. This decrease in blood TG and FFA levels following troglitazone administration were in agreement with previous reports.

Insulin resistance has two major effects on lipid metabo-
lism: enhanced synthesis of very low density lipoprotein (VLDL)-TG in the liver caused by increases in blood FFA and glucose levels due to peripheral insulin resistance, and enhanced synthesis of TG due to high blood insulin levels. The decreases in blood TG and FFA levels in the WSSP group in the present study are thought to be due to an improvement of insulin resistance in peripheral tissues, resulting in decreases in blood insulin levels.

Histological examinations of the pancreas showed remarkable inhibition of degranulation of β-cells after the admin-
istration of WSSP and troglitazone. This result suggests that WSSP and troglitazone remove the impairment of β-cells by inhibiting insulin over-secretion by secretory granules of β-cells.

In conclusion, WSSP was shown to improve both glucose levels and lipid metabolism by markedly suppressing insulin resistance in Zucker fatty rats. Antidiabetic components of WSSP are thought to be high-molecular-weight compounds not eliminated by dialysis and are inactivated in boiling water. Efforts are being made to purify them. Unfortunately, we do not really know how WSSP works; however, we are now investigating its mechanism of action. Data obtained by us to date clearly indicate that WSSP has unique therapeutic potential and useful activities which would allow it to replace medicine for the treatment of hyperglycemia associated with NIDDM.

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