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Central anti-diabetic action of biguanide and thizolidinediones in D-glucose fed and streptozotocin-treated mouse models

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HIGHLIGHTS

- I.c.v. with metformin or rosiglitazone slightly attenuated the blood glucose level.
- I.c.v. or i.t. with metformin attenuated the blood glucose level in STZ model.
- Metformin and rosiglitazone appear to be mediated via the brain regions.
- I.c.v. or i.t. with metformin may be effective for treating IDDM.

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ABSTRACT

Background: In the present study, the possible anti-diabetic action of biguanide and thiazolidinediones administered supraspinally or spinally was studied in ICR mice.
Methods: Mice were intracerebroventricular (i.c.v.) or intrathecal (i.t.) treated with 20 or 30 μg metformin, pioglitazone and rosiglitazone in D-glucose fed and streptozotocin-treated models, and blood glucose levels was measured at 30, 60 and 120 min after i.c.v. or i.t. administration.
Results: We found that i.c.v. injection with metformin or rosiglitazone slightly attenuated the blood glucose level in D-glucose fed model, whereas pioglitazone showed no effect on the blood glucose level in D-glucose fed model. The i.t. administration with metformin, pioglitazone or rosiglitazone did not alter the blood glucose level in D-glucose fed model. We also assessed the possible roles of biguanide and thiazolidinedione in the regulation of the blood glucose level in streptozotocin-treated model. We found in the present study that i.c.v. or i.t. administration with metformin caused a pronounced attenuation of the blood glucose level in streptozotocin-treated model. However, rosiglitazone administered i.c.v. did not affect the blood glucose level in streptozotocin-treated model.
Conclusions: Our results suggest that the anti-diabetic actions of metformin and rosiglitazone appear to be mediated via the brain regions as revealed in D-glucose fed animal model. Furthermore, metformin administered supraspinally or spinally may be effective for treating type I diabetes mellitus as revealed in streptozotocin-treated mouse model.

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1. Introduction

Diabetes mellitus is one of the chronic diseases and is rapidly growing in prevalence worldwide. The complications of diabetes mellitus contribute to a major health problem in modern societies. Type 2 diabetes mellitus is characterized by highly elevated concentrations of glucose in the blood, which is caused by decreased secretion of insulin from the β-cells of pancreas and diminished action of insulin. Biguanide and thiazolidinedione are widely used oral drugs for the treatment of type II diabetes mellitus. In an earlier clinical studies have also reported that the major blood glucose-lowering activity of biguanide appears to be primarily through restraint of hepatic glucose output. Its therapeutic normalizing action of blood glucose is dependent on the presence of circulating insulin [19,21]. In addition, biguanide also increases insulin's suppression of gluconeogenesis, and attenuates glucagon-stimulated gluconeogenesis in the liver [21]. On the other hand, thiazolidinedione exert their anti-diabetic pharmacological effects

Abbreviations: ICV, intracerebroventricular; IT, intrathecal; STZ, streptozotocin; PEC, polyethylene glycol 400-ethanol-sodium carboxymethylcellulose.

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in type 2 diabetes mellitus by improving insulin action, enhancing peripheral glucose uptake, and decreasing triglyceride levels [15]. Ibrahimi et al. have reported that thiazolidinedione appear to increase transcription of certain genes in adipose tissue [8]. This action leads to the adipose tissue binds a transcription factor confirmed as peroxisome proliferator-activated receptor gamma (PPARγ), finally resulting in increase of insulin sensitivity [20].

Accumulating data have shown that the central nervous system plays an important role for the regulation of the blood glucose level. The role of the spinal cord, numerous studies have demonstrated that the several regions of the brain also play crucial roles to keep the homeostatic status of the blood glucose level [2,3]. Supraspinal injection of certain drugs such as atropine methyl bromide (methylatropine) produces modulatory action in the regulation of the blood glucose and insulin levels [11]. In addition, supraspinal administration of IL-1 alpha produces a hyperglycemia, hyperglucagonemia and hyperinsulinemia that resulted from an early increase in hepatic glucose production [12]. Several lines of evidence have demonstrated that the spinal cord is one of the important sites for the regulation of the blood glucose level. In an earlier clinical study, Sala et al. have reported that less dose of insulin is used to regulate the blood glucose level in patients with spinal cord injury [14]. Furthermore, several studies have reported that spinal administration of the saporin (anti-D beta H-SAP) such as ribosome inactivating protein modulate of the blood glucose level [13]. Furthermore, we have recently reported that substance P or several pro-inflammatory cytokines such as TNF-α, IFN-γ and IL-1β administered spinally causes an elevation of the blood glucose level [18,17]. Taken together, both the brain and the spinal cord are important sites for the regulation of the blood glucose homeostasis.

The peripheral anti-diabetic actions of biguanide and thiazolidinedione have been well studied and characterized. Although the functions of the central nervous system for the regulation of the blood glucose level have been well reported by a number of studies, the possible central action of biguanide and thiazolidinedione in the regulation of the glucose level has not been well studied yet. Thus, in the present study, we assessed the effects of biguanide and thiazolidinedione administered spinally or supraspinally on the regulation of the blood glucose level in D-glucose fed and streptozotocin-treated mouse models.

2. Methods

These experiments were approved by the Hallym University Animal Care and Use Committee (Registration Number: Hallym 2009-05-01). All procedures were conducted in accordance with the 'Guide for Care and Use of Laboratory Animals' published by the National Institutes of Health and the ethical guidelines of the International Association for the Study of Pain.

Male ICR mice (MJ Co., Seoul, Korea) weighing 20–25 g were used for all the experiments. Animals were housed 5 per cage in a room maintained at 22 ± 0.5 °C with an alternating 12 h light–dark cycle. Food and water were available ad libitum. The animals were allowed to adapt to the laboratory for at least 2 h before testing and were only used once. Experiments were performed during the light phase of the cycle (10:00–17:00). The animals were fasted for 16 h. The behavioral scores were verified by repeat trials, and the observers of pain-induced behavior were blind to drug treatments.

Oral administration was performed with gavage in a volume of 1 ml/kg body weight. Intrathecal (i.t.) administration was performed in conscious mice following the method of Hylden and Wilcox using a 30-gauge needle connected to a 25 μl Hamilton syringe with polyethylene tubing [7]. The i.t. injection volume was 5 μl and the injection site was verified by injecting a similar volume of 1% methylene blue solution and determining the distribution of the injected dye in the spinal cord. The dye injected i.t. was distributed both rostrally and caudally but with short distance (about 0.5 cm) and no dye was found in the brain. The success rate for the injections was consistently found to be over 95%, before the experiments were done. The intracerebroventricular (i.c.v.) administration followed the method described by Haley [4]. Each mouse was grasped firmly without anesthesia by the loose skin behind the head. The skin was pulled taut. A 30-guage needle attached to a 25 μl syringe was inserted perpendicularly through the skull into the brain and solution was injected. The injection site was 2 mm from either side of the midline on a line drawn through the anterior base of the ears. The i.c.v. injection volumes were 5 μl, and the injection sites were verified by injecting a similar volume of 1% methylene blue solution and determining the distribution of the injected dye in the ventricular space. The success rate for prior injections with this technique was over 95%.

Diabetic mice were induced by a single intraperitoneal injection of STZ (150 mg/kg in citrate buffer, pH 4.5). Normal groups received the buffer only. On the 6th day after STZ administration, animals with non-fasting blood glucose concentration above 400 mg/dl were considered to be diabetic and used in current study.

The blood glucose level was measured at 30, 60 and 120 min after the various pain stimulation (n = 8–10). The blood was collected shortly as much as possible with a minimum volume (1 μl) from the tail-vein. The glucose level was measured using Accu-Chek Performa blood glucose monitoring system (glucometer) (Mannheim, Baden-Württemberg, Germany).

Metformin, pioglitazone, rosiglitazone and D-glucose were purchased from Sigma Chemical Co. (St. Louis, MO, USA). Streptozotocin was purchased from USB Co. (Cleveland, OH, USA). Metformin was dissolved in saline. Pioglitazone and rosiglitazone were prepared following steps: (A) 1 g of pioglitazone and rosiglitazone was dissolved in 0.5 ml of ethanol plus 0.5 ml of polyethylene glycol 400. (B) Separately, 100 mg of sodium carboxymethylcellulose was dissolved in 9 ml of distilled water. (C) Finally, solution (A) and solution (B) were vigorously mixed. This solution (PEC) excluding pioglitazone and rosiglitazone were used as vehicle control. All drugs were prepared just before use. Blood glucose meter, lancing device and strips were purchased from Roche Diagnostics (Accu-Chek Performa, Germany).

Statistical analysis was carried out by student t test GraphPad Prism Version 4.0 for Windows (GraphPad Software, San Diego, CA, USA). *P*-values less than 0.05 were considered to indicate statistical significance. All values were expressed as the mean ± S.E.M. In our study, we established the mean blood glucose value of the control group through many experiments under matching conditions. Selected mice of established blood glucose level were then used in replication experiments.

3. Results

Effects of biguanide and thiazolidinedione administered intracerebroventricularly on the blood glucose level in D-glucose fed model. Mice were pretreated i.c.v. with 20 or 30 μg of metformin, pioglitazone or rosiglitazone for 10 min. Then 2 g/kg of D-glucose were orally fed. The blood glucose level was measured at 30, 60 and 120 min after D-glucose administration. As shown in Fig. 1A and C, metformin or rosiglitazone administered i.c.v. attenuated the blood glucose level in D-glucose fed model. However, pioglitazone did not affect the blood glucose level in D-glucose fed model (Fig. 1B).

Effects of biguanide and thiazolidinedione administered intrathecally on the blood glucose level in D-glucose fed model. Mice were pretreated i.t. with 20 or 30 μg of metformin, pioglitazone or rosiglitazone for 10 min. Then 2 g/kg of D-glucose were

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