大豆イソフラボンが高飽和脂肪食摂取ラット肝臓のSREBP-1応答遺伝子の発現に与える影響

報　文

Alteration by dietary soy isoflavone of SERBP-1-dependent genes in the liver of rats fed a high saturated-fat diet

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Abstract

The effect of soy isoflavone on mRNA expression of sterol regulatory element-binding protein (SREBP)-1 isoforms and the target genes of SREBP-1 involved in fatty acid metabolism was examined in rats. Animals were fed a 20% palm oil diet containing 0, 0.05, 0.1, 0.2, or 0.4% of soy isoflavone for 14 d. The diets containing 0.1, 0.2, and 0.4% of isoflavone significantly increased the mRNA level of hepatic SREBP-1a to a similar level compared to a diet containing 0.05% of isoflavone or a diet free of isoflavone. In contrast, diets containing 0.05-0.2% isoflavone, compared to a diet free of isoflavone, did not influence the mRNA level of SREBP-1c. However, a diet containing 0.4% of isoflavone lowered this parameter to one half that observed with an isoflavone-free diet. Dietary isoflavone dose-dependently increased the mRNA levels of genes targeted by SREBP-1 (fatty acid synthase, stearoyl-CoA desaturase 1 and Δ^6-desaturase), and they peaked at a dietary level of 0.1 or 0.2%. However, a diet containing 0.4% of isoflavone decreased these parameters to the levels observed in rats fed an isoflavone-free diet. Thus, it is apparent that varying amounts of dietary isoflavone modulate mRNA expressions of SREBP-1a and -1c differently. The contours of the changes in the gene expressions of SREBP-1 isoforms may account for the biphasic modulation by different dietary levels of isoflavone in the mRNA expression of the genes targeted by these transcriptional factors.

Introduction

Soybean contains considerable amounts of compounds collectively called isoflavone, which mainly exist as glycoside. Among soy isoflavones, the predominant compounds of aglycon are daidzein, genistein and glycitein. Soy isoflavone has various meritorious physiological activities to prevent postmenopausal symptoms, prostate and breast cancers, cardiovascular disease, and osteoporosis[1]. Genistein, daidzein and its intestinal bacterial metabolite equol are considered to be ligands of estrogen receptor[2]. Also, genistein but not daidzein was found to be an activator of peroxisome proliferator-activated receptor (PPAR) α[3,4]. Therefore, it is possible that the pleiotropic physiological effects of isoflavone are mediated through the alterations in the expression of genes targeted by these nuclear receptors.

Sterol regulatory element-binding protein (SREBP)-1 is a transcription factor that regulates the expression of genes involved in lipogenesis[5]. Also, several genes involved in fatty acid desaturation are controlled by this transcription factor[5]. There are two isoforms of SREBP-1, termed SREBP-1a and -1c, that are derived from a single gene through the use of an alternative transcriptional start site. It has been reported that isoflavone aglycons decreased serum and liver triglyceride levels in rats[6] and diabetic mice[7]. In addition, dietary isoflavone lowered the activity of hepatic Δ^6-desaturase[6] which is known as one of the genes modulated by SREBP-1[8]. These studies raise the possibility that soy isoflavone not only affects nuclear receptor-dependent metabolic pathways, but

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also modulates the expression of the genes under the control of SREBP-1 and hence affects lipogenesis. The observation that genistein and daidzein did not affect SREBP-1 expression in cultured hepatic cells may be contrary to this notion[9,10]. However, studies regarding the impact of isoflavone on mRNA expression of SREBP-1 in experimental animals have been lacking. To examine the hypothesis that soy isoflavone modulates lipogenesis through SREBP-1-dependent mechanism, we analyzed the effect of a preparation rich in isoflavone glycosides made of soybean on gene expressions of SREBP-1a and -1c, and some of their target genes in rat liver. We used high saturated-fat diets for this purpose, since a previous study showed that a high saturated-fat diet evoked more than 7-fold and approximately 2-fold increase in mRNA expression of SREBP-1c and -1a, respectively, in mice[11].

Materials and Methods

Animals and diets

Male Sprague-Dawley rats obtained from Charles River Japan (Kanagawa, Japan) at 4 weeks of age were housed individually in a room with controlled temperature (20-22℃), humidity (55-65%), and lighting (lights on from 07:00 to 19:00 h) and fed a commercial nonpurified diet (Type NMF; Oriental Yeast, Tokyo, Japan). After 7 d of acclimatization in our housing condition, rats were randomly divided into 5 groups and fed for 14 d the purified experimental diets containing varying amounts (0, 0.11, 0.21, 0.43 and 0.85%) of a preparation rich in soy isoflavone glycosides (Soyaflavone HG) kindly donated from Fuji Oil Co. Ltd. Osaka, Japan. As the soy isoflavone preparation contained 47.0% (w/w) isoflavones, our experimental diets contained 0, 0.05, 0.1, 0.2 and 0.4% of soy isoflavone. The composition of the isoflavones in the preparation were (in weight %): daidzin, 33.8; glycitin, 16.4; genistin, 6.89; malonyl daidzin, 25.5; malonyl glycitin, 9.68; malonyl genistin, 6.09; acetyl daidzin, 0.54; acetyl glycitin, 0.80; acetyl genistin, 0.13; daidzein, 0.07; glycitein, 0.06, and genistein, 0.02. Thus, our experimental diets contained isoflavone aglycons in the following composition (in weight %): daidzein, 59.9; glycitein, 27.0, and genistein, 13.1. The basal composition of the experimental diet was (in weight %): casein, 20; palm oil, 20; corn starch, 15; cellulose, 2; mineral mixture[12], 3.5; vitamin mixture[12], 1.0; L-cystine, 0.3; choline bitartrate, 0.25 and sucrose to 100. Soy isoflavone was added to experimental diets instead of sucrose. Body weight at the start of experiment was 119-138 g. Animals had free access to the diets and water during the experiment. At the end of the experiment, the animals were sacrificed by bleeding from the abdominal aorta under diethyl ether anesthesia. Livers were then quickly excised and weighed. This study followed the institute's guidelines in the care and use of laboratory animals.

RNA analysis

RNA in the liver was extracted[13], and mRNA levels of specific genes were analyzed by a quantitative real-time PCR using a PRISM 7000 sequence detection system (Applied Biosystems, Foster City, CA) as detailed previously[14]. mRNA abundance was calculated as its ratio to the 18S rRNA level in each cDNA sample and the abundance was expressed as a percentage assigning the value in rats fed a isoflavone-free diet as 100. The nucleotide sequences of primers and probes to detect each mRNA were designed using the Primer Express Software (Applied Biosystems) according to the sequences available from the GenBank database. The nucleotide sequences of primers and probes for SREBP-1a, SREBP-1c, fatty acid synthase, and 18S rRNA were the same as reported elsewhere[15]. Those for forward and reverse primers and probes to detect mRNA of stearoly-CoA desaturase 1 were:
5'-TTGCCAGAGGGAATAGGGAAA-3',
5'-CTCTCCCATCCTTACTTACAAACCA-5', and
5'-ACCGTGCGTGCTAATTCTTCTCTCAAGGT-5', and of Δ^6-desaturase were 5'-ACCGCTGCTCATCCCTATGT-3',
5'-CACCCAGTCTCTGCGTCTGA-3', and
5'-TTCCAGTACCAGATCATCATGACCAT-3', respectively.

Analysis of isoflavone in serum

One hundred μl of 0.58 M acetic acid and 50 μl of a β-glucuronidase prepatation (Type HP2, Sigma, St. Louis, MO) were added to 1 ml of serum, and incubated at 37℃ for 4 h. After the enzymatic hydrolysis, each serum sample was spiked with 6 μg of fluorescein dissolved in 50 μl of methanol as an internal standard, and 4 ml of 70 mM sodium dihydrogenphosphate was added. Isoflavones in the samples were extracted using solid phase extraction cartridges (Sep-Pak C18 cartridge, Waters, Milford, MA). The cartridges were preconditioned with 6 ml each of methanol and 70 mM sodium dihydrogenphosphate. The samples were loaded onto

the cartridges and allowed to flow freely. The cartridges were then consecutively washed with 10 ml of 70 mM sodium dihydrogenphosphate and 2 ml of water. Isoflavones and an internal standard were eluted with 6 ml of methanol, then dried under nitrogen and re-constituted with 200 μl of methanol for HPLC analysis. Isoflavones were analyzed by a reversed-phase HPLC using a CAPCELL PAK AG120 C_{18} column (250 x 4.6 mm, Shiseido, Tokyo, Japan) with a mobile phase of 0.5% phospholic acid in water/acetonitrile (70:30, v/v), at a flow rate of 1.0 ml/min, monitoring at 259 nm for isoflavones and 224 nm for fluorescein.

Statistical analysis

The data were analyzed by one-way ANOVA, and a Tukey-Kramer post hoc analysis was used to detect significant differences between the means at a level of $p<0.05$.

Results

Animal growth and liver weights

No significant differences were detected in food intake among the groups of rats fed diets containing varying amounts of isoflavone (18.1-20.2 g/d). The growth was significantly lower in rats fed a diet containing 0.4% of isoflavone (127 ± 5 g/14 d) than in the animals fed diets containing 0.05 and 0.1% of isoflavone (145 ± 8 and 147 ± 7 g/14 d, respectively). However, significant differences were not detected among rats fed diets containing 0% (137 ± 4 g/14 d), 0.2% (143 ± 6) and 0.4% of isoflavone. Liver weight was significantly lower in rats fed a diet containing 0.4% of isoflavone (5.18 ± 0.14 g/100 g body weight) than in the animals fed a diet containing 0.2% of isoflavone (5.77 ± 0.18). No other significant differences in this parameter were detected among the groups.

Serum isoflavone concentrations

Isoflavone was not detected in the serum of rats fed on an isoflavone-free diet. As expected, serum concentrations of daidzein, glycitein and genistein progressively increased as dietary levels of isoflavone increased (Table 1). Daidzein, glycitein and genistein comprised 62.5, 25.2 and 12.3% of total isoflavone in the serum of rats fed a 0.05% isoflavone diet. These values were comparable to the proportions contained in experimental diets (58.5, 28.5 and 13.1%, respectively). However, the proportions of daidzein in serum were considerably higher in rats fed 0.1, 0.2 and 0.4% isoflavone diets (75.3-77.6%) than in the animals fed a 0.05% isoflavone diet. This was accompanied by the decreases in the proportions of both glycistein (14.7-18.3%) and genistein (5.0-7.7%).

mRNA levels of SREBP-1a and -1c and their target genes

We quantified the mRNA levels of SREBP-1a and -1c that were involved in the regulation of gene expression of various lipogenic enzymes[16] and some enzymes involved in fatty acid desaturation[8]. mRNA level of SREBP-1a was comparable between rats fed diets containing 0 and 0.05% of isoflavone (Fig. 1). However, diets containing 0.1, 0.2 and 0.4% of isoflavone, compared to an isoflavone-free diet, caused significant 68, 98, and 64% increases, respectively, in this parameter. Response to dietary isoflavone of mRNA expression of SREBP-1c was considerably different. Diets containing 0.05-0.2% of isoflavone, compared to an isoflavone-free diet, did not affect mRNA expression of SREBP-1c, but a diet containing 0.4% of isoflavone signifi-

Table 1. Serum concentration of isoflavones in rats fed diets containing varying amounts of soy isoflavone

Serum isoflavones	Dietary isoflavone (%)				
	0	0.05	0.1	0.2	0.4
Total isoflavones (μg/dl)	N.D.	63.7 ± 5.7^{b}	135 ± 20^{c}	192 ± 20^{c}	316 ± 33^{d}
Daidzein (μg/dl)	N.D.	39.9 ± 4.9^{a}	103 ± 16^{b}	144 ± 16^{b}	245 ± 30^{c}
Glycitein (μg/dl)	N.D.	16.1 ± 2.0^{a}	24.7 ± 2.8^{ab}	34.7 ± 3.9^{b}	46.3 ± 5.6^{c}
Genistein (μg/dl)	N.D.	7.81 ± 1.61^{a}	6.77 ± 1.13^{a}	12.5 ± 1.4^{a}	24.3 ± 4.4^{b}

Values represent means ± SE of 7 or 8 rats.
Values in same row with different superscript differ significantly at $p<0.05$.

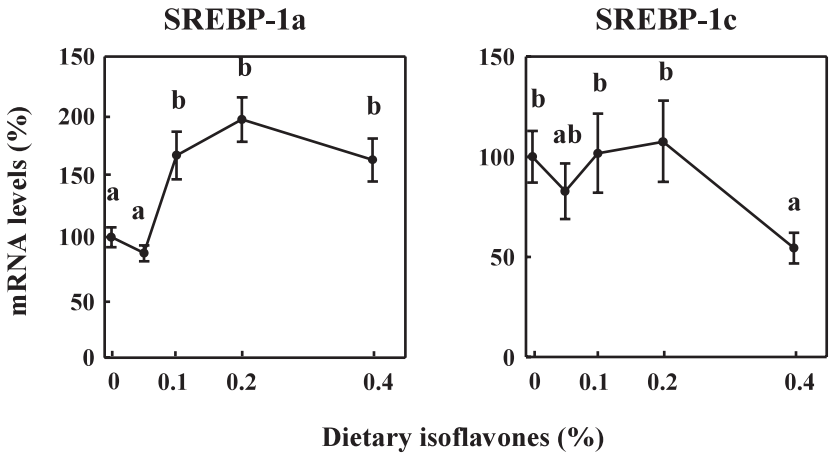

Fig .1 Effect of dietary soy isoflavone on mRNA levels of SREBP-1a and -1c.
The values were expressed as percentages, assigning the value in animals fed a diet free of isoflavone as 100. Values represent means ± SE of 7 or 8 rats. Values with different superscript differ significantly at $p<0.05$.

cantly reduced the mRNA level (Fig. 1).

The mRNA levels of SREBP-1-dependent genes, involved in fatty acid synthesis (fatty acid synthase[17]), and fatty acid desaturation (stearoyl-CoA desaturase 1[18] and Δ^6-desaturase[8]) were also analyzed (Fig. 2). The responses of mRNA expression of these enzymes to dietary isoflavone were biphasic. Increasing dietary levels of isoflavone up to 0.1% up-regulated the mRNA levels of these enzyme genes. However, a diet containing 0.2% isoflavone failed to cause additional increases in the mRNA levels, and isoflavone at a 0.4% dietary level decreased the mRNA levels comparable to those observed in rats fed an isoflavone-free diet.

Discussion

Previous studies have demonstrated that soy isoflavone lowers serum triacylglycerol concentration in experimental animals[19-21]. We hypothesized in the present study that alterations in the gene expression of SREBP-1 and consequently of its target genes may account for triacylglycerol-lowering effect of genistein and daidzein in experimental animals. Our study showed that dietary isoflavone modulates mRNA expression of SREBP-1a and -1c isoforms differently in the liver according to its dietary levels. These changes were accompanied by the alterations in the mRNA expression of some SREBP-1-dependent enzymes.

The present study demonstrated that a relatively high dose of dietary isoflavone down-regulates mRNA level of SREBP-1c, whereas isoflavone at dietary levels greater than 0.1% increases the mRNA level of SREBP-1a. Shimomura et al. reported that mRNA level of SREBP-1c exceeded that of SREBP-1a in tissues of mice, including liver (8.8-fold in liver)[22]. Thus, it is generally considered that SREBP-1c but not SREBP-1a is primarily involved in the regulation of lipogenesis and fatty acid desaturation in the liver. On the other hand, it is reported that transcriptional activity of SREBP-1c is much weaker than that of SREBP-1a due to its shorter transcriptional regulatory domain[23]. In fact, Amemiya-Kudo et al. demonstrated that over-expression of SREBP-1a in mice profoundly increased mRNA levels of several genes involved in lipogenesis in liver, whereas SREBP-1c over-expression caused only moderate increase in these values[17]. In the present study, isoflavone at dietary levels of 0.1 and 0.2% increased mRNA expression of SREBP-1-dependent genes (Fig. 2). The contours of the changes paralleled that of SREBP-1a but not of SREBP-1c (Fig. 1). This observation suggests that the former but not the latter is mainly involved in the regulation of SREBP-1-dependent genes under these nutritional conditions. A diet containing 0.4% of isoflavone decreased mRNA expression of SREBP-1-dependent genes even though SREBP-1a mRNA level was still sustained at a high level (Fig. 2). Thus, the down-regulation of the expression of SREBP-1c observed at this dietary level of isoflavone may counteract the physiological activity of SREBP-1a to increase the expression of genes involved in lipogenesis and fatty acid desaturation.

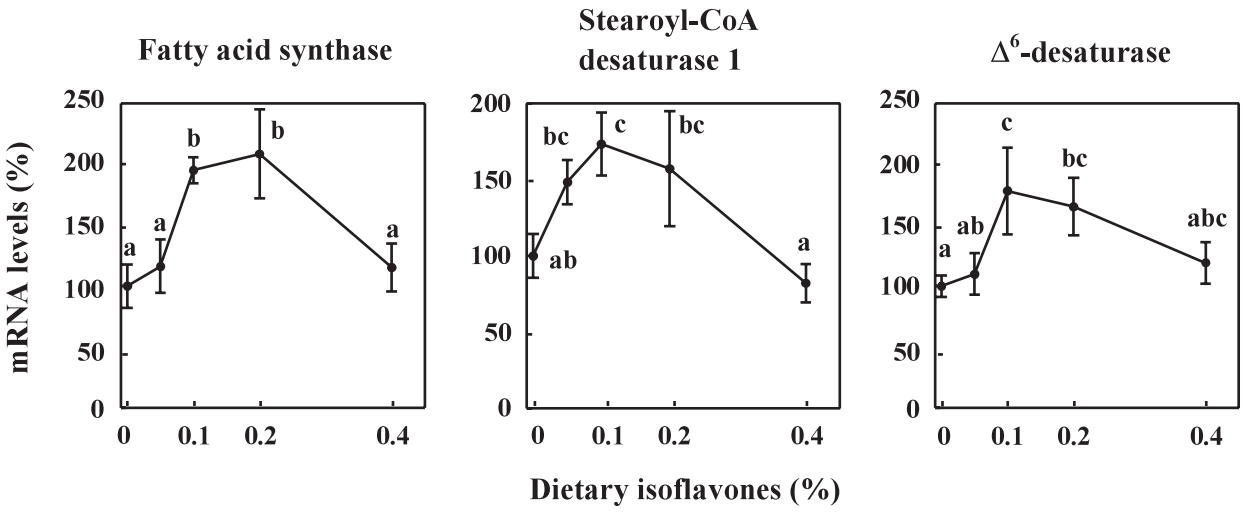

Fig .2 Effect of dietary soy isoflavone on mRNA levels of SREBP-1-dependent genes.
The values were expressed as percentages, assigning the value in animals fed a diet free of isoflavone as 100. Values represent means ± SE of 7 or 8 rats. Values with different superscript differ significantly at $p<0.05$.

We showed that isoflavone at low dietary levels increased mRNA expression of SREBP-1-dependent genes, whereas a diet high in isoflavone decreased these parameters. Genistein and daidzein have similar molecular weights and structural characteristics to that of 17β-estradiol and hence exerts estrogenic or anti-estrogenic action[24]. In addition, genistein and daidzein affect adipogenesis through PPARγ-dependent mechanism[4]. Dang and his colleagues[25] demonstrated that genistein at a low concentration (1 μM) stimulates osteogenesis and suppresses adipogenesis through the interaction with estrogen receptors. However, at high concentrations (>1 μM), genistein acted as a ligand for PPAR γ and hence up-regulated adipogenesis and down-regulated osteogenesis. Furthermore, it has been demonstrated that the growth of estrogen-responsive breast cancer cells was stimulated by genistein at the concentration of 10^{-2} μM, was but was suppressed at the concentration of 10 μM[26]. Apparently, physiological responses to varying doses of genistein were biphasic in several cases. Therefore, the observed biphasic alterations by different dietary levels of isoflavone in mRNA expressions of SREBP-1-dependent genes are not surprising.

In conclusion, our study showed that isoflavone at dietary levels greater than 0.1% increased the mRNA level of SREBP-1a in liver; while a diet containing 0.4% of isoflavone decreased the value of SREBP-1c. Diets containing 0.1-0.2% of isoflavone compared to an isoflavone-free diet significantly increased mRNA expressions of SREBP-1-dependent genes. However, the 0.4% isoflavone diet decreased mRNA expression of these genes to the level observed in rats fed an isoflavone-free diet. Therefore, present study demonstrated that varying amounts of dietary isoflavone modulated the mRNA expressions of SREBP-1a and -1c differently. The observed changes in mRNA levels may account for the biphasic modulations by different dietary levels of isoflavone in the expression of SREBP-1-dependent genes.

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大豆イソフラボンが高飽和脂肪食摂取ラット肝臓の SREBP-1応答遺伝子の発現に与える影響

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大豆イソフラボンが脂肪酸代謝に関わる転写因子、ステロール調節エレメント結合タンパク質（SREBP）-1と、SREBP-1に応答する脂肪酸代謝系遺伝子の発現に及ぼす影響をラットで調べた。ラットに0、0.05、0.1、0.2、または0.4％の大豆イソフラボンを含む20％パーム油食を与え、14日間飼育した。肝臓のSREBP-1aのmRNA発現量は、イソフラボン無添加食群、または0.05％イソフラボン食群と比べ、0.1％以上のイソフラボンを含む食餌群で増加した。SREBP-1cの発現は、イソフラボン無添加食群と比べ0.05-0.2％イソフラボン食群では差はなかったが、0.4％イソフラボン食群では約50％減少した。SREBP-1に応答する脂肪酸合成酵素や脂肪酸不飽和化酵素の遺伝子発現は、食餌へのイソフラボン添加で増加し、0.1または0.2％イソフラボン食群で最大値を示したが、0.4％イソフラボン食群ではイソフラボン無添加食と同程度の発現量にまで減少した。以上のように、SREBP-1aとSREBP-1cのmRNA発現量は食餌中のイソフラボン添加量に従って互いに異なった変化を示した。食餌へのイソフラボン添加量に呼応したSREBP-1依存性遺伝子発現量の二相性の変化は、このようなSREBP-1アイソフォームのmRNA発現変化に起因すると考えられた。