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Effects of Goshajinkigan on insulin resistance in patients with type 2 diabetes

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Abstract

We investigated the effects of Goshajinkigan (GJG), a Chinese herbal medicine, on insulin sensitivity in patients with type 2 diabetes using the homeostasis model assessment of insulin resistance (HOMA-R) and the euglycemic insulin clamp procedure. Daily oral administration of GJG (7.5 g/day) was performed for 1 month in 71 type 2 diabetes patients: the GJG treatment group. HOMA-Rs were calculated before and after 1 month of GJG treatment and compared with those of 44 controls who were matched in terms of sex, age, body mass index (BMI) and HbA1c levels with the experimental group. In 64 patients out of the GJG treatment group, HOMA-R was calculated 1 month after discontinuation of treatment. In addition, euglycemic clamp was conducted in eight patients before and after the GJG treatment. HOMA-R was 4.78 ± 0.37 (means $\pm$ S.E.) before GJG treatment and significantly decreased to 4.02 ± 0.25 after GJG treatment ($P = 0.019$). No significant change was observed in the control group. HOMA-R returned to the pre-treatment level ($P = 0.018$) 1 month after GJG treatment discontinuation. Glucose infusion rates and metabolic clearance rates determined by the high-dose euglycemic clamp increased after 1 month of GJG treatment (from 9.6 ± 1.1 to 11.1 ± 0.7 mg/kg/min, $P = 0.045$ and from 7.9 ± 0.8 to 9.1 ± 0.8 ml/kg/min, $P = 0.046$, respectively). These results indicate that GJG administration might be useful for improving insulin resistance in patients with type 2 diabetes.
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Keywords: Chinese herbal medicine; Goshajinkigan; Insulin resistance; HOMA-R; Euglycemic clamp

1. Introduction

Goshajinkigan (GJG), a traditional Chinese complex of herbal medicines, has been widely used as a regimen for treatment of diabetic neuropathy in Japan. Several clinical studies have reported that GJG could ameliorate subjective symptoms and the vibratory threshold of patients with diabetic neuropathy, having better effect than mecobalamin [1–3]. Additionally, in the animal study, Nishizawa et al. revealed that GJG prevents deterioration of the sciatic nerve conduction

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velocity in streptozotocin (STZ)-induced diabetic neuropathy [4].

In a recent animal study, Hu et al. reported further effect of GJG on insulin action [5]. In this study, GJG improved the peripheral insulin resistance in STZ-induced diabetic rats. However, up till now it has not been analyzed whether GJG has similar effects in humans. In this study, we investigated the effects of GJG administration on insulin sensitivity in type 2 diabetes patients using two methods: the homeostasis model assessment of insulin resistance (HOMA-R) and the euglycemic insulin clamp procedure.

2. Subjects and methods

2.1. HOMA-R and other clinical characteristics before and after GJG treatment

All participants of this study were outpatients with type 2 diabetes. Without changing diet and daily life, 7.5 g/day of GJG (Tsumura Co., Tokyo, Japan) was orally administered to 71 patients before the meals for 1 month (GJG treatment group). Forty-four patients who were matched in terms of sex, age, body mass index (BMI) and HbA1c levels with the patients of the GJG treatment group were selected as the control group.

Anthropometrical measurements and blood sampling were performed before and after the GJG treatment period for the two groups following an overnight fast. All measurements were carried out once again in 64 patients of the GJG treatment group 1 month after GJG treatment discontinuation.

Plasma insulin was assayed with a radioimmunological assay kit (Phadeseph Insulin RIA, Pharmacia AB, Stockholm, Sweden). Fasting blood glucose (FBG), total cholesterol (TC), HDL-cholesterol (HDL-C), and triglyceride (TG) were measured using routine enzymatic techniques. HbA1c was measured using the TKSgel G7 (Variant) Hsi column (HLC-723G7, Tosoh Co., Tokyo, Japan).

HOMA-R was calculated using FBG and fasting immunoreactive insulin (FIRI) values and was used for the evaluation of insulin sensitivity [6]. The insulin sensitivity level was calculated using the following formula: HOMA-R = FIRI (μU/ml) $\times$ FBG (mg/dl)/405.

We informed the participants about adverse reactions of GJG that might occur and obtained consent from all of them.

2.2. Glucose infusion rates (GIRs) and metabolic clearance rates (MCRs) determined by the euglycemic clamp procedure before and after GJG treatment

Insulin action in eight patients with type 2 diabetes was evaluated using the euglycemic clamp procedure before and after the 1-month GJG treatment period (7.5 g/day). After an overnight fast, a primed intravenous infusion of 800 mU of short-acting human insulin (Novolin-R, Novo Nordisk A/S, Denmark) was carried out over 10 min and was followed by a constant infusion of insulin at 40 mU/m^2/min for 80 min (low dose clamp: insulin sensitivity evaluation). Then, the continuous infusion rate of insulin was increased to 400 mU/m^2/min for the remaining 60 min of the experiment (high-dose clamp: insulin responsiveness evaluation). During insulin infusion, the basal blood glucose level was maintained constant by determining the blood glucose concentration (Lifescan, Johnson & Johnson, Los Angeles, USA) every 5 min and adjusting a simultaneous infusion of a 20% (w/v) glucose solution. Under this steady-state condition for glucose (euglycemia) GIRs provide the total whole body glucose turnover, since insulin at this dose level has been shown to inhibit hepatic glucose production. The GIR was defined as the mean glucose infusion rate during the last 30 min of insulin infusion at each rate [7,8]. In order to compare in vivo insulin action of subjects with different basal plasma glucose levels, MCRs were calculated by dividing GIR by the mean plasma glucose [9].

We informed all participants of the nature, purpose and possible risks of the euglycemic clamp procedure and obtained written consent. This study was approved by the Institutional Review Board of the Research Center of Health, Physical Fitness and Sports, Nagoya University.

2.3. Statistical analysis

Values are expressed as means $\pm$ S.E. unless otherwise indicated. All statistical analyses were performed using the StatView software Version 5.0 (SAS Institute Inc., Cary, NC, USA). Values before

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