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The plasma glucose lowering action of tetrandrine in streptozotocin-induced diabetic rats

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Abstract

The effect of tetrandrine, an active principle of *Stephaniae tetrandrae*, on the plasma glucose level in streptozotocin-induced diabetic rats (STZ-diabetic rats) was investigated. A single intravenous injection of tetrandrine decreased the plasma glucose in a dose-dependent manner in STZ-diabetic rats. Moreover, tetrandrine (1.0 mg kg^{-1}) significantly attenuated the rise in plasma glucose induced by the intravenous glucose challenge test in normal rats. A stimulatory effect of tetrandrine on glucose uptake was obtained in soleus muscles isolated from STZ-diabetic rats with a concentration-dependent manner from 0.01 to 10.0 μmol L^{-1}. The increase in glucose utilization by tetrandrine was further characterized using the enhancement of glycogen synthesis in the hepatocytes of STZ-diabetic rats. These results suggest that tetrandrine has the ability to enhance glucose utilization in peripheral tissue, resulting in the lowering of plasma glucose in diabetic rats lacking insulin.

Introduction

Diabetes, which ranks highly among the top ten causes of mortality around the world, often leads to disability from the vascular complications of coronary artery disease, cerebrovascular disease, renal failure, blindness and limb amputation in addition to neurological complications and premature death (Lopez-Candales 2001). With recent rapid advancements in medicine, novel treatments with fewer side-effects have became feasible for the control of this disorder.

Tetrandrine (6,6′,7,12-tetramethoxy-2,2′-dimethylberbaman; Figure 1) is a bisbenzyl tetrahydroisoquinolin e alkaloid extracted from a herb, the dry root of *Stephaniae tetrandrae* S. Moore (Menispermaceae), which has been widely used as an analgesic or anti-hypertensive drug in Oriental countries (Sutter & Wang 1993). The main ingredients in this herb are tetrandrine and fangchinoline (Sutter & Wang 1993). Tetrandrine works as a calcium entry blocker (Felix et al 1992), showing various actions, such as the modulation of cardiovascular disorders (Huang & Hong 1998), and anti-tumour (Lee et al 2002) and anti-inflammatory effects (Shen et al 1999). Fangchinoline is thought to be less potent than tetrandrine as a vasodilator or calcium channel blocker (Kim et al 1997). Tetrandrine has also been documented to have antioxidant properties (Cao 1996). Moreover, tetrandrine has been reported to prevent the development of spontaneous diabetes in BioBreeding rats (Lieberman et al 1992) and to protect pancreatic islet beta cells from the injuries caused by alloxan (Sun et al 1994). These results indicate that tetrandrine may be helpful in the prevention and/or handling of diabetes. However, the direct effect of tetrandrine on glucose metabolism is still unclear. Thus, we investigated the effect of tetrandrine on plasma glucose in diabetic rats lacking insulin.

Materials and Methods

Materials

Streptozotocin, tetrandrine and cytochalasin B were purchased from Sigma-Aldrich, Inc. (St Louis, MO) and 2-[1-^{14}C]-deoxy-D-glucose ([^{14}C]-2-DG) and [U-^{14}C]-glucose

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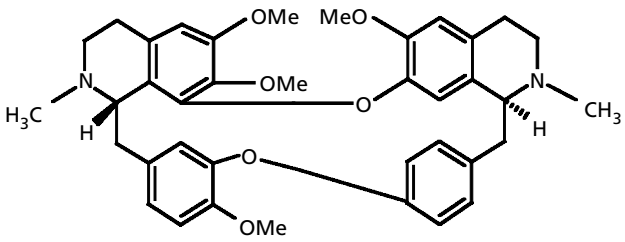

Figure 1 Chemical structure of tetrandrine.

were obtained from NEN Research (Boston, USA). Bovine insulin was obtained from Novo Nordisk (Bagsvaerd, Denmark). Protein assay kit was the product of BioRad (Richmond, CA). All other standard reagents were purchased from Sigma-Aldrich, Inc. (St Louis, MO).

Animals

Male Wistar rats, weighing 200–250 g, were obtained from the Animal Center of the National Cheng Kung University Medical College. Streptozotocin-induced diabetic rats (STZ-diabetic rats) were prepared by intravenous (i.v.) injection of STZ ($60.0\,mg\,kg^{-1}$) into male Wistar rats, 8–10 weeks of age. Animals were considered to be diabetic if they had plasma glucose concentrations of $20\,mmol\,L^{-1}$ or greater in addition to polyuria and other diabetic features. Plasma insulin levels in STZ-diabetic rats were reduced to $1.33 \pm 0.8\,pmol\,L^{-1}$ ($n = 8$) following STZ injection, a level markedly lower than that of the normal rats ($161.1 \pm 3.4\,pmol\,L^{-1}$; $n = 8$), indicating insulin-dependent diabetes mellitus. All studies were carried out 2 weeks after the injection of STZ. All animal procedures were performed according to the *Guide for the Care and Use of Laboratory Animals* of the National Institutes of Health, as well as the guidelines of the Animal Welfare Act.

Effect of tetrandrine on plasma glucose concentrations in STZ-diabetic rats

After fasting overnight, STZ-diabetic rats received an i.v. injection of tetrandrine into the femoral vein at the desired doses. Under anaesthesia with sodium pentobarbital ($30.0\,mg\,kg^{-1}$, i.p.), blood samples (0.1 mL) were collected from the tail vein for measurement of plasma glucose concentrations. In the preliminary experiments, tetrandrine at $1.0\,mg\,kg^{-1}$ was found to produce the maximal plasma glucose lowering effect in STZ-diabetic rats 30 min after a single i.v. injection. Thus, the effects of tetrandrine on plasma glucose were determined using blood samples collected 30 min after the injection. Comparative studies of the change in mean arterial blood pressure were also carried out in STZ-diabetic rats treated with tetrandrine. STZ-diabetic rats that received a similar injection of the same volume of vehicle (distilled water containing 0.9% (w/v) sodium chloride) used to dissolve tetrandrine were used as controls.

Intravenous glucose challenge test

The basal plasma glucose level was obtained from normal Wistar rats under pentobarbital anaesthesia prior to the intravenous glucose challenge test (IVGCT). A solution of tetrandrine at $1.0\,mg\,kg^{-1}$, the effective dose for lowering plasma glucose in rats, or the same volume of vehicle was injected into the femoral vein of rats. Thirty minutes later, a glucose dose of $60.0\,mg\,kg^{-1}$ was injected to induce IVGCT. Blood samples from the tail vein were also drawn at 5, 10, 20, 30, 60, 90 and 120 min following IVGCT for measurement of plasma glucose levels. The blood samples (0.1 mL) obtained immediately from the tail veins of these rats were regarded as 0 min samples. Rats were maintained under pentobarbital anaesthesia throughout the IVGCT.

Laboratory determinations

The concentration of plasma glucose was measured by the glucose oxidase method using an analyser (Quik-Lab, Ames, Miles Inc., Elkhart, IN). Mean arterial blood pressure was measured using a non-invasive tail-cuff monitor (UR-5000, Ueda Company, Tokyo, Japan) in conscious diabetic rats. Blood pressure was expressed as the mean of at least four measurements.

Measurement of glucose uptake into soleus muscle

Soleus muscle was isolated from STZ-diabetic rats and divided into long longitudinal strips (35–25 mg per strip) as described previously (Cheng et al 2001). After a 30-min pre-incubation period, the muscle tissue was transferred to fresh incubation flasks, then incubated with tetrandrine at the desired concentrations at 37 °C for 30 min under continuous shaking at 40 cycles min^{-1}. The muscle tissue was subsequently incubated with 50 μL Krebs–Ringer bicarbonate buffer (KRBB) containing [^{14}C]-2-DG ($1\,\mu Ci\,mL^{-1}$) for 5 min in the presence of tetrandrine at 37 °C. Reactions were terminated by quickly blotting the muscles and dissolving them in 0.5 mL of 0.5 M NaOH for 45 min before neutralization with 0.5 mL 0.5 M HCl. After centrifugation, 800 μL of each supernatant was mixed with 1 mL of aqueous counting scintillant and the radioactivity was determined using a β-counter (Beckman LS6000). Uptake of [^{14}C]-2-DG, assessed after pre-incubation of the muscle with $20\,\mu mol\,L^{-1}$ cytochalasin B, was subtracted from the total muscle-associated radioactivity. Specific [^{14}C]-2-DG uptake was expressed as pmol in 5 min or as the percentage of basal level that was obtained from sample incubated with KRBB only.

Measurement of glycogen synthesis in hepatocytes

The measurement of glycogen synthesis in hepatocytes isolated from STZ-diabetic rats was carried out as described previously (Cheng et al 2001). After the 30 min pre-incubation period in KRBB at 37 °C, 2×10^6 hepatocytes were transferred to fresh incubation flasks containing

[U-^{14}C]-glucose (0.25 μCi mL^{-1}) and then incubated with tetrandrine at the desired concentrations at 37 °C for 1 h, the optimal time obtained from preliminary experiments, under continuous shaking. The incorporation of [U-^{14}C]-glucose into glycogen was determined by ethanol precipitation. The incorporation into glycogen was expressed as nanomoles per milligram of cell protein in 1 h or as the percentage of basal level that was obtained from hepatocytes incubated with KRBB only. Protein content was determined using the BioRad protein dye-binding assay.

Statistical analysis

Data are expressed as the mean ± s.e.m. for the number (n) of animals in the group, as indicated in the figures. Repeated measures of analysis of variance (ANOVA) were used to analyse the changes in plasma glucose and other parameters. The Dunnett range post-hoc comparisons were used to determine the source of significant differences where appropriate. The concentration that produced 50% of the maximum effect (EC_{50}) was obtained from nonliner regression analysis. A P value < 0.05 was considered statistically significant.

Results

Effects of tetrandrine on plasma glucose concentration in STZ-diabetic rats

Figure 2 shows a dose-dependent decrease of plasma glucose in STZ-diabetic rats that received treatment with tetrandrine; the maximal effect (24.2 ± 1.8%) was achieved with 1.0 mg kg^{-1} of tetrandrine. Increasing the tetrandrine dose to 1.5 mg kg^{-1} resulted in no further decrease in plasma glucose. Thus, 1.0 mg kg^{-1} of tetrandrine was employed in subsequent experiments.

However, the plasma glucose level in normal rats was not modified at 30 min after an i.v. injection of tetrandrine at the dose that was effective in STZ-diabetic rats. The plasma glucose level in normal rats was reduced by 35 min after the injection of tetrandrine. As shown in Figure 2, tetrandrine lowered the plasma glucose in normal rats by about 8.2 ± 1.0, 13.6 ± 1.4 and 18.3 ± 1.7% after dosing with 0.1, 0.5 and 1.0 mg kg^{-1}, respectively.

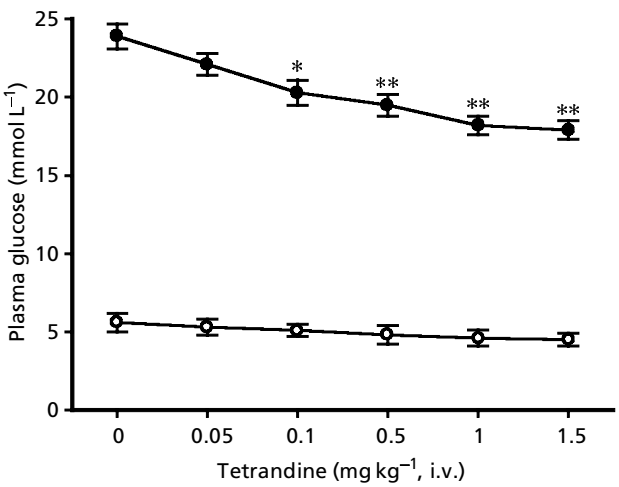

Figure 2 The plasma glucose lowering activity produced by an intravenous injection of tetrandrine into normal Wistar rats ○ and STZ-diabetic rats ●. Values (means ± s.e.m.) were obtained from each group of eight animals. Vehicle (0.9% NaCl in distilled water) was given at the same volume. *P < 0.05 and **P < 0.01 vs data from animals treated with vehicle (0).

Effects of tetrandrine on mean arterial blood pressure in STZ-diabetic rats

The effect of tetrandrine on mean arterial blood pressure at a dose (1.0 mg kg^{-1}) sufficient to lower plasma glucose was investigated. After injection of STZ for 1 week, the mean arterial blood pressure in diabetic rats was elevated to 128.5 ± 2.2 mmHg in a way markedly different (P < 0.05) to that in vehicle-treated control rats (105.4 ± 3.1 mmHg; n = 8). However, the mean arterial blood pressure in diabetic rats was not influenced (P > 0.05) by an i.v. injection of 1.0 mg kg^{-1} tetrandrine for 30 min (125.6 ± 2.8 mmHg; n = 8).

Effect of tetrandrine on the IVGCT

The effect of tetrandrine on the response of normal Wistar rats to the IVGCT is showed in Figure 3. The basal plasma glucose concentration in Wistar rats was 5.3 ± 0.5 mmol L^{-1}. Thirty minutes after i.v. treatment with tetrandrine (1.0 mg kg^{-1}), the plasma glucose level

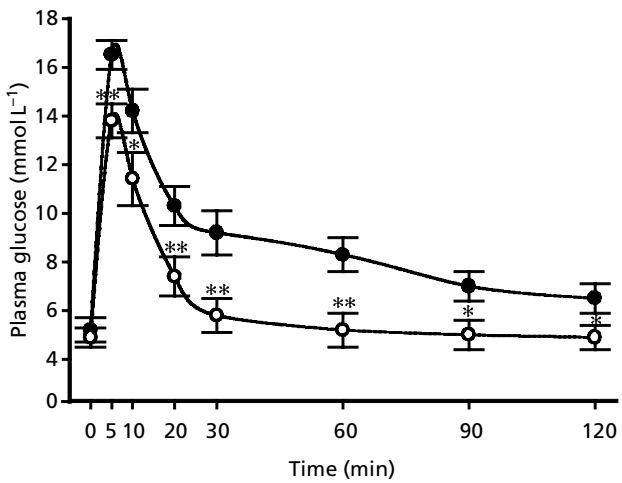

Figure 3 Effect of tetrandrine on plasma glucose concentration in normal rats receiving an IVGCT. Tetrandrine (1.0 mg kg^{-1}) was injected into the tail vein (○) and compared with the control group of rats receiving a similar injection of vehicle (0.9% NaCl in distilled water) at the same volume (●). The IVGCT was performed with an intravenous injection of glucose at 60.0 mg kg^{-1} into the two groups of rats 30 min later and the plasma glucose in samples obtained immediately was indicated as 0 min. Values (means ± s.e.m.) were obtained from eight rats in each group. *P < 0.05 and **P < 0.01 vs data from control group.

in rats was 4.9 ± 0.4 mmol L^{-1} in rats compared with 5.2 ± 0.5 mmol L^{-1} in vehicle-treated rats; these values were not significantly ($P > 0.05$) different from the basal level. Five minutes after the IVGCT, the plasma glucose concentration was elevated to 16.5 ± 0.6 mmol L^{-1} in vehicle-treated rats but was 13.8 ± 0.7 mmol L^{-1} in tetrandrine-treated rats. Tetrandrine at 1.0 mg kg^{-1} significantly attenuated the increase of plasma glucose following the IVGCT and the plasma glucose lowering activity was obtained 5 min after the IVGCT. The plasma glucose concentration in the tetrandrine-treated group undergoing the IVGCT was decreased almost to the basal level for the 30-min observation period.

Effect of tetrandrine on glucose uptake into soleus muscle

The time course of the stimulatory effect of tetrandrine on glucose uptake into soleus muscle was preliminarily determined. Glucose uptake was enhanced within 5 min of exposure to tetrandrine at 1.0 μmol L^{-1}. This action of tetrandrine was increased gradually. The longer incubation time achieved half-maximal stimulation at 10 min and maximal stimulation at 30 min, which was the optimal time used in the experiments. Stimulation of [^{14}C]-2-DG uptake by soleus muscle after a 30-min exposure of 1 nmol L^{-1} bovine insulin was about $212.5 \pm 4.5\%$ of the basal [^{14}C]-2-DG uptake (732.2 ± 20.2 pmol 5 min^{-1}) that was taken as 100% from samples incubated with KRBB only ($n = 6$). Tetrandrine increased the [^{14}C]-2-DG uptake into soleus muscle in a concentration-dependent manner (Figure 4). The EC_{50} of tetrandrine required to increase [^{14}C]-2-DG uptake into soleus muscle was about 0.1 μmol L^{-1}. Maximal [^{14}C]-2-DG uptake obtained in samples treated with tetrandrine at 1.0 μmol L^{-1} was 1319.4 ± 44.2 pmol 5 min^{-1}, which was about $180.2 \pm 5.7\%$ of the basal uptake although the activity was about 85% of that induced by bovine insulin at 1 nmol L^{-1}. The stimulatory effect of tetrandrine at 10.0 μmol L^{-1} was 1345.5 ± 52.4 pmol 5 min^{-1}, which is similar to the value obtained from 1.0 μmol L^{-1} of tetrandrine.

Effect of tetrandrine on glycogen synthesis in hepatocytes

In hepatocytes of STZ-diabetic rats, a 30-min exposure of 1 nmol L^{-1} bovine insulin increased the level of [^{14}C]-glucose incorporation into glycogen (3.6 ± 0.4 nmol mg^{-1} protein 1 h^{-1}) to about 2.4-fold of the basal glycogen synthesis (1.5 ± 0.3 nmol mg^{-1} protein 1 h^{-1}) that was taken as 100% from samples treated with same volume of KRBB ($n = 6$). Incubation with tetrandrine increased glycogen synthesis into the hepatocytes of STZ-diabetic rats significantly ($P < 0.05$) in a concentration-dependent manner, although the activity was less than that of bovine insulin (Figure 5). Tetrandrine at 1.0 μmol L^{-1} increased the glycogen synthesis in hepatocytes of STZ-diabetic rats to 2.5 ± 0.2 nmol mg^{-1} protein 1 h^{-1}, which was about 1.7 times the basal level. Even at 10 μmol L^{-1}, the higher concentration used, tetrandrine did not increase [^{14}C]-glucose incorporation into glycogen more markedly. The maximal activity of 1.0 μmol L^{-1} tetrandrine was about 75% of that induced by bovine insulin at 1 nmol L^{-1}. Similar to the effect on glucose uptake, the EC_{50} of tetrandrine on glycogen synthesis was about 0.1 μmol L^{-1}.

Discussion

In the present study we found that tetrandrine can lower the plasma glucose level in STZ-diabetic rats, an experimental model for type 1-like diabetes mellitus. Tetrandrine can also

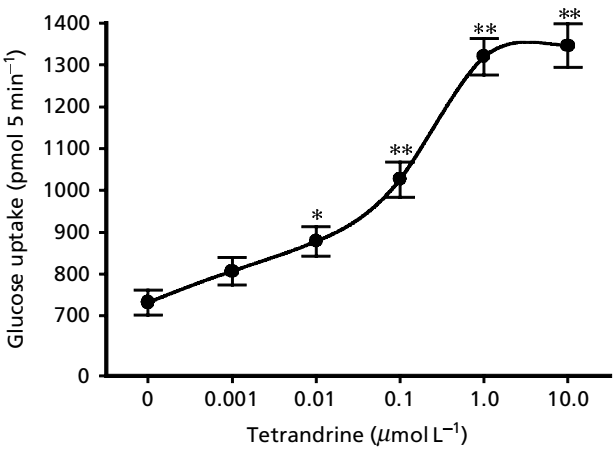

Figure 4 Effect of tetrandrine on the glucose uptake into soleus muscle isolated from STZ-diabetic rats. Values (mean ± s.e.m.) were obtained from each group of 10 animals. *$P < 0.05$ and **$P < 0.01$ vs data from samples incubated only with KRBB (0), respectively.

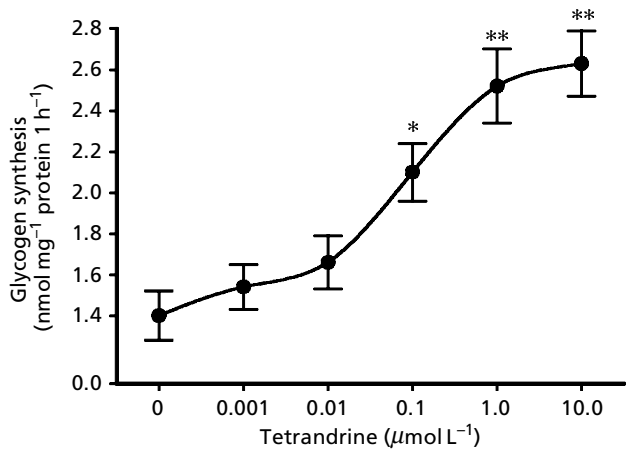

Figure 5 Effect of tetrandrine on the glucose incorporation into glycogen in hepatocytes isolated from STZ-diabetic rats. Values (mean ± s.e.m.) were obtained from each group of 10 animals. *$P < 0.05$ and **$P < 0.01$ vs data from samples incubated with only KRBB (0), respectively.

lower the plasma glucose level in normal rats but the onset time was slower (35 min) than in diabetic rats. The difference of onset time for intravenous injection of tetrandrine was only 5 min between diabetic and normal rats. It seems that the pharmacokinetic parameters for tetrandrine are similar between the two kinds of animals. However, the real mechanisms remain obscure and require further investigation.

Usually, diabetes mellitus is associated with hypertension (Cerielo et al 1997). Some hypoglycaemic agents, such as metformin and troglitazone, showed hypotensive effects in the animal model of diabetes (Kosegawa et al 1999). It has been documented that tetrandrine at a dose of 15.0 mg kg^{-1} acts as a calcium entry blocker to effectively lower blood pressure (Felix et al 1992) and mean arterial pressure (Hu et al 1987). Thus, the blood pressure measurement was performed to identify whether the plasma glucose lowering action of tetrandrine is linked to the reduction in blood pressure. In the present study, treatment with tetrandrine at doses sufficient to lower plasma glucose concentration failed to modify the mean arterial pressures in STZ-diabetic rats. The effective dose of tetrandrine for lowering of plasma glucose was less than that required for a decrease in blood pressure. The plasma glucose lowering effect of tetrandrine in STZ-diabetic rats therefore seems not to be related to the change in blood pressure.

Several methods have been established to assess glucose utilization and/or insulin sensitivity in animals and humans (Bessesen 2001). Using the IVGCT, we observed that tetrandrine (1.0 mg kg^{-1}) significantly attenuated the increase in plasma glucose following the IVGCT in Wistar rats when compared with the vehicle-treated group. Thus, enhancing glucose utilization can be considered for the plasma glucose lowering action of tetrandrine in vivo.

In diabetes, elevation of blood glucose is a consequence of increased hepatic glucose output together with reduced peripheral glucose utilization (Consoli et al 1989). Skeletal muscle is a major site for glucose disposal (Baron et al 1988). Glucose transportation, which depends on insulin-stimulated translocation of glucose carriers to the cell membrane, is the rate-limiting step in the carbohydrate metabolism of skeletal muscle (Ziel et al 1988). Reduction in insulin-mediated glucose uptake in diabetes has been reported (Berger et al 1989). In fact, insulin action is greater in the red type I fibres of soleus muscle (James et al 1985). With this in mind, we prepared soleus muscle samples from STZ-diabetic rats to evaluate the effect of tetrandrine on glucose uptake. We found that tetrandrine caused an increase in glucose uptake into soleus muscles isolated from STZ-diabetic rats. The effective dose of tetrandrine (1.0 mg kg^{-1}) required to lower the higher plasma glucose of STZ-diabetic rats was about 1.6 μmol L^{-1}, a value near to that (1.0 μmol L^{-1}) produced maximum effect on glucose uptake into soleus muscles. The results obtained therefore indicate that tetrandrine could increase the utilization of glucose in peripheral tissue to regulate glucose homeostasis via an insulin-independent mechanism.

Mammalian cells store glycogen in the liver for production of glucose 6-phosphate during glycolysis (Bollen et al 1998). Insulin deficiency is clearly associated with changes in hepatic metabolism (Hanson & Reshef 1997). Thus, we used liver samples to investigate the effect of tetrandrine on the incorporation of glucose into glycogen that can be related to the decrease in plasma glucose. Although not as effective as bovine insulin, tetrandrine markedly increased glycogen synthesis in hepatocytes isolated from diabetic rats. These results can be used to link the increase in glucose utilization by tetrandrine in peripheral tissue to the lowering of plasma glucose in an insulin-deficient state. However, the major mechanism of tetrandrine for lowering plasma glucose needs to be characterized in the future. It has been mentioned that long-term treatment of dogs with tetrandrine at the higher oral dose of 40.0 mg kg^{-1} may induce focal necrosis of liver cells (Tainlin et al 1982). However, a beneficial effect of tetrandrine at an oral dose of 10 mg kg^{-1} per day on experimental hepatic fibrosis induced by bile duct ligation and scission in rats has also been documented (Park et al 2000). In the present study, the dose of tetrandrine effective for lowering plasma glucose in STZ-diabetic rats is less than that required to produce these effects in the liver. Although tetrandrine was not as effective as bovine insulin in lowering plasma glucose in STZ-diabetic rats, our data showed that tetrandrine is useful as an attractive adjuvant for the handling of diabetic patients in the future. The oral pharmacological usefulness and potency of tetrandrine in the regulation of plasma glucose under the insulin deficient state will be investigated in the future.

It has been documented that the demethylation of the 7-O position and/or addition of a 2- or 2′-N-oxide side chain in bis-benzylisoquinoline compounds in Stephania has a role in the induction of anti-hyperglycemic actions in STZ-diabetic mice (Tsutsumi et al 2003). However, the compound of tetrandrine used in the present study is non-demethylated. This variation of the structure modification of tetrandrine on the plasma glucose lowering action might be related to the differences in animal species in the ddY and Wistar strains. It has also been reported that tetrandrine causes the death of malignant lymphoid and myeloid cells (Teh et al 1991). Tetrandrine seems to be a valuable anti-neoplastic agent. However, the apoptotic effect of tetrandrine linked to the plasma glucose lowering effect shall be investigated in the future.

Conclusions

The data obtained in this study suggest that intravenous injection of tetrandrine can lower plasma glucose in STZ-diabetic rats due to an increase of glucose utilization in peripheral tissues via non-insulin-mediated mechanisms.

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