Differential regulation of intestinal lipid metabolism-related genes in obesity-resistant A/J vs. obesity-prone C57BL/6J mice

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Obesity is a well-known risk factor for non-insulin-dependent diabetes mellitus, hypertension, and heart disease (4, 14, 20, 29, 40). Many studies (1, 33, 39, 42) have demonstrated that obesity is a multifactorial syndrome influenced by both genetic and behavioral factors. Excessive intake of dietary fat and low levels of physical activity are representative behavioral factors. However, genetic polymorphisms in the β3-adrenergic receptor and peroxisome proliferator-activated receptor (PPAR)-γ gene have been reported to be associated with obesity in humans (11, 37).

Several studies (15, 44, 45, 48) have also demonstrated a difference in the sensitivity to dietary fat among mouse strains; particular strains readily develop an obesity syndrome after chronic consumption of high-fat (HF) diets. C57BL/6J (B6) mice develop severe obesity accompanied by hyperglycemia when fed a HF diet. Therefore, B6 mice are among the several strains of mice classified as sensitive to diet-induced obesity. In contrast, A/J mice become only moderately obese on HF diets and are classified as resistant to diet-induced obesity.

These mouse strains that differ in obesity sensitivity provide excellent experimental models to study the developmental pathophysiology of an obesity syndrome (35, 47). Watson et al. (47) have shown that leptin and uncoupling proteins were induced by the HF diet to higher levels in the adipose tissue of A/J mice compared with B6 mice, suggesting that the thermogenic capacity in adipose tissue is a factor responsible for the development of the diet-induced obesity.

On the other hand, it is well known that the small intestine plays an indispensable role in the digestion and absorption of lipids derived from the diet. The small intestine has enzymes involved in triacylglycerol resynthesis, such as monoacylglycerol-O-acyltransferase (MOGAT) and diacylglycerol-O-acyltransferase (DGAT). In addition, this tissue also expresses β-oxidation-related enzymes, such as acyl-coenzyme A (CoA) oxidase (ACOX1) and medium-chain acyl-CoA dehydrogenase (ACADM), at comparable levels to the liver (21, 31).

In this study, to address the relationship between the lipid metabolism in the small intestine and the susceptibility to obesity, we examined the effects of HF feeding on gene expression in the small intestine of the obesity-resistant and obesity-prone mice. Preliminary studies using microarrays for RNA samples from a limited number of animals suggested that the expression of fatty acid metabolism-related genes were altered in obesity-resistant and obesity-prone mice in response to HF feeding. Therefore, we performed the following studies using quantitative RT-PCR (qRT-PCR) to analyze changes of gene expression and compared the responses of the two strains of mice to HF feeding.

MATERIALS AND METHODS

Animals and diets. Male A/J and B6 mice were obtained from Jackson Laboratory (Bar Harbor, ME) at 7 wk of age and were maintained at 23 ± 2°C under a 12:12-h light-dark cycle (lights on from 7 AM to 7 PM). The mice were fed laboratory chow for 1 wk to...
stabilize metabolic conditions. Both strains of mice were each randomly divided into two groups (n = 6, 3 mice/cage) and were allowed ad libitum access to water and one of two powder diets for 2 wk. We used a dome-type cover, Roden CAFE (Oriental Yeast, Tokyo, Japan), to avoid scattering of the power diets. At the beginning of the experiment there was no significant difference in body weight among the groups. The synthetic diets were as follows: low-fat (LF) diet containing 5% (wt/wt) triacylglycerol (TG) oil, 20% casein, 4% cellulose, 3.5% mineral mixture, 1% vitamin mixture (AIN-76), 13% sucrose, and 53.5% potato starch; a high-fat (HF) diet containing 30% (wt/wt) TG oil, 20% casein, 4% cellulose, 3.5% mineral mixture, 1% vitamin mixture (AIN-76), 13% sucrose, and 28.5% potato starch. The fatty acid composition of the TG oil used in this study was as follows, 0.05% C14:0; 5.4% C16:0; 0.2% C16:1; 2.0% C18:0; 37.1% C18:1; 46.0% C18:2; 7.3% C18:3; 0.5% C20:0; 0.9% C20:1; 0.2% C22:0; 0.1% C22:1. Fat intake was measured on a per-cage basis throughout the study every 2 or 3 days. This study was approved by the Animal Care Committee of Kao Tochigi Institute.

Total RNA isolation. After 2 wk of HF or LF feeding, the upper part of the small intestine (0–15 cm from the pylorus) was excised from mice in a nonfasting state between 9 AM and 11:30 AM and washed with 10 ml of ice-cold PBS. Then the intestine was opened lengthwise on an ice-cold aluminum plate, and the mucosal side was intensely scraped off using a glass microscope slide so that any variation in the scraping procedure was minimized. Histological examination of the remaining tissue revealed that the mucosal scraping obtained by this procedure contained mucosal epithelium, mucosal connective tissue, mucosal muscles and pliable connective tissue layer, remaining circular and longitudinal muscle layers, and serosa. The intestinal mucosa, liver, muscle, and epididymal white adipose tissue (WAT) were homogenized in Isogen (Nippon Gene, Toyama, Japan). Total RNA was extracted from the homogenate according to the manufacturer’s instructions and purified using an RNeasy Mini kit (Qiagen, Tokyo, Japan).

qRT-PCR analysis. qRT-PCR analysis was performed for gene expression analysis, because highly quantitative characteristics are required for individual analysis for multiple samples. cDNA was required for individual analysis for multiple samples. cDNA was synthesized from total RNA with a PrimeScript™ RT Reagent Kit (Takara Bio Inc., Kusatsu, Shiga, Japan). Quantitative detection of gene expression was analyzed using the SYBR® Green Master Mix kit (Applied Biosystems, Foster City, CA). Real-time PCR was performed on an ABI-Prism 7000 using the SYBR Green Master Mix kit (Applied Biosystems, Foster City, CA). Real-time PCR was performed on an ABI-Prism 7000 using the SYBR Green Master Mix kit (Applied Biosystems, Foster City, CA). Real-time PCR was performed on an ABI-Prism 7000 using the SYBR Green Master Mix kit (Applied Biosystems, Foster City, CA).

Subcellular fractionation was performed according to the methods described by de Duve et al. (13). After the centrifugation of the homogenate of the intestinal mucosa at 600 g for 10 min, the supernatant was centrifuged at 12,500 g for 20 min. The resultant precipitate containing mitochondria was resuspended in sucrose buffer and used for the measurement of CPT and ß-oxidation activity as a mitochondrial fraction. The supernatant was centrifuged at 100,000 g for 30 min, and the obtained supernatant was used for the measurement of ME activity as a cytosol fraction. Protein concentrations were determined using a Micro BCA protein assay kit (Pierce, Rockford, IL).

The NADPH-dependent cytosolic ME activity was measured spectrophotometrically with a UV-2550 by observing the appearance of NADPH at 340 nm at 30°C according to the method described previously (5). The reaction mixture contained 50 mM Tris-HCl (pH 7.5), 2.0 mM dithiothreitol, 1 mM L-carnitine, 1 mM nicotinamide adenine dinucleotide, 0.06 mM flavin adenine dinucleotide, 13,197–13,217 and nt 13,330–13,353); apolipoprotein C-II (Apoc2; XM_894981, nt 1,289 and nt 1,537–1,558); DGAT2 (BC029397, nt 2,234–2,255 and nt 2,368–2,387); solute carrier family 27 member 4 (Slc27a4; AF072759, nt 1,108–1,126 and nt 1,371–1,391); leptin (Lep; NM_013076, nt 258–278 and nt 471–490), Arbp (MMARPP, nt 632–651 and nt 862–881).

Measurement of enzyme activity. The intestine was excised between 9 AM and 11:30 AM. Mice were fasted for 3 h before the start of dissection to minimize contamination of the mucosal samples by lipids. Mucosal scraping was obtained as described in Total RNA isolation and homogenized on ice with 8 vol (wt/vol) of 250 mM sucrose buffer containing 0.1 mM EDTA and 2 mM HEPEs (pH 7.5). Subcellular fractionation was performed according to the methods described by de Duve et al. (13). After the centrifugation of the homogenate of the intestinal mucosa at 600 g for 10 min, the supernatant was centrifuged at 12,500 g for 20 min. The resultant precipitate containing mitochondria was resuspended in sucrose buffer and used for the measurement of CPT and ß-oxidation activity as a mitochondrial fraction. The supernatant was centrifuged at 100,000 g for 30 min, and the obtained supernatant was used for the measurement of ME activity as a cytosol fraction. Protein concentrations were determined using a Micro BCA protein assay kit (Pierce, Rockford, IL).

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CPT activity was measured spectrophotometrically as described by Markwell et al. (24). The reaction mixture (final 500 µl) contained 58 mM Tris-HCl (pH 8.0), 1.25 mM EDTA, 0.25 mM 5,5'-dithiobis(2-nitrobenzoic acid) (DTNB), 40 µM palmitoyl-CoA, 0.1% Triton X-100, and 1.25 mM L-carnitine, and the solution was equilibrated at 30°C. The reaction was initiated by the addition of 100 µg of the mitochondrial fraction, and the rate was followed at 412 nm on a UV-2550 spectrophotometer (Shimazu, Kyoto, Japan). The L-carnitine-independent rate was determined using a reaction mixture identical with the above, except for the omission of L-carnitine. The CPT activity and L-carnitine-dependent rate for the formation of CoA was calculated from the difference between the rates with and without L-carnitine, using the molecular extinction coefficient 13,600 M/cm for 2-nitro-5-thiobenzoic acid, which was generated by the reaction of CoA and DTNB.

The ß-oxidation activity was measured according to the method described by Singh et al. (38), with minor modifications. The reaction mixture contained 10 mM phosphate buffer (pH 7.4), 140 mM NaCl, 2.5 mM KCl, 2 mM MgCl2, 1 mM dithiothreitol, 2 mM ATP, 1 mM L-carnitine, 1 mM nicotinamide adenine dinucleotide, 0.06 mM flavin adenine dinucleotide, 0.25 mM CoA, 25 µM [1-14C]palmitic acid (1.25 µCi/ml) and the mitochondrial fraction containing 50 µg protein in a final volume of 200 µl. The reaction was performed at 37°C for 10 min and terminated by adding 200 µl of 0.6 N perchloric acid, followed by centrifugation at 2,000 g for 10 min. The supernatant was extracted three times with 800 µl of n-hexane to remove the residual radiolabeled palmitate. The radioactivity of the aqueous phase was measured using a liquid scintillation counter (Packard, Meriden, CT).
Blood analysis. The serum glucose concentrations were determined using L-type Wako Glu2 enzyme assay kits (Wako). The serum insulin and leptin level were measured using an insulin EIA kit (Morinaga, Yokohama, Japan) and a mouse leptin assay kit (Morinaga), respectively.

Statistical analysis. All values are presented as means ± SE. Statistical analyses were performed with two-factor factorial analysis of variance (ANOVA). One-factor ANOVA analyses were conducted when two-factor factorial ANOVA revealed a significant interaction between the factors (i.e., strain and diet). Differences between individual group means were analyzed by Fisher’s protected least significant difference test. Analyses were performed using StatView 5.0 software (SAS Institute, Cary, NC). Statistical significance was defined as $P < 0.05$.

RESULTS

Growth characteristics and serum hormone concentrations. The body weights 2 wk after the LF or HF feeding and average daily food intake during the period are shown in Table 1. There was no significant difference in body weight at the time point among the four mouse groups, and the food intake also did not differ between A/J and B6 mice. The serum glucose level in the B6 mice was significantly higher than that in the A/J mice under the HF diet condition. The serum insulin levels were not significantly different. The serum leptin level in the A/J mice was significantly higher than that in the B6 mice under the LF diet condition. In the B6 mice, HF feeding showed a trend of increase in the serum leptin level compared with LF feeding, but the increase was not significant. In another set of experiments, B6 mice fed the HF diet for 12 wk exhibited significantly higher body weights than A/J mice (30.0 ± 2.6 g in B6 mice, 26.7 ± 2.6 g in A/J mice, $P < 0.05$, $n = 6$).

Effects of HF feeding on expression of fatty acid metabolism-related genes in the small intestine. To identify genes that change in response to HF feeding, oligonucleotide microarray analyses were performed for the A/J or B6 mice fed on LF or HF diet for 2 wk, a short time during which body weight did not significantly differ among the experimental groups, but which was considered to be long enough for HF ingestion to affect gene expression, according to a previous report (47). qRT-PCR analysis revealed that HF feeding significantly increased expression levels of lipid metabolism-related genes.

The genes included Mod1, Cyp4a10, Hmgcs2, Acot1, Acot2, Pdk4, Acaal1b, Cpt1, Fabp1, and Acadl (Fig. 1). The expression of the genes in the intestine was markedly increased by HF feeding in both mouse strains, and the expression levels of the genes were significantly higher in obesity-resistant A/J mice than in obesity-sensitive B6 mice (Fig. 1). Acadm, Acox1, Ucp2, and Cd36 were not increased by HF feeding; however, the expression levels of Acadm, Ucp2, and Cd36 in A/J mice were significantly higher than those in B6 mice (Fig. 1). The expression of Dci was increased by HF feeding only in A/J mice. The expression of Ppara, which encodes a nuclear factor responsible for the expression of lipid metabolism-related genes, was not affected by HF feeding but was higher in A/J mice than in B6 mice under both diet conditions.

The primary function of the small intestine as it relates to lipid metabolism is the resynthesis of TG and the secretion of TG as chylomicrons. However, qRT-PCR analysis revealed that HF feeding did not affect Mogat2, Dgat1, and Dgat2 expression, although the expression level of these TG synthesis-related genes was slightly higher in A/J mice compared with B6 mice under both diet conditions (Fig. 1). On the other hand, gene expression of Alob was reduced in A/J mice. Gene expression of Apoc2 was upregulated by HF feeding in both mouse strains, whereas the gene expression of Apoc3 was reduced by HF feeding. The levels of these genes were significantly higher in A/J mice.

Gene expression in liver, muscle, and adipose tissue. Changes in the expression levels of the lipid metabolism-related genes were also examined for the liver, muscle, and WAT from the obesity-resistant A/J and obesity-prone B6 mice fed the LF or HF diet for 2 wk.

In the liver, the strain difference in expression was not as obvious as in the small intestine. Unlike in the intestine, the gene expression of Mod1 and Cyp4a10 in the liver was significantly increased in A/J mice by HF feeding (Fig. 2A). Gene expression of Cyp4a10 and Hmgcs2 was slightly increased by HF feeding only in B6 mice. Similar results were obtained for the other lipid metabolism-related genes (i.e., Cpt1, Fabp1, Acadm, Acox1, Ucp2, and Cd36; Fig. 2A). Unlike that in the intestine, there was no clear strain difference in the gene expression levels in the liver. The expression levels of Cpt1

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<th>Table 1. Body weight, food intake, tissue weights, and serum parameters of A/J and C57BL/6J mice fed on LF or HF diets for 2 wk</th>
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Values for body weight, tissue weights, and serum parameters are means ± SE of 6 mice. Values for food intake are means ± SE of 6 measurements performed during the experiment. LF, low fat; HF, high fat; WAT, white adipose tissue. Means in a column with symbols without common symbol are different at $P < 0.05$.
and Fabp1 were slightly, but significantly, higher in A/J mice compared with B6 mice under both diet conditions. Gene expressions of Acox1 and Ucp2 were increased only in B6 mice by HF feeding.

In the muscle, the response to the HF diet and the strain differences in the lipid metabolism-related genes were negligible or subtle for all of the examined lipid metabolism-related enzymes and fatty acid transporters (Fig. 2B).

In the WAT, 2 wk of ingestion of the HF diet did not increase the expression of Mod1, Hmgcs2, Aco1, Acot2, Pdk4, or Acaa1b (Fig. 2C). Mod1 expression was rather significantly decreased by HF feeding in A/J mice. In agreement with the previous report (47), Ucp2 expression in the WAT of obesity-resistant A/J mice was significantly higher compared with obesity-prone B6 mice under both diet conditions (Fig. 2C). Its expression was slightly increased by feeding of the HF diet to A/J mice (P < 0.01).

Changes in enzyme activity. To confirm the predominant intestinal lipid metabolism in obesity-resistant A/J mice, suggested by gene expression analysis, lipid metabolism-related enzyme activities were examined.

The cytosolic ME activity in the small intestine was increased in response to the HF feeding, reflecting the expression pattern of the Mod1 gene. The activity was increased 3.3-fold in A/J mice and 1.5-fold in B6 mice. The activity was 2.5-fold higher in A/J mice compared with B6 mice under the HF diet condition (Fig. 3A).

CPT activity was significantly increased by 2 wk of HF feeding in the small intestines of both strains of mice (1.5-fold in A/J mice and 1.7-fold in B6 mice). In parallel with the gene expression pattern, the activities in A/J mice were significantly higher than those in B6 mice under the LF and HF diet conditions (Fig. 3B).

The HF feeding also increased the β-oxidation activity in both strains of mice (1.9-fold in A/J mice and 2.9-fold in B6 mice). The activities were not significantly different between the strains (Fig. 3C).

DISCUSSION

In this study, we demonstrated that the ingestion of a HF diet induced the expression of several genes related to lipid metabolism and the basal and upregulated expression levels were higher in the obesity-resistant A/J mice compared with the obesity-prone B6 mice. Furthermore, the increased intestinal lipid metabolism in A/J mice was confirmed at the levels of the
enzyme activities; ME activity, CPT activity, and β-oxidation activity were increased in response to the ingestion of the HF diet, and the basal enzyme activities and/or the activities upregulated by the HF feeding were higher in the A/J mice compared with those in the B6 mice.

A notable change in gene expression by HF feeding was observed in Mod1, Cyp4a10, Hmgcs2, Acot1, Acot2, Pdk4, and Acaa1b. Expression of these genes was significantly higher in obesity-resistant A/J mice than in obesity-prone B6 mice. There is little information about the functions of the genes in the small intestine, but previous studies have shown their physiological roles in liver and muscle. ME encoded by Mod1 is known as a representative lipogenic enzyme in the liver. The enzyme catalyzes the synthesis of pyruvate and NADPH from malate and NADP⁺, and the NADPH generated by the reaction promotes fatty acid synthesis (5).

Cyp4a10 belongs to the CYP4A subfamily encoding several cytochrome P450 enzymes that catalyze the ω-oxidation of fatty acids (3). Because CYP4A subfamily enzymes require NADPH as a coenzyme, the increase of ME activity in the small intestine could result in the stimulation of the ω-oxidation of fatty acid by generating NADPH. Hmgcs2 is highly expressed in the liver and plays a role as a rate-limiting enzyme in the synthesis of ketone bodies from the acetyl-CoA generated by fatty acid β-oxidation (12, 49). Acot1 and Acot2 encode acyl-CoA thioesterases that catalyze the hydrolysis of acyl-CoA of various chain lengths to free fatty acids and CoA. It has been proposed (26, 41, 46) that these enzymes promote ω-oxidation by modulation of the cellular concentrations of acyl-CoA and CoA or by acting in concert with uncoupling protein 3 in the liver and skeletal muscle. Thus all of the genes mentioned above are possibly associated with the β- or ω-oxidation in the small intestine. Pdk4 encodes an isozyme of the enzyme that catalyzes pyruvate dehydrogenase complex phosphorylation. It has been reported (43) that the upregulation of Pdk4 expression in the kidney facilitated the entry of acetyl-CoA derived from β-oxidation into the TCA cycle via the increased carboxylation of pyruvate to oxaloacetate. Acaa1b has been identified as a gene for an enzyme involved in the peroxisomal β-oxidation (10). In the present study, it has been demonstrated that the intestinal

![Graph A](image1)

![Graph B](image2)

![Graph C](image3)

**Fig. 2.** Gene expression in the liver, skeletal muscle, and white adipose tissue (WAT). Total RNA isolated from the liver (A), gastrocnemius muscle (B), and epididymal WAT (C) was subjected to qRT-PCR analysis as described in MATERIALS AND METHODS. *Hadha*, hydroxyacyl-CoA dehydrogenase; *Slc27a1*, solute carrier family 27, member 1; *Slc27a4*, solute carrier family 27, member 4; *Lep*, leptin. Values are means ± SE of 6 mice. *P < 0.05; **P < 0.01.
l lipid metabolism-related genes were expressed at higher levels in obesity-resistant A/J mice than in obesity-prone B6 mice. Previous studies have reported that the upregulation of fatty acid catabolism induced by PPARα-specific activators in liver and/or brown adipose tissue was associated with a reduction in body weight gain and fat accumulation in rodent models of HF diet-induced or genetic insulin resistance (2, 16). Taken together, it is likely that the capacity for fatty acid catabolism in the small intestine also relates to body weight gain and fat accumulation; i.e., low levels of intestinal fatty acid catabolism may result in a reduced energy expenditure and, therefore, the development of obesity on a long-term basis.

HF feeding also affected the gene expression of Apoc2 and Apoc3. It has been reported (7, 19) that the lipid-binding domain of apoC-II is essential for the activation of lipoprotein lipase (LPL) (19, 32) and that apoC-III inhibits LPL activity. Because LPL catalyzes the hydrolysis of the TG circulating as chylomicrons or very low-density lipoproteins, the putative activation of LPL may promote utilization by peripheral tissues of free fatty acids and 2-monoacylglycerol. The observed changes in the gene expression of apoCs may also be an adaptive response to the excess intake of lipid. However, the physiological importance needs to be clarified by further study.

It has been demonstrated (3, 8, 17, 18, 22, 36, 50) that the expression of Mod1, Cyp4a10, Hmgs2, Acot1, Acot2, Pdk4, and Acaa1b was upregulated by hypolipidemic fibrate, and most of the genes have a PPAR response element in their promoter region. Therefore, the increase in the expression of these lipid metabolism-related genes in response to the HF feeding might be explained by the increased cellular concentration of free fatty acids, an endogenous ligand for PPAR, in the intestinal mucosa. The different expression levels of PPARα observed in this study (Fig. 1) may be a factor responsible for the strain difference in the expression of the lipid metabolism-related genes. Indeed, previous studies (23, 25) have shown that the infusion or oral administration of PPARα ligands caused an increase in the mRNA levels of these PPAR-dependent genes such as Acot1 and Fabp1. Poirier et al. (34) have shown that the PPARδ isoform plays a role as a transcription factor for Fabp1 in the small intestine of PPARα-null mice, suggesting its contribution to the metabolic adaptation of the small intestine to changes in the lipid content of the diet. However, we could not find any strain difference in the expression of PPARδ in the small intestines of A/J and B6 mice by qRT-PCR analysis (data not shown).

Consistent with previous reports (35, 47), we confirmed a significant increase of Ucp2 expression due to the HF diet in the WAT of A/J mice. Furthermore, Ucp2 expression in WAT was higher in A/J mice compared with that in B6 mice. Therefore, the thermogenic capacity of the adipose tissue may contribute to the development of obesity. Previous studies (6, 9, 30) using other rodent models have shown that HF feeding induced the upregulation of the β-oxidation activity and the gene expression of the related enzymes in the liver and muscle. Brady et al. (6) have demonstrated that 4 wk of HF feeding increased the enzyme activity and mRNA expression of mitochondrial and peroxisomal CPT. Cheng et al. (9) have shown that Long-Evans rats fed a HF diet exhibited a higher CPT activity in muscle compared with rats fed laboratory chow diets. However, in the present study, changes in the expression of lipid metabolism-related genes in the small intestine were more prominent than those in the liver, muscle, and adipose tissue after 2 wk of HF feeding, suggesting that the small intestine is one of the organ’s most sensitive to dietary lipids. Longer term HF feeding may be required for the upregulation of lipid metabolism in the liver and muscle in A/J and B6 mice under our experimental condition.

Because the small intestine is directly exposed to dietary fat, the activation of intestinal fatty acid catabolism by ingestion of large amounts of fat may result in a substantial reduction in the amount of lipid entering the bloodstream. Because the small intestine is also exposed to other orally ingested substances and the surface area of the villus mucosa is quite large, the regulation of the intestinal lipid metabolism by food ingredients or chemicals may become an efficient measure for pre-
vent the development of obesity. Indeed, it has been reported (27, 28) that dietary diacylglycerol reduced the HF-induced body weight gain in B6 mice and genetic body weight gain in C57BL/6J db/db mice accompanied by the stimulation of intestinal β-oxidation.

In the present study, we demonstrated that the intestine is highly responsive to fat ingestion and that the activation by HF feeding of the lipid metabolism-related genes in the intestine was more pronounced in obesity-resistant A/J mice than in obesity-prone B6 mice. These findings suggest that the capability for fatty acid catabolism in the small intestine is associated with the development of obesity.

REFERENCES


