Effects of fisetin supplementation on hepatic lipogenesis and glucose metabolism in Sprague–Dawley rats fed on a high fat diet

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The modulatory effects of daily fisetin supplementation for 8 weeks on genes involved in hepatic lipogenesis and gluconeogenesis in rats fed a high fat (HF) diet were evaluated. Elevated levels of triglyceride (TG), along with hepatic TG content and glucose concentrations in a high fat diet group were found to be reduced by fisetin supplementation. Fisetin significantly increased hepatic mRNA expressions of PPARY, SREBP\textsubscript{1c} and SCD-1 genes in comparison to the control diet, which was subsequently reversed by supplementation with fisetin. In addition, fisetin supplementation significantly reduced hepatic mRNA abundance of FAS, ATPL and G6Pase compared to the control group. Finally, epididymal mRNA abundance of GLUT4 was significantly increased by fisetin supplementation, compared to levels in the control and HF groups. Enhancement of GLUT4 expression by fisetin was further confirmed in differentiated 3T3-L1 adipocytes. Fisetin supplementation decreases cardiovascular risks by ameliorating hepatic steatosis and lowering circulating glucose concentrations.

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\textbf{1. Introduction}

Several lines of evidence have demonstrated that obesity induces metabolic dysregulation, such as impairments of glucose and lipid homeostasis in the liver, which ultimately produces hepatic steatosis (Denechaud \textit{et al.}, 2008; Fabbrini, Sullivan, & Klein, 2010; Ferre & Foufelle, 2010). Hepatic steatosis is an important pathogenesis of metabolic conditions for type 2 diabetes mellitus (T2DM) and cardiovascular diseases (CVD) (Kimira, Arai, Shimoi, & Watanabe, 1998). Fisetin has been reported to have various pharmacological properties, such as anticancer (Suh \textit{et al.}, 2010), inhibition of angiogenesis (Fotsis \textit{et al.}, 1998), antiallergenic (Cheong \textit{et al.}, 1998) and antithyroid (Divi & Doerge, 1996) effects. In addition, a few studies have reported that fisetin modulates glucose metabolism in vitro and within animals (Constantin \textit{et al.}, 2010; Prasath & Subramanian, 2011a, 2011b). The mechanism underlying the hypoglycemic effects of fisetin include that fisetin down-regulates both glycogenolysis and gluconeogenesis \textit{in vitro} (Constantin \textit{et al.}, 2010). In line with this, it has been demonstrated that fisetin exhibited a hypoglycemic effect by attenuating the key enzymes of carbohydrate metabolism in hepatic and renal tissues of streptozotocin-induced diabetic rats (Prasath & Subramanian, 2011a, 2011b). However, the metabolic effects of fisetin on hepatic triglyceride (TG) accumulation or peripheral insulin resistance, both of which are associated with hepatic steatosis, have not been studied.

In the present study, we tested the modulatory effects of daily fisetin supplementation on genes involved in hepatic lipogenesis and gluconeogenesis in rats fed a high fat diet. In addition, we examined whether fisetin consumed \textit{ad libitum} reduces hyperglycemia through affecting glucose transporter 4 (GLUT4) expression, which plays an important role in the regulation of blood glucose.
levels (Huang & Czech, 2007) in the adipose tissue of high fat diet rats. This study provides novel information on whether fisetin may exert protective properties against hepatic steatosis in relation to hepatic lipogenesis and insulin resistance.

2. Materials and methods

2.1. Animals and study design

Five week old male Sprague–Dawley rats were randomly assigned into 3 groups after a 1 week adaptation period: control (n = 8), high fat diet (HF, n = 8) and high fat diet with fisetin (HF + F, n = 8). They were under specific pathogen-free (SPF) conditions (18–24 °C, room humidity 50–60%) and provided with specified diets (3 groups) and water for 8 weeks. Daily feed intake and weekly body weight gain were routinely recorded throughout the experimental period, using a computing scale (Acomin Co., Korea). The control diet was based on the AIN-76 rodent diet composition. The HF diet was identical to the control diet, except that 200 g fat/kg (170 g lard plus 30 g corn oil) and 1% cholesterol were added to it. Fisetin supplementation of the high fat diet was conducted at a dose of 10 mg/kg body weight. All the experimental procedures were approved by the Committee on Animal Experimentation and Ethics of Korea University.

2.2. Sample collection (blood, liver & adipose tissues) and measurements of biochemical parameters in plasma

At the end of the experimental period, rats were fasted overnight (12 h). They were then anaesthetised with diethyl ether, blood samples were obtained from the abdominal inferior vena cava to analyse biochemical parameters. Liver and epididymal adipose tissue were weighed and then transferred to liquid nitrogen and stored in the freezer at −80 °C prior to determinations. The plasma glucose concentrations were measured using the glucose oxidase method with a Beckman Glucose Analyzer. The concentrations of triglyceride (TG) in plasma were measured using a total glycerol test kit (Roche, USA). The images were captured using a Sigma EXDG camera (Nikon, Japan). The intensity of the bands was quantitated using AlphaView software (Alpha Innotech, USA). Values were expressed in arbitrary units. The mRNA levels were determined relative to that of an endogenous GAPDH gene, and were expressed as fold change over the control.

2.3. RNA extraction from animal liver and epididymal adipose tissue and semi-quantitative RT-PCR

Liver and epididymal adipose tissue samples (0.05 g) were homogenised in 0.4 mL of lysis buffer (Qiagen, USA) using a Dounce homogenizer. Total RNA was extracted from liver tissue using RNeasy Lipid Tissue Mini Kit (Qiagen, USA) according to the manufacturer’s protocol. cDNA was synthesized from 1 g of RNA using oligo-dT and Superscript TM II reverse transcriptase (Invitrogen, USA). 1 μg of cDNA was used for PCR. Rat primer sequences tested and stored in a freezer at −80 °C were subjected to the 1st differentiation medium (DMEM, 10% FBS) starting on day 0, for 3 days. Then the medium was replaced with the second differentiation medium (DMEM, 10% FBS, 1 μg/mL insulin) starting on day 0, for 3 days. The medium was replaced with the second differentiation medium (DMEM, 10% FBS) for an additional 2 days. The cells were maintained at 37 °C in a humidified atmosphere of 95% air and 5% CO₂. The growth medium was replenished every 2 days. Isobutyl-1-methylxanthine, dexamethasone and insulin were obtained from Sigma–Aldrich (St. Louis, USA). 3T3-L1 cells were obtained from the American Type Culture Collection (ATCC, Rockville, MD, USA). High-glucose Dulbecco’s Modified Eagle’s Medium (DMEM) was purchased from HyClone (USA). Bovine serum (FBS), bovine calf serum (BCS) and antibiotics (100,000 Unit/L penicillamine and 100 mg/L streptomycin) were purchased from Gibco (Germany). 3-[4,5-Dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT) was purchased from Amresco (USA).

Table 1

<table>
<thead>
<tr>
<th>Gene description</th>
<th>Primers Sequences(5′ → 3′)</th>
<th>Annealing temperature (°C)</th>
</tr>
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<tr>
<td>PPAR-γ F</td>
<td>CTGCGCATATTTATAGCCTATTATT</td>
<td>60</td>
</tr>
<tr>
<td>R</td>
<td>TGTCTCTGAGGCCGCTCAC</td>
<td></td>
</tr>
<tr>
<td>SREBP-1c F</td>
<td>GGCAGAAAATCCGACTTGGG</td>
<td>58</td>
</tr>
<tr>
<td>R</td>
<td>TCGAGTCTGAGCCAAGG</td>
<td></td>
</tr>
<tr>
<td>SCD-1 F</td>
<td>TCTGTCATGTGTCCTATCC</td>
<td>58</td>
</tr>
<tr>
<td>R</td>
<td>GATGTTCTTCCGAGGATTGA</td>
<td></td>
</tr>
<tr>
<td>ACC F</td>
<td>CATCTCTTATACGACCATCG</td>
<td>56</td>
</tr>
<tr>
<td>R</td>
<td>CAGCTGTTCTTCAAATGCGT</td>
<td></td>
</tr>
<tr>
<td>FAS F</td>
<td>TCCAGACATCTGGTGCCG</td>
<td>58</td>
</tr>
<tr>
<td>R</td>
<td>TCAAAGAAGTGATCCACAGG</td>
<td></td>
</tr>
<tr>
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</tr>
<tr>
<td>R</td>
<td>AGGACAGCTGTCGTTGTAATA</td>
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</tr>
<tr>
<td>PEPCK F</td>
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</tr>
<tr>
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<td>56</td>
</tr>
<tr>
<td>R</td>
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<tr>
<td>GLUT4 F</td>
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</tr>
<tr>
<td>R</td>
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<td></td>
</tr>
<tr>
<td>GAPDH F</td>
<td>TGCAGACATCCGCGCTGAGA</td>
<td>58</td>
</tr>
<tr>
<td>R</td>
<td>TGGAGGCATCTAGGGCCGCTG</td>
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</table>

PPAR-γ, peroxisome proliferator-activated receptor gamma; SREBP-1c, sterol regulatory element binding transcription factor; 1; SCD-1, stearoyl-Coenzyme A desaturase 1; ACC, acetyl-CoA carboxylase; FAS, fatty acid synthase; G6Pase, glucose-6-phosphatase; PEPCK, Phosphoenol pyruvate carboxykinase; ATPIF: ATP citrate lyase; GLUT4: insulin-responsive glucose transporter 4; GAPDH: glyceraldehyde-3-phosphate dehydrogenase.

2.4. Cell culture and preadipocyte differentiation

Mouse 3T3-L1 cells were grown in high-glucose Dulbecco’s minimum essential medium (DMEM) supplemented with 10% heat-inactivated bovine calf serum (BCS) containing 100,000 Unit/L penicillamine and 100 mg/L streptomycin. Prior to the experiments, 1 × 10⁶ cells were seeded on a 6 well plate and grown to confluence for 7 days. At day 8 post-confluence, the cells were subjected to the 1st differentiation medium (DMEM, 10% FBS, 0.5 mM 3-isobutyl-1-methylxanthine, 0.5 μM dexamethasone, 2 μg/mL insulin) starting on day 0, for 3 days. Then the medium was replaced with the second differentiation medium (DMEM, 10% FBS, 1 μg/mL insulin). Two days later, the cells were grown in regular medium (DMEM, 10% FBS) for an additional 2 days. The cells were maintained at 37 °C in a humidified atmosphere of 95% air and 5% CO₂. The growth medium was replenished every two days. Isobutyl-1-methylxanthine, dexamethasone and insulin were obtained from Sigma–Aldrich (St. Louis, USA). 3T3-L1 cells were obtained from the American Type Culture Collection (ATCC, Rockville, MD, USA). High-glucose Dulbecco’s Modified Eagle’s Medium (DMEM) was purchased from Hyclone (USA). Bovine serum (FBS), bovine calf serum (BCS) and antibiotics (100,000 Unit/L penicillamine and 100 mg/L streptomycin) were purchased from Gibco (Germany). 3-[4,5-Dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT) was purchased from Amresco (USA).

2.5. Fisetin treatment, MTT assay and Immunoblotting

Fully differentiated mouse 3T3-L1 cells were tested with increasing concentrations of fisetin for 24 h. Cell viability was ana-
lysed after the addition of 1 g/mL 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT) (Amresco, USA) in each well and following incubation for 3 h at 37 °C. After removal of the medium, cells were lysed with DMSO. The absorbance was detected at 560 nm of wavelength using a microplate reader. The cells were scraped from the plates with lysis buffer (40 mM HEPES pH 7.5, 120 mM NaCl, 1 mM EDTA, 1% Triton X-100) containing a protease inhibitor cocktail (Roche, Germany). After incubation on ice for 20 min, cell lysates were centrifuged at 12,000 g for 15 min at 4 °C. Total protein in cell supernatants was quantified using the BCA protein assay (Sigma, USA). Protein lysates were resolved on 10% sodium-dodecyl sulfate polyacrylamide gels (SDS–PAGE) and then transferred to a polyvinylidenedifluoride (PVDF) membrane. Anti-GLUT4 antibody (Cell Signaling, USA) was used to detect GLUT4.

2.6. Statistical analysis

Statistical analysis was performed using SPSS (Statistical Package for the Social Science, SPSS Ins., Chicago, IL, USA). The results are presented as means ± S.E. and the differences among the experimental groups were analysed using one-way analysis of variance (ANOVA) with Duncan’s multiple range (for animal experiments) with p < 0.05 as the criterion of significance.

3. Results

3.1. Body weight gain and food efficiency ratio in animals fed control diet, high fat diet and high fat diet supplemented with fisetin

As shown in Fig. 1, there were significant differences in body weight gains in animals fed different diets ad libitum over the eight week period. Animals on the high fat diets gained more weight than those on the control diet. Fisetin supplementation did not further affect the body weight of HF-fed rats during the experimental period. Calculated food efficiency ratios (FERs), which represented weight gain efficiency based on the amount of total food intake, were significantly higher in animals fed high fat diets, both with and without fisetin supplementation (0.26 ± 0.01, p < 0.01 and 0.26 ± 0.01, respectively, p < 0.01), compared to the control group (0.21 ± 0.01).

3.2. Effects of daily fisetin supplementation on circulating TG and glucose and hepatic TG content

Compared to the control group, animals on the high fat diet demonstrated elevated levels of triglyceride in blood and the liver (Fig. 2A and B). Fisetin supplementation on the high fat diet significantly decreased hepatic TG content (Fig. 2B). Animals on the high fat diet supplemented with fisetin displayed a tendency of reduced circulating TG levels, which did not reach statistical significance (Fig. 2A). With respect to circulating glucose, elevated levels of blood glucose in animals fed the high fat diet were significantly reduced by fisetin supplementation (Fig. 2C).

3.3. Effects of fisetin supplementation on hepatic lipogenesis in rats fed a high fat diet

Based on the measurable effects of fisetin supplementation on hepatic TG content, we tested whether fisetin supplementation influences genes involved in hepatic lipogenesis. The results showed that a high fat diet significantly increased mRNA abundance of peroxisome proliferator-activated receptor (PPARγ), sterol regulatory element-binding protein (SREBP1C) and stearoyl-Coenzyme A desaturase-1 (SCD-1). These changes in transcript levels caused by the high fat diet were reversed by the supplementation with fisetin, to the levels of the control diet (Fig. 3A–C). The

Fig. 1. Effect of fisetin supplemented diet on weight gain over an 8-week period. There were significant differences in body weight gains between the group on the control diet and the groups on the high fat diet resulting from 3-weeks of supplementation. CTL (n = 8): control diet, HF (n = 8): high fat diet, HF + F (n = 8): high fat diet with supplemented fisetin. The results were expressed as means ± S.E. Tested by ANOVA with Duncan’s multiple range test. *p < 0.05, vs CTL group.
high fat diet did not affect mRNA abundance of fatty acid synthase (FAS) and acetyl-CoA carboxylase (ACC). However, fisetin supplementation of the high fat diet significantly reduced mRNA abundance of FAS in those animals compared to the animals on the control diet (Fig. 3D and E). In addition, fisetin supplementation significantly reduced hepatic mRNA abundance of ATP citrate lyase (ATPCL) compared to animals of the control group (Fig. 3F).

3.4. Effects of fisetin supplementation on genes involved in hepatic gluconeogenesis in rats fed a high fat diet

We examined whether fisetin supplementation affects gene expression involved in hepatic gluconeogenesis including glucose-6-phosphatase (G6Pase) and phosphoenolpyruvate carboxykinase (PEPCK). Fisetin remarkably reduced mRNA abundance of G6Pase compared to that in the livers of control and HF groups (Fig. 4A). In contrast, hepatic PEPCK expression tended to decrease with fisetin supplementation, but this reduction did not reach statistical significance (Fig. 4B).

3.5. Effects of fisetin supplementation on expressions of GLUT4 in epididymal adipose tissue of rats fed a high fat diet and in 3T3-L1 adipocytes

To elucidate the underlying mechanism by which fisetin exerts its hypoglycemic functionality, we tested whether fisetin influences GLUT4 gene expression in epididymal fat depots. The results showed that epididymal mRNA abundance of GLUT4 was significantly increased by fisetin supplementation compared to the levels in the control and HF groups (Fig. 5A). We further tested the effects of fisetin on GLUT4 expressions in fully differentiated adipocytes. According to the MTT assay, fisetin did not adversely affect cell viability at concentrations up to 10 μM (Fig. 5B). Using the same range of concentrations, we examined the effects of fisetin on GLUT4 protein levels after 24 h incubation with fisetin in fully differentiated 3T3-L1 adipocytes. Fisetin treatment of 100 nM increased GLUT4 expression (Fig. 5C). The GLUT4 expressions gradually increased up to 1 μM of the addition of fisetin, but slowly decreased thereafter.

4. Discussion

Selective hepatic insulin resistance, a hallmark of obesity, is manifested by a failure to inhibit gluconeogenesis, but with continued lipogenesis in response to insulin (Brown & Goldstein, 2008). Thus, hepatic insulin resistance contributes to hyperglycemia as well as hyperlipidemia (Laplante & Sabatini, 2010), which is the underlying mechanism for the further development of T2DM (Yecies et al., 2011).
the master gene known to be responsible for lipid accumulation in the liver induced by a HF diet (Horton, Goldstein, & Brown, 2002; Li, Brown, & Goldstein, 2010). Furthermore, in animal models with fatty liver, PPARγ is transcriptionally up-regulated and consequently activates the lipogenic target genes, thus exacerbating hepatic steatosis (Gavrilova et al., 2003). These genes stimulate the key lipogenic genes, including those encoding the ACC and the FAS (Najjar et al., 2005). Considering that SREBP1c and PPARγ are mainly responsible for inducing lipogenic gene expression and promoting fatty acid synthesis in the liver (Najjar et al., 2005), fisetin supplementation may have a beneficial effect in ameliorating hepatic steatosis through inhibiting TG accumulation. With regard to the gene expressions of downstream SREBP1c and stearoyl-Coenzyme A desaturase 1 (SCD1), encoding for the rate-limiting enzyme in monounsaturated fatty acid (MUFA) synthesis, were up-regulated in HF fed rats, which was reversed by fisetin supplementation. MUFA are a key component in the formation of TG, cholesterol esters and phospholipid (Flowers & Ntambi, 2008;
Miyazaki, Kim, Gray-Keller, Attie, & Ntambi, 2000). It indicated that fisetin inhibited hepatic TG formation by modulating SCD1 expression. On the other hand, mRNA abundance of ACC and FAS was reduced by the HF diet, which might be due to a regulatory feedback mechanism in response to HF feeding. This is in line with a previous speculation (Kim et al., 2004) that the uptake of fatty acids into the liver was augmented by a chronic HF diet, resulting in subsequent accumulation in TG in the liver, and that hepatic TG accumulation might have driven the up-regulation of genes involved in lipid catabolism and the down-regulation of lipogenic genes by feedback mechanism. In the present study, however, we observed that mRNA levels of FAS were significantly reduced by fisetin supplementation compared to the control group, whereas ACC remained unchanged by fisetin. These results indicate that fisetin exerts its inhibitory effects on TG formation and fatty acid synthesis by modulating SCD1 and FAS. Taken together, it can be speculated that fisetin attenuates HF diet-induced hepatic steatosis through modulation in hepatic expressions of genes involved in lipogenesis. ATP citrate lyase (ATPCL) is a crucial lipogenic enzyme linking cellular glucose catabolism and de novo lipid synthesis (Sreer, 1959). It regulates the flow of glucose carbons to cytosolic acetyl-coenzyme A (CoA) by generating acetyl-CoA from citrate (Watson, Fang, & Lowenstein, 1969). It has been suggested that ATPCL plays an important role in lipid and glucose metabolism, which is deregulated in an obese and diabetic mouse model with spontaneous progression of liver steatosis (Wang et al., 2009). In a study by Wang et al. (2010), hepatic ATPCL abrogation was shown to reduce hepatic acetyl-CoA and malonyl-CoA, accompa-
nied by decreases in circulating TG and free fatty acids. Our findings showed that fisetin suppressed hepatic ATPC expression, indicating the beneficial effect of fisetin in attenuating hepatic steatosis, at least in part. Moreover, experimental evidence that hepatic ATPC ablation resulted in down-regulation of genes involved in gluconeogenesis (Wang et al., 2009) indicates the underlying mechanism linking hepatic lipogenesis to hepatic insulin resistance. It is conceivable that our results substantiate the contribution of fisetin to selective hepatic insulin resistance by modulating ATPC gene expression.

In the present study, we observed hypoglycemic effects of fisetin supplementation in the diets of rats on a high fat diet. Based on this, we further hypothesised that fisetin may alleviate obesity-induced insulin resistance in the liver, and improve peripheral insulin sensitivity, thereby exerting beneficial effects against obesity induced elevations in blood glucose. To prove this, we examined the effects of fisetin supplementation on gene expressions involved in hepatic glucogenesising, including G6Pase, and PEPCK. Effects of fisetin on GLUT4 expression in adipose tissue were also tested. G6Pase is a crucial gluconeogenic enzyme, mainly found as an integral protein in the lumen of the endoplasmic reticulum of liver tissues, the action of which is to catalyse the dephosphorylation of glucose-6-phosphate to glucose (van Schaftingen & Gerin, 2002). Hepatic expression of G6Pase was suppressed by 8 weeks of fisetin supplementation in obese, insulin resistant rats, which can be implicated to reduce glucose levels in the blood. This is consistent with recent findings that fisetin modulated key enzymes involved in carbohydrate metabolism, including G6Pase in streptozotocin-induced diabetic rats (Prasath & Subramanian, 2011b). In contrast, fisetin failed to suppress PEPCK gene expression, a critical rate limiting enzyme in glucogenesising, raising the question as to the differential transcriptional regulation between G6Pase and PEPCK. Finally, another mechanism that could contribute to the reductions in circulating glucose is an improvement in insulin sensitivity within the adipose tissue. GLUT4 is well known to play an important role in modulating glucose levels in circulation (Huang & Czech, 2007). Insulin stimulates the translocation of GLUT4 to the plasma membrane to mediate glucose transport in peripheral tissues. An enhanced expression of GLUT4 in epidymal fat by fisetin can lead to an increase in GLUT4 protein levels in the plasma membrane for glucose uptake upon the stimuli. Enhancement of GLUT4 expression by fisetin was further confirmed in differentiated 3T3-L1 adipocytes. Taken together, it can be speculated that the hypoglycemic effect of fisetin supplementation observed in the present study might have been caused through the suppression of hepatic gluconegenic enzymes and/or enhancement of GLUT4 gene expression in adipose tissue.

In conclusion, we have shown that fisetin supplementation reduces cardiovascular risk by ameliorating hepatic steatosis and lowering circulating glucose concentrations. Moreover, we report that these effects were achieved by modulating genes involved in hepatic lipogenesis and glucogenesising in the liver, and insulin sensitivity in the adipose tissue. Several recent studies have reported favourable effects of strawberry consumption on blood lipid profiles and fasting glucose concentrations in humans (Basu et al., 2009; Jenkins et al., 2008; Zunino et al., 2011). Our study may support the results of previous human studies mechanistically. Fisetin, as a major functional component in strawberries (Kimira, Arai, Shimoi, & Watanabe, 1998), may confer potentially beneficial metabolic effects on cardiovascular risks associated with and glucose metabolism.

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References


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