

## マウス脂肪組織の遺伝子発現に与える食餌タンパク質の影響

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## Effect of Dietary Protein on Adipose Tissue Gene Expression in Mice

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### Abstract

To investigate the effect of dietary protein sources on gene expression of proteins involved in the regulation of lipid, glucose and energy metabolism in white and brown adipose tissues and skeletal muscle, male ICR mice were fed an experimental diet containing either casein, soybean protein or whole egg protein for 21 days. The serum glucose level was significantly higher in mice fed whole egg protein than in the other groups. However, no protein-dependent changes were seen in serum lipid levels. Compared to casein and soybean protein, whole egg protein significantly decreased glucose transporter 4 mRNA abundance in perirenal white adipose tissue and interscapular brown adipose tissue. Uncoupling protein 2 mRNA level in perirenal white adipose tissue and brown adipose tissue was significantly higher in mice fed soybean protein than in those fed casein. Compared to other protein sources, whole egg protein increased uncoupling protein 2 mRNA level in skeletal muscle. Whole egg protein, compared to other proteins, significantly increased the hepatic peroxisomal fatty acid oxidation rate. However, mitochondrial fatty acid oxidation rate was the lowest in mice fed whole egg protein among the animals fed different proteins.

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### Introduction

The type of dietary protein appears to be a crucial factor affecting various indices for lipids, glucose and energy metabolism in experimental animals<sup>1-9)</sup> and humans.<sup>10,11)</sup> Studies indicate that soybean protein, compared to casein, reduces serum triacylglycerol and cholesterol levels in rats and mice.<sup>1-4)</sup> Suppression of hepatic fatty acid synthesis<sup>1,2,6)</sup> and intestinal absorption of dietary fat<sup>5)</sup> may account for the lipid-lowering effect of soybean protein. Available information<sup>4,6)</sup> also suggested that egg protein, casein and soybean protein affect lipid metabolism differently in the rat. Regarding the physiological activity of dietary protein affecting energy metabolism, some studies indicate that soybean

protein, compared to casein, reduces body fat mass in rats and mice.<sup>3,5)</sup> Mikkelsen et al.<sup>10)</sup> also reported that pork protein and soybean protein exert different effects on 24-h energy expenditure in human subjects. It has been shown that dietary soybean protein increases insulin receptor gene expression in the liver and adipose tissue of rats fed a diet low in polyunsaturated fatty acids and thus may affect glucose metabolism.<sup>8)</sup> These observations strongly suggest that various dietary proteins of animal and plant origins exert different physiological activity to affect glucose, lipid and energy metabolism in organisms. However, information regarding the effect of dietary protein on gene expression of proteins involved in the regulation of lipid, glucose and energy metabolism in adipose tissue has still been scarce. In this context, we compared the effect of different dietary proteins on

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mRNA levels of leptin, glucose transporter 4 (Glut 4), peroxisome proliferator activated receptor gamma (PPAR  $\gamma$ ) and uncoupling proteins (UCPs) in white and brown adipose tissues, and skeletal muscle in the mice. In addition, hepatic mitochondrial and peroxisomal fatty acid oxidation rates were analyzed.

## Materials and Methods

### 1. Animals and diets

Male ICR mice were obtained from Charles River (Kanagawa, Japan) at 5 weeks of age. Mice were housed individually in a room with controlled temperature (20-22 °C), humidity (55-60%), and lightning (lights on from 07:00 to 19:00 h) and fed a commercial non-purified diet (Type NMF, Oriental Yeast, Tokyo, Japan). After a 7-day adaptation period to the housing conditions, mice were randomly divided into three groups consisting of 7 or 8 animals each, and were fed purified experimental diets containing either milk casein, soybean protein or whole egg protein for 21 days. Milk casein and whole egg protein were purchased from Wako Pure Chemicals, Osaka, Japan and Taiyo Kagaku Co., Yokkaichi, Japan, respectively. Soybean protein was kindly donated by Fuji Oil Co., Osaka, Japan. Table 1 shows the compositions of the experimental diets. Different proteins were added to the diets at an amount corresponding to 3.2% nitrogen in lieu of sucrose. The compositions of mineral and mixtures were those recommended by the American Institute of Nutrition.<sup>12)</sup> Animals had free access to experimental diets and water during the experimental period. Body weight

Table 1. Compositions of experimental diets

Ingredients (g/100g)	Dietary proteins		
	Soybean	Casein	Egg
Casein	-	23.5	-
Soybean protein	23.40	-	-
Whole egg protein	-	-	21.2
Cornstarch	15	15	15
Corn oil	10	10	10
Sucrose	44.9	44.8	47.1
Cellulose	2	2	2
Mineral mix	3.5	3.5	3.5
Vitamin mix	1	1	1
Choline bitartrate	0.2	0.2	0.2

at the start of the experiment ranged 25-34 g. At the end of experimental period, blood was withdrawn from the inferior vena cava under diethyl ether anesthesia. Epididymal and perirenal white adipose tissues, interscapular brown adipose tissue, liver and skeletal muscle were immediately excised. Brown fat was carefully cleaned from the surrounding muscular tissue and the white adipose tissue.

### 2. Extraction and analysis of RNA

Tissue RNA was extracted using the acid guanidinium thiocyanate-phenol-chloroform extraction method.<sup>13)</sup> mRNA abundance of leptin, Glut 4, PPAR  $\gamma$ , and UCP 1, 2 and 3 were analyzed by quantitative reverse transcription-polymerase chain reaction (RT-PCR) as detailed previously.<sup>14)</sup> The reaction was conducted in a final volume of 25  $\mu$ l using specific sense and antisense primers,<sup>14)</sup> and 24  $\mu$ l of the reaction mixture was heat-denatured and applied to a nylon membrane using a slot-blot apparatus and fixed with UV-irradiation. DNA fragments on the nylon membrane were then hybridized with specific cDNA probes labeled with alkaline phosphatase and reacted with CDP-Star<sup>TM</sup> detection reagent to generate chemiluminescence. mRNA level for each protein was corrected for the value of  $\beta$ -actin. mRNA levels were expressed relative to a value of 100 for rats fed a diet containing casein as a protein source.

### 3. Assays for hepatic fatty acid oxidation rate

About 0.6 g of each liver was homogenized with 6 ml of 0.25 M sucrose containing 1 mM EDTA and 3 mM Tris-HCl (pH 7.2). Mitochondrial and peroxisomal palmitoyl-CoA oxidation rates were analyzed using whole liver homogenate as an enzyme source as detailed previously.<sup>15)</sup>

### 4. Statistical analysis

The data were analyzed by one-way analysis of variance and subsequently examined for significant differences of the means using a Tukey-Kramer post-hoc analysis.<sup>16, 17)</sup>

## Results

Growth and energy intake were significantly higher in mice fed whole egg protein than in the other groups, but no significant differences in these parameters were seen between animals fed casein and soybean protein (Table 2). There were no significant differences in the weights of epididymal and

Table 2 . Effect of dietary protein on growth parameters and tissue weight in mice

	Dietary proteins		
	Soybean	Casein	Egg
Body weight gain (g/21 days)	7.50 ± 0.69 <sup>a</sup>	9.83 ± 0.89 <sup>a</sup>	12.9 ± 1.0 <sup>b</sup>
Energy intake (kJ/day)	92.4 ± 1.9 <sup>a</sup>	91.1 ± 3.1 <sup>a</sup>	102 ± 3 <sup>b</sup>
Epididymal white adipose tissue (g/100 g body weight)	3.24 ± 0.34	3.10 ± 0.24	3.81 ± 0.19
Perirenal white adipose tissue (g/100 g body weight)	0.93 ± 0.09	1.12 ± 0.14	1.08 ± 0.14
Interscapular brown adipose tissue (g/100 g body weight)	0.65 ± 0.05	0.62 ± 0.05	0.83 ± 0.11
Liver (g/100 g body weight)	4.85 ± 0.19	5.32 ± 0.27	5.20 ± 0.12

Values represent mean ± SE of 7 or 8 mice.

Values in the same row with different superscript differ significantly at  $P < 0.05$ .

Table 3. Effect of dietary protein on serum lipid and glucose levels in mice

Serum lipids ( μ mol/dl)	Dietary proteins		
	Soybean	Casein	Egg
Triacylglycerol	62.0 ± 2.9	65.0 ± 3.7	67.3 ± 6.1
Cholesterol	542 ± 34	458 ± 24	514 ± 45
Phospholipid	408 ± 18	394 ± 14	402 ± 25
Free fatty acids	122 ± 7	132 ± 8	128 ± 7
Glucose	1213 ± 63 <sup>a</sup>	1290 ± 67 <sup>a</sup>	1583 ± 110 <sup>b</sup>

Values represent mean ± SE of 7 or 8 mice.

Values in the same row with different superscript differ significantly at  $P < 0.05$ .

perirenal white adipose tissues, and interscapular brown adipose tissue among the groups.

No dietary protein-dependent changes in serum lipid concentrations were seen (Table 3). However, serum glucose level became significantly higher in mice fed whole egg protein than in the other groups.

Compared with casein and soybean protein, whole egg protein significantly decreased gene expression of Glut 4 in perirenal, but not in epididymal, white adipose tissue (Table 4). Leptin mRNA levels tended to be higher in the whole egg protein group than in the other groups in both perirenal and epididymal white adipose tissues. PPAR mRNA level in epididymal white adipose tissue was significantly higher in mice fed whole egg protein than in those fed casein and soybean protein. However, no such protein-dependent changes were seen in perirenal white adipose tissue. Soybean protein compared to other proteins increased the UCP 2 mRNA level in perirenal white adipose tissue.

In brown adipose tissue, whole egg protein compared to other proteins decreased the mRNA level of Glut 4. The leptin mRNA level in this tissue of mice fed soybean protein

declined to about one-half those in the animals fed casein and whole egg protein. However, the differences were not statistically significant. Compared to soybean protein, whole egg protein significantly increased the gene expression of PPAR in brown adipose tissue. Soybean protein relative to casein significantly increased the gene expression of brown adipose tissue UCP 2. The values were comparable between animals fed soybean and whole egg proteins. No significant differences in UCP 1 and UCP 3 mRNA levels were seen among the groups.

Compared with other proteins, whole egg protein significantly increased the mRNA level of UCP 2 in skeletal muscle. However, there were no significant differences in mRNA levels of Glut 4 and UCP 3 among the groups.

The mitochondrial palmitoyl-CoA oxidation rate was the highest in mice fed soybean protein, and the value being the lowest with whole egg protein and casein produced an intermediate value (Table 5). The difference between the animals fed soybean protein and whole egg protein was significant. In contrast, the peroxisomal palmitoyl-CoA oxidation rate was the highest with whole egg protein, intermediate with casein

Table 4. Effect of dietary protein on gene expression in the adipose tissues and skeletal muscle of mice

mRNA levels (%)	Dietary proteins		
	Soybean	Casein	Egg
Epididymal white adipose tissue			
Glucose transporter 4	111 ± 14	100 ± 4	97.9 ± 5.9
Leptin	92.7 ± 16.4	100 ± 18	139 ± 11
PPAR	100 ± 11 <sup>a</sup>	100 ± 12 <sup>a</sup>	167 ± 9 <sup>b</sup>
Uncoupling protein 2	114 ± 8	100 ± 13	125 ± 14
Perirenal white adipose tissue			
Glucose transporter 4	90.5 ± 10.3 <sup>b</sup>	100 ± 17 <sup>b</sup>	54.6 ± 7.4 <sup>a</sup>
Leptin	111 ± 11 <sup>ab</sup>	100 ± 13 <sup>a</sup>	145 ± 16 <sup>b</sup>
PPAR	115 ± 14	100 ± 18	79.7 ± 5.4
Uncoupling protein 2	138 ± 10 <sup>b</sup>	100 ± 6 <sup>a</sup>	103 ± 12 <sup>a</sup>
Interscapular brown adipose tissue			
Glucose transporter 4	105 ± 6 <sup>b</sup>	100 ± 8 <sup>b</sup>	70.4 ± 2.5 <sup>a</sup>
Leptin	46.6 ± 12.1	100 ± 28	91.1 ± 25.8
PPAR	67.7 ± 10.9 <sup>a</sup>	100 ± 12 <sup>ab</sup>	126 ± 15 <sup>b</sup>
Uncoupling protein 1	77.6 ± 6.9	100 ± 13	90.4 ± 6.0
Uncoupling protein 2	140 ± 14 <sup>b</sup>	100 ± 11 <sup>a</sup>	134 ± 11 <sup>ab</sup>
Uncoupling protein 3	76.0 ± 13.4	100 ± 15	100 ± 12
Skeletal muscle			
Glucose transporter 4	87.9 ± 6.8	100 ± 11	95.3 ± 7.0
Uncoupling protein 2	104 ± 4 <sup>a</sup>	100 ± 10 <sup>a</sup>	156 ± 23 <sup>b</sup>
Uncoupling protein 3	120 ± 11	100 ± 18	133 ± 23

Values represent means ± SE of 7 or 8 mice.

Values in the same row with different superscript differ significantly at  $P < 0.05$ .

Table 5. Effect of dietary protein on hepatic palmitoyl-CoA oxidation in mice

Palmitoyl-CoA oxidation rate (nmol/min/mg protein)	Dietary proteins		
	Soybean	Casein	Egg
Mitochondrial	2.80 ± 0.28 <sup>c</sup>	2.37 ± 0.19 <sup>bc</sup>	2.09 ± 0.22 <sup>b</sup>
Peroxisomal	4.93 ± 0.19 <sup>b</sup>	5.76 ± 0.30 <sup>c</sup>	6.69 ± 0.29 <sup>d</sup>

Values represent means ± SE of 7 or 8 mice.

Values in the same row with different superscript differ significantly at  $P < 0.05$ .

and the lowest with soybean protein.

## Discussion

In the present study, protein-dependent changes in fat pad mass were not observed in ICR mice. Some studies indicated that soybean protein, compared to casein, lowered body fat mass in rodents. Shinjo et al.<sup>3)</sup> reported that soybean protein, compared to casein, did not change total body fat content but

significantly lowered the weight of intra-abdominal fat in Wistar rat. Aoyama et al.<sup>4)</sup> reported that soybean protein reduced body fat mass compared to casein in yellow KK mice but not in Sprague-Dawley rats. In their experiment, animals were first made obese by feeding a high-fat diet containing 30% fat. The diet was then changed to energy-restricted, low-fat (5.0%), and high-protein diet containing either 35% casein or soybean protein. After four weeks of feeding body fat content became significantly lower in KK mice fed soy-

bean protein compared to those fed casein. But, no such protein-dependent change was confirmed in Sprague-Dawley rats. Given the above, it is likely that the impact of dietary protein on body fat mass depends on various factors including species and strains of experimental animals employed as well as diet composition and feeding protocol.

UCP 1 is specifically expressed in brown adipose tissue mitochondria and is involved in the regulation of energy expenditure mediating non-shivering thermogenesis by creating a pathway to allow dissipation of the proton electrochemical membrane.<sup>18)</sup> Recently discovered UCP 1 homologues may also play a crucial role in regulating energy expenditure in the organisms. In addition, there is the possibility that these homologues may have functions distinct from those of UCP 1.<sup>19, 20)</sup> Iritani et al.<sup>21)</sup> recently reported that the mRNA expressions of UCP 1, 2 and 3 were elevated in the epididymal white adipose tissues of Wistar rats fed soybean protein as compared to those fed casein, and that of UCP 2 was also elevated in the brown adipose tissue. Protein-dependent change in mRNA expression of UCP 2 was greater than those of UCP 1 and 3. Consistent with this observation, we found that soybean protein compared to casein increased the mRNA level of UCP 2 in perirenal white adipose tissue and brown adipose tissue in ICR mice even though the change was not confirmed in epididymal white adipose tissue and muscle. We further showed that the impact of egg protein affecting UCP 2 mRNA expression was distinct from those of soybean protein and casein. As protein types did not affect fat mass in the present study, the physiological significance of the changes in UCP 2 mRNA level is not clear at present.

Previous study indicated that no differences exist in plasma glucose and insulin concentrations, nor in the mRNA level of insulin receptor in adipose tissue and liver between rats fed casein and soybean protein.<sup>8)</sup> Consistent with this observation, serum glucose concentration was the same between mice fed casein and soybean protein in this study. However, we observed that whole egg protein compared to casein and soybean protein increased serum glucose level in mice. Glut 4 is the insulin-responsive glucose transporter highly expressed in muscle and adipose tissue and plays an important role in regulating serum glucose level.<sup>22)</sup> Dietary regulation of Glut 4 is tissue specific. Kahn<sup>23)</sup> reported that down-regulation by a high-fat diet of Glut 4 expression was much greater in adipose tissue than in muscle. Fasting caused a decrease in Glut 4 mRNA level in adipose tissue but not in muscle.<sup>23)</sup>

However, relative contribution of muscle and adipose tissue to whole-body glucose homeostasis remained to be clarified. In the present study, mRNA level of Glut 4 in perirenal white adipose tissue and brown adipose tissue became significantly lower in mice fed whole egg protein compared to the other groups. Therefore, there is the possibility that down-regulation of Glut 4 reduced glucose transport and utilization in these tissues and hence increased serum glucose level in mice fed whole egg protein. However, this consideration still needed to be sustained by extensive studies because types of dietary protein were totally ineffective in affecting Glut 4 mRNA level in epididymal white adipose tissue and skeletal muscle.

An alternative factor that modifies whole-body glucose utilization is the rate of fatty acid oxidation in muscle and liver. Glucose and fatty acids are the major oxidative fuels in mammals. Therefore, metabolism of these compounds are reciprocally regulated by each other.<sup>24, 25)</sup> According to the concept of the glucose-fatty acid cycle first proposed by Randle et al.,<sup>24)</sup> it is expected that up-regulation of fatty acid oxidation in muscle and liver compensatory decreases glucose oxidation in these tissues and hence increases serum glucose concentration. In the present study, dietary egg protein, compared to soybean protein and casein, significantly increased the peroxisomal fatty acid oxidation rate in the liver. Therefore, it is possible that up-regulation of hepatic fatty acid oxidation can account for the increase in serum glucose level in mice fed egg protein. However, the mitochondrial fatty acid oxidation rate was the lowest in the egg protein group among mice fed different proteins. So, it is rather difficult to conclude that alteration in hepatic fatty acid oxidation is a factor accounting for the difference in the serum glucose levels in mice fed different proteins. It is expected that muscle, in addition to liver, plays a crucial role in metabolizing glucose and fatty acid in the body. Therefore, the analysis of fatty acid oxidation rate in muscle in mice fed different proteins is still required to account for the differential effect of types of dietary protein affecting serum glucose level.

PPAR plays a crucial role in affecting adipogenesis.<sup>26)</sup> It is generally considered that up-regulation of PPAR mRNA level results in the stimulation of adipocyte differentiation. In the present study, egg protein, compared to other proteins, increased the mRNA level of this transcription factor in epididymal white adipose tissue and brown adipose tissue. However, egg protein was ineffective in affecting weights of

these tissues. In relation to this observation, studies indicated that adipogenesis is controlled by a complex interplay of PPAR and other transcription factors including PPAR, members of CCAAT/enhancer binding protein (C/EBP), and, sterol regulatory element binding protein-1 (SREBP-1) and cAMP response element binding protein (CREBP).<sup>26)</sup> It is also reported that up-regulation of GATA-binding transcription factors (GATA-2 and -3) suppress adipocyte differentiation.<sup>26)</sup> It is possible that egg protein also affected expression of transcription factor(s) other than PPAR and hence resulted in an unalteration of tissue mass.

In conclusion, we observed that dietary whole egg protein compared to casein and soybean protein increased the serum glucose level accompanying the down-regulation of Glut 4 mRNA levels in perirenal white adipose tissue and brown adipose tissue in mice. Also, it was suggested that types of dietary proteins affect hepatic fatty acid oxidation differently. Therefore, the alterations in glucose metabolism in perirenal white adipose tissue, brown adipose tissue and liver may account for the protein-dependent changes in the serum glucose level.

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## マウス脂肪組織の遺伝子発現に与える食餌タンパク質の影響

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雄ICRマウスにカゼイン、大豆タンパク質あるいは全卵タンパク質を含む飼料を21日間与え、白色脂肪組織、褐色脂肪組織および筋肉の脂質、糖及びエネルギー代謝に与える影響を調べた。

全卵タンパク質は他の食餌タンパク質と比較し、血糖値を上昇させた。しかし、血清脂質レベルには食餌タンパク質のタイプによる変化はなかった。

カゼインおよび大豆タンパク質と比較し、全卵タンパク質は腎臓周辺白色脂肪組織と褐色脂肪組織のグルコース輸送担体4のmRNAレベルを減少させた。

大豆タンパク質はカゼインと比較し、腎臓周辺白色脂肪組織と褐色脂肪組織の脱共役タンパク質2のmRNAレベルを上昇させた。また、全卵タンパク質は他のタンパク質と比較し、骨格筋の脱共役タンパク質2のmRNAレベルを上昇させた。

全卵タンパク質は他の食餌タンパク質と比較し、肝臓のペルオキシゾーム脂肪酸酸化活性を増加させた。しかし、肝臓のミトコンドリアの脂肪酸酸化活性は全卵タンパク質群でもっとも低値を示した。