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Anti-diabetic effect of Yukmijihwangtang-Jahage in obese Zucker rats

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Abstract

The effect of the traditional herbal medicine Yukmijihwangtang-Jahage (YJ) on the improvement of insulin resistance and lipid profile was studied using a model for non-insulin dependent diabetes mellitus, lean (Fa/-) and obese (fa/fa) Zucker rats. Yukmijihwangtang-Jahage feeding for 4 weeks resulted in a significant decrease in the concentration of plasma triglyceride in both lean and obese Zucker rats. Furthermore, Yukmijihwangtang-Jahage markedly decreased both plasma cholesterol and fasting plasma insulin levels, and significantly decreased the postprandial glucose level at 30 min during oral glucose tolerance test in obese Zucker rats. Although there was no statistical significance, the crude glucose transporter 4 protein level of Yukmijihwangtang-Jahage dieted obese rats tended to increase when compared to that of obese control rats. Therefore, the present results suggested that Yukmijihwangtang-Jahage may be useful in prevention and improvement of metabolic disorders characterized by hyperinsulinemia states such as non-insulin dependent diabetes mellitus, syndrome X and coronary artery disease.

Key words – Yukmijihwangtang-Jahage, Insulin resistance, Zucker rats, Lipid metabolism

Introduction

Diabetes mellitus is not a single disease, but a group of disorders of varying etiology and pathogenesis that are characterized by increased fasting and postprandial blood glucose concentrations, insulin deficiency and decreased insulin action, abnormalities of glucose, lipid and protein metabolism and the development of both acute and longterm complications [2].

Insulin resistance, which is associated with hyperinsulinemia and impaired glucose tolerance (IGT), has been well documented in obesity and non-insulin dependent diabetes mellitus (NIDDM) patients [6,27,30] and animal models [28,33]. Although the mechanisms for this insulin resistance remain undefined, the defective glucose transport system may play an important role in the pathogenesis of peripheral insulin resistance, because glucose transport appears to be a rate-limiting step for glucose utilization in muscle [25].

On the other hand, previous epidemiologic studies have suggested that both hyperinsulinemia and insulin resistance contribute to the etiology of hypertension in patients with obesity and NIDDM [23,36] and are also associated with syndrome X and increased risk for coronary artery disease (CAD) [31,32]. Patients with untreated hypertension, as compared with matched normotensive control subjects, are not only resistant to

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insulin-stimulated glucose uptake but also are hyper insulinemic [10,11,34,37]. These patients exhibit elevated plasma triglyceride levels when compared with control subjects [34]. Based on these considerations, improvement of insulin resistance could be required in preventing development of disorders accompanied by insulin resistance. Thus, physical training [9,15] and dietary approaches [3] have been devised as a means of reducing insulin resistance. Recent reports have also documented new compounds that reduce insulin resistance or potentiate insulin action in genetically diabetic and/ or obese animals [4,13,41].

The herbal medical system known as 'Hanbang medicine' is a traditional Korean therapeutic system. It has been used for the treatment of various diseases for hundreds of years, including the clinical treatment of hyperglycemia, hypercholesterolemia, diabetes and obesity. Yukmijihwangtang-Jahage (YJ) has been used for the therapies of diabetic disease in traditional oriental medicine. However, the pharmacological mechanism of Yukmijihwangtang-Jahage (YJ) on lipid metabolism and diabetes mellitus are poorly understood.

The present study was performed to examine the therapeutic effects of Yukmijihwangtang-Jahage (YJ) on the abnormality of lipid metabolism caused by insulin resistance and the improvement of insulin resistance in genetically obese animal models.

Materials and Methods

Preparation of Yukmijihwangtang-Jahage (YJ)

Yukmijihwangtang-Jahage (YJ) used in this study was obtained from Oriental Hospital, Dongguk University, and is a dried decoctum of a mixture of six medicinal plants as follows: *Rehmannia glutinosa* LIBOSCH (16 g), *Dioscorea japonica* THUNB (8 g), *Cornus officinalis* SIEB. et. ZUCC (8 g), *Smilax glabra* ROXB (6 g), *Paeonia sufruticosa* AVDR. (6 g) and *Alisma plantago-aquatica var. orientale* SAMUELS (6 g). An extract of YJ was preapred by boiling for 5 h a mixture of six medicinal plants with 500 ㎖ of distilled water. These aqueous extracts were evaporated with Rotavapor (Buchi RE121, Switzerland) under vacuum. The crude extracts were then filtered and concentrated by lyophilization. This decoction was spray-dried to give a powdered extract.

Animals and diets

Obese (fa/fa) and their lean littermates (Fa/-) Zucker rats [5] were purchased from Tokyo Experimental Animals

Table 1. Composition of control and experimental diets (%)

Ingredient	Control diet	Experimental diet
Casien	20.0	20.0
Sucrose	10.0	10.0
Corn Starch	50.0	50.0
Lard	5.0	5.0
Corn oil	5.0	5.0
Mineral Mixture[1]	3.5	3.5
Vitamin Mixture[1]	1.0	1.0
DL-methionine	0.5	0.5
Cellulose	5.0	4.5
YJ powder[1]	-	0.5

[1]This is identical with AIN-76 mixture.
[2]Yukmijihwang-tang.

(Tokyo, Japan) at three months of age and maintained on a laboratory chow diet consisting of 52.7% carbohydrate, 23.6% protein, 4.4% fat, 4.9% fiber, 6.6% minerals and vitamins (CE-2, Clea Japan Incorp., Tokyo) for 1 week, and water. They were individually housed in stainless steel cages and kept in an isolated room at a controlled temperature (23-24℃) and ambient humidity (50-60%). Lights were mantained on a reversed 12-h light/dark cycle. Obese and Zucker rats (13 weeks-old, male) were divided into two groups (YJ diet and control diet groups, each with 5 rats, respectively). Table 1 shows composition of the control and experimental diets. The control group received a diet with 5% cellulose, and the experimental group had diet containing 0.5% (w/w) YJ powder. Except for the oral glucose tolerance test (OGTT), the animals were always allowed free access to the diet for 4 weeks. At 18 weeks of age, the animals were anesthetized via intraperitoneal injection of pentobarbital sodium (5 mg/100 g of body weight) after an overnight fast, followed by OGTT.

Oral glucose tolerance test (OGTT)

After an overnight fast, D-glucose (1 g/kg body weight) was given by oral tube. Blood samples were obtained by cutting the tail end before glucose loading, and at 30, 60 and 120 min after glucose loading, respectively. Blood glucose levels were determined with TIDEX glucose analyzer (Miles, Slough, U.K.).

Plasma measurement

After anesthesia, blood was drawn from the inferior vena cava and centrifuged at 4℃. Plasma was used for measurements of glucose, immunoreactive insulin, triglyceride and total cholesterol. After blood was collected, gastrocnemius skeletal muscle from each leg was quickly

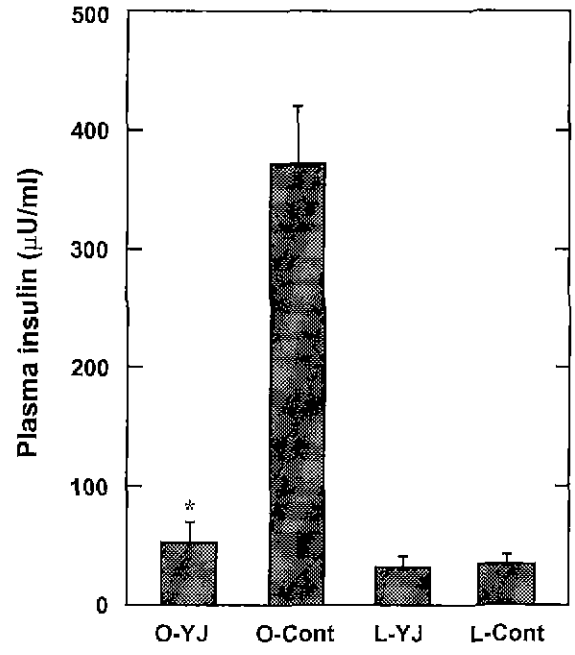

Fig. 1. The effect of Yukmijihwangtang-Jahage (YJ) diet on plasma insulin levels in Zucker rats. O-YJ.; obese Zucker rats fed YJ diet, O-Cont; obese Zucker rats fed control diet, L-YJ; lean Zucker rats fed YJ diet, L-Cont; lean Zucker rats fed control diet. Values are mean±SE for the five samples. Asterisk indicates statistically significant difference between obese Zucker rats fed YJ diet and obese control rats fed control diet at $P< 0.05$.

Table 2. Effect of Yukmijihwang-tang(YJ) on body weight, plasma glucose, triglyceride, and cholesterol concentrations

Animal	Body weight (g)	Plasma glucose (mg/dl)	Plasma triglyceride (mg/dl)	Plasma cholesterol (mg/dl)
Obese-YJ	565 ± 8^{a}	95 ± 2^{a}	232 ± 24^{a}	173 ± 12^{a}
Obese-Control	578 ± 12^{a}	110 ± 5^{a}	403 ± 49^{b}	238 ± 5^{b}
Lean-YJ	375 ± 5^{b}	96 ± 3^{b}	44 ± 5^{c}	75 ± 5^{c}
Lean-Control	387 ± 14^{b}	104 ± 2^{b}	76 ± 7^{d}	78 ± 3^{c}

Values are mean ± SE; N = 5 rats. Values within a column with different superscript letters are significantly different from each other ($p<0.05$).

excised, weighed, clamp-frozen in liquid nitrogen, and stored at -80℃ until analysis. Immunoreactive insulin was measured by radioimmunoassay as described previously [9] using human insulin as the standard. The concentrations of triglyceride and total cholesterol were measured by enzyme assay with Determiner TG and Determiner TC555 (Kyowa Medics, Tokyo, Japan), respectively.

Immunoblotting

Crude membrane fraction from gastrocnemius skeletal muscle was prepared in accordance with a previously described method [9]. The protein separated by SDS-PAGE was electrophoretically transferred to polyvinylidine difluoride sheets (Immobilion, Millipore, Bedford, MA), and immunoblotted with an antiserum specific for C-terminal amino acid sequence of glucose transporter 4 (GLUT4) and then ^{125}I-labeled protein A as described previously [9]. To quantify GLUT4, pieces of sheet containing the GLUT4 protein were cut out and radioactivity was counted on a gamma-counter.

Statistical analysis

Data were expressed as mean±SE for five rats in each group. Statistical analysis was performed by one-way analysis of variance (ANOVA), and differences between means were tested using Duncan's multiple range test. Values of $P<0.05$ were considered to be significant.

Results

Final body weight and plasma concentrations of glucose, triglyceride and total cholesterol in obese and lean Zucker rats are summarized in Table 2. YJ feeding had no statistically significant effects on body weight between these animals.

In the fasting plasma glucose values, there were no significant differences between obese (110±5 mg/dl) and lean (104±2 mg/dl) Zucker rats. However, in obese Zucker rats, YJ feeding caused a 42% reduction in plasma

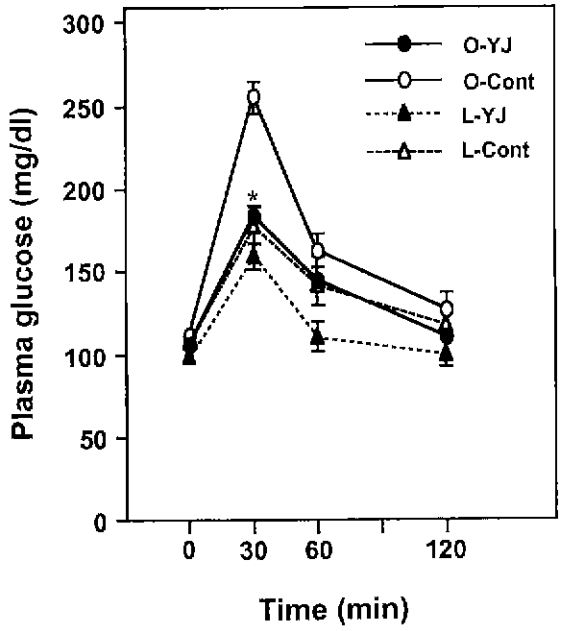

Fig. 2. The effect of dietary Yukmijihwangtang-Jahage (YJ) feeding on oral glucose tolerance tests in Zucker rats. O-YJ; obese Zucker rats fed YJ diet, O-Control; obese Zucker rats fed control diet, L-YJ; lean Zucker rats fed YJ diet, L-Control; lean Zucker rats fed control diet. Values are mean±SE for the five samples. Asterisk indicates statistically significant difference between obese Zucker rats fed YJ diet and obese control rats fed control diet at $P< 0.05$.

triglyceride concentration (403±49 vs. 232±24 mgl/dl) and a 27% decrease in cholesterol concen- tration (238±5 vs. 173±12 mg/dl). In addition, for triglyceride values, YJ feeding resulted in a 42% de- crease (76±7 vs. 44±5 mg/dl) in lean Zucker rats. Fig. 1 shows the effect of YJ on plasma insulin level in Zucker rats.

As expected, an excessive degree of hyperinsulinemia was exhibited in obese Zucker rats, and a normal range was observed in their lean littermates. The fasting plasma insulin level of obese Zucker rats, which was eleven fold higher than that of their lean control (372± 43 vs. 34±6 μU/ml, respectively), significantly decreased in YJ diet group. In lean Zucker rats which have

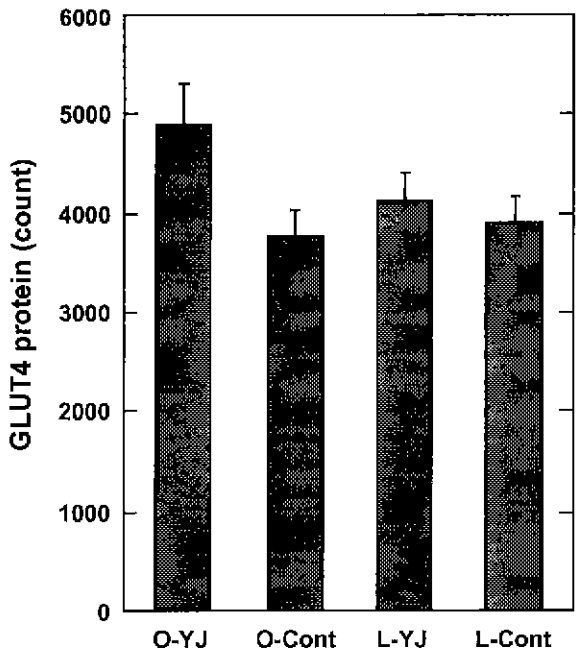

Fig. 3. The effect of dietary Yukmijihwangtang-Jahage (YJ) feeding on GLUT4 protein level in gastrocnemius skeletal muscle of Zucker rats. Protein (50 g) from mixed gastrocnemius skeletal muscle was extracted, subjected to SDS-PAGE, transferred to immobilion membrane, and immunoblotted with polyclonal antibody to GLUT4 protein in accordance with a previously described methods [9]. O-YJ; obese Zucker rats fed YJ diet, O-Cont; obese Zucker rats fed control diet, L-YJ; lean Zucker rats fed YJ diet, L-Cont; lean Zucker rats fed control diet. GLUT4 protein was measured by gamma-counter obtained from immunoblotting analysis. Values are mean±SE for the five samples.

been shown to exhibit normal insulin levels the insulin level in YJ feeding group tended to increase but the difference was not significant. To determine the functional effects of dietary YJ, OGTTs were performed. As shown in Fig. 2, there was no significant difference in fasting plasma glucose levels between obese and lean Zucker rats. However, dietary YJ feeding resulted in significant decrease in plasma glucose level at 30 min after glucose loading in obese Zucker rats. From these results, dietary YJ, when compared to control diet, caused a significant decrease in lipid levels and improvement of insulin resistance in obese Zucker rats. To elucidate the mechanism involved in improvement of insulin resistance, GLUT4 protein levels were determined in gastrocnemius skeletal muscle of Zucker rats by immunoblotting using a polyclonal antisera. The quantification by gamma counter is showed in Fig. 3. There was no significant difference in GLUT4 protein levels between obese Zucker rats and their lean littermates as control groups. However, GLUT4 protein levels tended to increase in obese Zucker rats fed YJ diet when compared to obese controls.

Discussion

We investigated the effect of dietary YJ on improvement of insulin resistance and lipid metabolism by using the rodent model of obesity with insulin resistance, (fa/fa) Zucker rat, and their lean littermates (Fa/-). Dietary YJ feeding significantly reduced plasma triglyceride and total cholesterol levels in obese Zucker rats. In addition, YJ feeding resulted in the improvement of impaired glucose tolerance (IGT) and reduction of hyperinsulinemia. These results indicate that dietary YJ is effective on abnormal glucose and lipid metabolisms associated with insulin resistance responsible for diabetic syndromes (hyperglycemia, glucose intolerance, hypertriglyceridemia, and hyperinsulinemia).

Hyperlipidemia, in particular hypertriglyceridemia, is one of the most prominent features of obese (fa/fa) Zucker rats. This study showed that the abnormality was significantly improved by treatment with YJ. The association of hyperlipidemia with insulin resistance has been documented: the increase in hepatic very-low-density lipoprotein (VLDL)-triglyceride secretion caused by hyperinsulinemia and the reduction of the rate of removal of VLDL-triglyceride from plasma that accompanies insulin resistance has been shown to cause hy-

pertriglyceridemia [24]. It is thus conceivable that the amelioration of hyperlipidemia through feeding YJ diet is due to the improvement of hyperinsulinemia through augmentation of insulin sensitivity.

Skeletal muscle is the predominant tissue responsible for insulin-stimulated glucose disposal and a major site of insulin resistance in diabetes [30]. The genetically obese (fa/fa) Zucker rat has proven to be a useful model for the study of mechanisms of insulin resistance because of the well characterized defect in insulinstimulated glucose uptake by skeletal muscle [7, 16, 35]. Glucose transport in skeletal muscle is regulated primarily via GLUT4 [8,22,40]. The defect of GLUT4, which is responsible for facilitated glucose transporter in response to insulin, may have a significant contribution to whole body insulin resistance. The increase of the amount of GLUT4 could contribute to the improvement of insulin resistance. In the present study, however, despite the improvement of insulin resistance by dietary YJ feeding, GLUT4 protein level was not significantly affected in skeletal muscle of obese Zucker rats. These findings suggest that, in genetically insulin-resistant rodents, the increase in the level of GLUT4 protein does not necessarily reflect the improvement of insulin resistance. This suggestion is supported by previous results obtained from obese (fa/fa) Zucker rats, in which the insulin resistance in the genetic form of obesity is not due to depletion of GLUT4 protein in skeletal muscle [12]. Some studies have reported changes of glucose uptake associated with insulin resistance without a significant change of GLUT4 protein level [17,20,29] It has been demonstrated that insulin-resistant states such as obesity and NIDDM in which decreased glucose uptake into skeletal muscle cannot be explained by a decrease in GLUT1 or GLUT4 [17,20,29]. Very recently, metformin, an antihyperglycemic agent used in the treatment of NIDDM, reduced the extent of hyperglycemia and hyperinsulinemia, consistent with a reduction of insulin resistance without increasing either new synthesis of GLUT1 and GLUT4 or numbers of these transporters in the muscle membrane of dexamethasone-treated mice [39]. Thus, we could speculate on the other factors for reduction of fasting plasma insulin levels such as increase of translocation and/or intrinsic activity of GLUT4 and improvement of insulin sensitivity and/or responsiveness in the skeletal muscle. This may be supported from significant decrease of postprandial 30 min glucose level on OGTT.

On the other hand, it is well known that impairment of insulin-stimulated glucose uptake is associated with hyperinsulinemia, glucose intolerance, increased plasma triglyceride, decreased HDL-cholesterol concentration and high blood pressure. This cluster of phenomena has been called syndrome X [6]. Insulin resistance may play a role in the etiology of this syndrome, and all of these proposed consequences of insulin resistance have been shown to be associated with increased risk for CAD [31]. Based on these considerations, if insulin resistance can be improved, development of this syndrome will be reduced, and the risk for CAD will be minimized. In the previous paper [18], Kim et al. reported that dietary Platycodon grandiflorum (P. g.) grown for 22 years has shown a beneficial effect on preventing hypercholesterolemia and hyperlipidemia in diet-induced hyperlipidemia rats. Morever, dietary P. g. grown for 22 years markedly decreased both plasma cholesterol and fasting plasma insulin levels, and significantly decreased the postprandial glucose level at 30 min during oral glucose tolerance test in obese Zucker rats [19]. In the present study, it is noteworthy that dietary YJ has shown a significant lipid-lowering effect in genetically obese Zucker rats.

The present results suggest that dietary YJ may be useful in reducing the incidence of metabolic disorders characterized by hyperinsulinemia such as NIDDM, syndrome X and CAD.

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초록 : 비만 실험동물쥐 (obese Zucker rats)에서의 육미지황탕의 항당뇨 효과

서은경[1] · 강동휘[1] · 서진우[1] · 김경숙[2] · 이태균[1] · 이영춘[2] · 남경수[3] · 김철호[1]
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한방에서 당뇨병 치료제로서 사용되는 육미지황탕의 인슐린저항성 개선과 지질대사에 미치는 효과를 인슐린 비의존형 당뇨병 실험동물인 lean(Fa/) Zucker rat와 obese (fa/fa) Zucker rat를 이용하여 조사하였다. 육미지황탕이 함유된 식이를 4주동안 투여한 결과, lean(Fa/) Zucker rat와 obese (fa/fa) Zucker rat 모두에서 혈장 triglyceride 농도가 유의적으로 감소되었다. 또한 육미지황탕은 obese (fa/fa) Zucker rat에서 혈장 콜레스테롤과 혈장 인슐린 농도를 유의적으로 감소시킬 뿐 만 아니라, 포도당 부하검사에서 30분후에 혈당수준을 유의적으로 감소시켰다. 포도당 수송단백질인 GLUT4양의 변화에 대한 육미지황탕의 효과는 통계적인 유의성에서는 큰 차이가 없었지만, 대조구에 비해서는 GLUT4양이 증가하는 경향을 나타내었다. 따라서 본 연구에서의 결과는 육미지황탕이 인슐린 비의존형 당뇨병이나 syndrome X, 관상동맥질환과 같은 고인슐린혈증 상태와 관련이 깊은 대사이상 질환의 예방이나 치료에 유용할 수 있다는 사실을 제시하고 있다.