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Dietary soy isoflavones increase insulin secretion and prevent the development of diabetic cataracts in streptozotocin-induced diabetic rats

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Abstract

Soy isoflavone–containing diets have been reported to be beneficial in diabetes. This present study investigated the hypoglycemic effects of isoflavones in streptozotocin (STZ)-induced diabetes. Diabetes was induced in male Sprague-Dawley rats by intraperitoneal injection of 100 mg/kg STZ. Diabetic rats were then randomly divided into 3 groups and received a special diet supplemented with casein (control), low-isoflavone soy (LIS) protein, and high-isoflavone soy protein (HIS) for 8 weeks. Compared with the control or LIS groups, those rats on the HIS diet had significantly increased body weight and serum insulin levels and reduced serum glucose and methylglyoxal levels. Serum glutathione levels were also increased in rats given the HIS diet compared with those in the control or LIS ($P < .01$). Serum high-density lipoprotein cholesterol level was significantly higher in HIS-fed rats than that of the control or LIS rats ($P < .05$). More importantly, the death rate and incidence of cataracts in the diabetic rats were markedly decreased in the HIS group. In conclusion, ingestion of high-isoflavone soy protein not only lowers glucose levels but also reduces the incidence of cataracts in diabetic rats. The beneficial effects of soy isoflavones are attributed to increased insulin secretion, a better glycemic control, and antioxidant protection.

Keywords: Soy isoflavones; Streptozotocin; Diabetes; Insulin; Methylglyoxal; Rats
Abbreviations: STZ, streptozotocin; LIS, low-isoflavone soy protein; HIS, high-isoflavone soy protein; MG, Methylglyoxal; GSH, reduced glutathione; PPAR-γ, peroxisome proliferator–activated receptor-gamma; HDL, high-density lipoprotein.

1. Introduction

Diabetes mellitus is characterized by hyperglycemia, which is the primary cause of the long-term complications of diabetes [1]. Hyperglycemia induces auto-oxidation of glucose [2], glycation of proteins [3], and activation of polyol metabolism [4]. These changes play an important role in the pathogenesis of diabetes and accelerate the development of diabetic complications. Methylglyoxal (MG) is a glucose metabolite and is correlated to glucose levels [5]. It is highly elevated in diabetic patients [6,7]. It is considered a very active free radical. Studies suggest that an increase in MG and decrease in the level of reduced glutathione (GSH), a strong antioxidant, contribute to the pathophysiology of diabetes and its complications [8-10]. Methylglyoxal reacts with the amino groups of proteins to form so-called advanced glycation end products, which are an important

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Table 1
Composition of the experimental diets fed to rats

Ingredient	Control (g/kg diet)	LIS	HIS
Casein	200	–	–
Soy protein	–	200	200
Sucrose	100	100	100
Cornstarch	435	435	435
Maltodextrin 10	125	125	125
Corn oil	40	40	40
Cellulose	50	50	50
Mineral mix	35	35	35
Vitamin mix	10	10	10
L-Cystine	3	3	3
Choline bitartrate	2.5	2.5	2.5
t-Butylhydroquinone	0.008	0.008	0.008
Total isoflavones[a]	0	0.012	0.55

Protein was either low- or high-isoflavone soy protein, SUPRO SOY brand isolated soy protein (a Solae protein, a gift from Solae Company). All other ingredients were purchased from the BioDAQ Company (New Brunswick, NJ).

[a] Of the total isoflavones, the amount of genistein equivalents in the control, LIS, and HIS was 0, 0.004, and 0.222 g/kg diet, respectively, and the amount of aglycone isoflavones was 0, 0.008, and 0.334 g/kg diet, respectively.

contributor to diabetic complications such as cardiovascular disease, renal failure, cataracts, and retinopathy [8].

Isoflavones, mainly derived from soybean, are a group of biologically active substances with a chemical structure similar to that of estrogen [11]. Epidemiological studies have associated a diet rich in isoflavones with a lower risk of diabetes and diabetes-related complications such as cardiovascular disease [12-14]. Evidence suggests that soy isoflavones possess a hypolipidemic effect through their antioxidative, mild estrogenic activity, and gene regulation involved in lipogenesis or lipolysis [12,14,15]. A recent study has shown that soy consumption lowers elevated plasma glucose concentrations [16]. Nutritional intervention studies performed in animals and humans suggest that ingestion of soy protein associated with isoflavones improves glucose metabolism control and insulin sensitivity [14,17-19].

Although emerging evidence from epidemiological, clinical, and animal studies have shown the beneficial effects of soy protein consumption on diabetes, the effective components of soy protein in glucose reduction have not been clearly elucidated, and the underlying mechanisms of isoflavones involved in glucose reduction and prevention of diabetic complications have not been fully investigated. The effect of soy isoflavones on pancreatic β-cells and insulin secretion has not yet been demonstrated in vivo [17]. Moreover, there have been no data showing whether the consumption of isoflavone supplements could reduce the production of MG and prevent the complications of diabetes, particularly cataracts. We hypothesize that soy isoflavone could be the key component in glycemic control and the prevention of diabetic complications through regulation of insulin secretion and MG production. In this study, we therefore determined the effects of soy isoflavones on glucose metabolism and prevention of cataracts using streptozotocin (STZ)-induced diabetic rats. This study shows that soy isoflavone consumption can protect β-cell function and reduce serum MG levels and the incidence of cataracts, which could suggest that soy consumption may be beneficial in human diabetes.

2. Methods and materials

2.1. Animal

Six-week-old male Sprague-Dawley rats, weighing 200 to 250 g (Charles River, Constant, Quebec, Canada) were used in this study. The experimental protocol was approved by the University Committee on Animal Care and Supply of the University of Saskatchewan. All animals were treated in accordance with the Guidelines of the Canadian Council on Animal Care. Rats were maintained on a 12-hour light/dark cycle (lights on 0700-1900 hours) in a constant temperature (21-23°C) and 55% ± 10% relative humidity colony room, with free access to water.

2.2. Induction of diabetes

Streptozotocin is used to induce type 1 diabetes by selectively destroying pancreatic β-cells. Studies have shown that high-dose STZ (100 mg/kg)-induced diabetes is associated with higher hyperglycemia and more chronic complications of diabetes [20], which is a preferable model to study the pathogenesis of diabetes and its complications. Diabetes was induced in male rats by STZ injection after an overnight fast. Streptozotocin (Sigma Chemical Co., St. Louis, MO) was dissolved in 0.01 mol/L sodium citrate buffer, pH 4.5 [20]. Three injections of STZ (total 100 $mg \cdot kg^{-1}$ body weight, on days 1, 3, and 5) were given intraperitoneally within 1 week. Baseline glucose levels were determined before STZ injection, using an automated blood glucose analyzer (Glucometer Elite XL; Bayer Diagnostics, Tarrytown, NY). Rats were adjusted to their diabetic state for 7 days before initiating the soy diet. Blood glucose concentrations were determined 7 days after the first STZ injection. Rats with a blood glucose concentration above 16 mmol/L were declared diabetic [20].

2.3. Diets and experimental protocol

To determine the effects of soy isoflavones, the STZ-induced diabetic rats were randomly divided into 3 groups (n = 9 each group) and received a special diet supplemented with high-isoflavone soy protein (HIS group), low-isoflavone soy protein (LIS group), or casein (control group) 1 week after the injection of STZ. There were no statistical differences in the baseline body weight or fasting glucose levels between the groups. The diabetic rats in the control group were fed with 20% casein, those in the LIS group were fed with 20% LIS, and those in the HIS group were fed with 20% HIS. With the exception of the protein source, all 3 diets were identical and contained similar amounts of protein, fat,