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BASIC INVESTIGATION

Antihyperglycemic and antihyperlipidemic action of cinnamaldehyde in C57blks/j Db/db mice

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Abstract

OBJECTIVE: To investigate the effects of cinnamaldehyde (CA), an active and major compound in cinnamon, on glucose metabolism and insulin resistance in C57BLKS/J db/db mice.

METHODS: Sixteen male C57BLKS db/db mice were randomly divided into control and CA treatment groups. CA was given (20 mg·kg^{-1}·day^{-1}, p.o.) for 4 weeks. Pure water was given to control and db/+ mice. Subsequently, the levels of fasting blood glucose (FBG), fasting serum insulin, triglyeride, cholesterol, low-density lipoprotein -cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), and free fatty acids (FFA), as well as the mRNA content of adiponectin and tumor necrosis factor (TNF)-α in adipose tissue, glucose transporter type 4 (GLUT-4) in skeletal muscle, and protein expressions of Akt, phospho-Akt (Thr308), AMPKα, phospho-AMPKα (Thr172) in skeletal muscle were measured.

RESULTS: 1) CA decreased serum levels of FBG and insulin as well as body weight in db/db mice; 2) CA increased serum HDL-C levels; 3) CA significantly decreased the mRNA expression of TNF-α in adipose tissue and upregulated mRNA expression of GLUT-4 in skeletal muscle; 4) protein expression of p-Akt was increased in CA-treated mice, but Akt, AMPKα and p-AMPKα showed no change.

CONCLUSION: CA has antihyperglycemic and antihyperlipidemic actions in db/db mice and could be useful in the treatment of type-2 diabetes.

Key words: Cinnamaldehyde; Diabetes mellitus, Type 2; Insulin resistance

INTRODUCTION

Type-2 diabetes mellitus (T2DM) is a chronic metabolic disorder known to have affected »4% of adults aged ≥ 20 years in 1995, and is expected to affect 380 million by 2025.[1] The cause of T2DM is not known, although genetic and environmental factors (e.g. obesity, lack of exercise) appear to play a part. T2DM occurs if the pancreas does not produce sufficient amounts of insulin or if the body cannot effectively use the insulin it produces.[2] Insulin resistance is a major contributor to the pathogenesis of T2DM and has a key role in associated metabolic abnormalities such as hyperlipidemia and hypertension.[3]

Several types of anti-diabetic medicines have been studied for their ability to lower blood glucose and ultimately lower the prevalence of secondary complications of this disease. There is growing interest in folk remedies using herbs due to the side effects associated

with the synthetic medicines used in the treatment of T2DM. Cinnamon is the bark of Cinnamomi cassise (Lauraceae). It is a traditional folk medicine used in China, Korea and Russia for the treatment of T2DM.4 Interest in this herb has increased since the discovery of its potential effects on insulin5 and its ability to reduce levels of fasting blood glucose (FBG) and plasma lipids in humans.[6] Subsequently, some studies have reported that cinnamon extract decreases blood glucose,[7] improves glucose uptake in adipocytes,[8] and improves the function of pancreatic islets[9] in Wistar rats, as well as slowing down absorption of carbohydrates in the small intestine.[10] Cinnamon extract significantly increases insulin sensitivity possibly by regulating the peroxisome proliferator-activated receptor (PPAR)-medicated metabolism of glucose and lipids[11] as well as increasing the amount of proteins involved in insulin signaling, glucose transport, and anti-inflammatory/anti-angiogenesis responses.[11,12]

The active compounds of cinnamon have been reported. These include water-soluble polyphenol type-A polymers,[8,11,13] cinnamaldehyde (CA)[14-17] and procyanidin oligomers.[18] As a major and effective compound isolated from cinnamon,[19,20] CA possesses anti-hypoglycemic and anti-hypolipidemic effects in streptozotocin (STZ)-induced T2DM in rats[14,17] and improves the function of pancreatic islets.[9] However, reports on the effect of CA on the metabolism of glucose and lipids in T2DM are lacking. The aim of the present study was to investigate the effect of CA in db/db mice, which are used as models of obesity, insulin resistance and T2DM.

METHODS

Ethical approval of the study protocol

The experimental protocols were approved by the Animal Care and Use Committee of Beijing University of Chinese Medicine (Beijing, China).

Animals

Sixteen 7-week-old male BKS. Cg-+ Leprdb/+ Leprdb/Jcl (db/db) mice and 8 non-diabetic littermate control mice (db/+) were supplied by the Model Animal Resource Center of Nanjing University (Nanjing, China). The animals were kept in the air-conditioned Animal House of the Beijing University of Chinese Medicine at 25° C-30° C and 45%-55% relative humidity. They were fed standard food (Beijing Ke Ao Xie Li, Beijing, China) ad libitum under a 12 h light-dark cycle throughout the study.

Oral administration

After being fed for 1 week, 16 db/db mice were divided into two equal groups: CA and control. Mice in the CA group received CA solution (0.5% dimethyl sulfoxide (DMSO), 20 $mg \cdot kg^{-1} \cdot day^{-1}$; Shanghai Winherb Medical Science, Shanghai, China). Mice in the db/+ group and control group were given an equivalent volume of pure water alone (0.5% DMSO) by intragastric administration once a day for 4 weeks. The CA dosage was chosen based on that used in three reports.[10,14,17]

Measurement of FBG, serum insulin, HOMA-IR, blood lipids and body weight

FBG was measured immediately with a Glucometer (ACC U-Check; Roche, Basel, Switzerland) in tail-vein blood (≈5 μL each time) after fasting for 8 h on days 7, 14, 21 and 28. After treatment for 4 weeks, mice were fasted overnight and anesthetized with pentobarbital sodium (50 mg/kg, i.p.). Blood was collected from the abdominal aorta. Serum levels of insulin were assayed with an enzyme-linked immunoassay (ELISA) kit (Linco Research, St Charles, MO, USA). Indices of insulin resistance were calculated using the homeostasis model of insulin resistance (HOMA-IR) index[21] whereby:

HOMA-IR=fasting blood glucose level (mmol/L) × serum insulin level (ng/mL)/22.5

Serum levels of triglyceride (TG), total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C) and free fatty acids (FFAs) were measured using commercial kits (Beijing North Institute of Biological Technology, Beijing, China) with an Automatic Biochemical Analyzer (AU400 Biochemistry Analyzer, Olympus, Tokyo, Japan). Body weight was measured on days 7, 14, 21 and 28.

Preparation of total RNA

Frozen samples of quadriceps muscle and epididymal fat tissues were crushed in liquid nitrogen. Total RNA was extracted using Trizol reagent (Invitrogen, Carlsbad, CA, USA). The relative purity of RNA was assessed by spectrophotometric means. The ratio of absorbance at 260 nm to that at 280 nm was 1.7-2.0 for all preparations. The integrity of RNA was confirmed in 1% agarose gel.

mRNA analyses:

Total RNA was reverse-transcribed by a Reverse Transfer kit (Beijing North Institute of Biological Technology) with oligo dT primers following the manufacturer's instructions. The sequences of sense and antisense primers used for amplification are shown in Table 1.

GAPDH, glyceraldehyde 3-phosphate dehydrogenase; TNF-α, tumor necrosis factor-α, GLUT4, glucose transporter type 4.

Amplification was undertaken with an initial denaturation at 95°C for 5 min followed by 30 cycles at 95°C (30 s), 55°C (30 s), and then extension at 72°C (30 s). The polymerase chain reaction (PCR) products were separated on 1.0% agarose gel and stained with ethidium bromide. Glucose transporter type 4 (GLUT4) mRNA was measured by denaturation at 95°C for 2 min followed by 45 cycles of PCR (95°C for 20 s, 58°C for