Improvement of Obesity and Glucose Tolerance by Acetate in Type 2 Diabetic Otsuka Long-Evans Tokushima Fatty (OLETF) Rats

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Received November 27, 2006; Accepted January 21, 2007; Online Publication, May 7, 2007 [doi:10.1271/bbb.60668]

Acetate has been found to have an inhibitory effect on the activity of carbohydrate-responsive element-binding protein (ChREBP) in cultured hepatocytes, this being a transcription factor that regulates several genes required for the conversion of glucose to fatty acids in the liver. The aim of this study was to investigate whether an oral administration of acetate would contribute to reducing lipogenic genes and protecting against obesity. We orally injected 5.2 mg/kg BW of acetate to obesity-linked type 2 diabetic Otsuka Long-Evans Tokushima Fatty (OLETF) rats. The treatment with acetate showed a marked reduction in lipid accumulation in the adipose tissue, protection against accumulation of fat in the liver, and improved glucose tolerance. An analysis by Northern blotting revealed that the transcripts of several lipogenic genes in the liver of OLETF rats were decreased by the acetate treatment. On the basis of those results, it was indicated that acetate was a potential compound to improve obesity and obesity-linked type 2 diabetes.

Key words: acetate; lipid metabolism; obesity; Otsuka Long-Evans Tokushima Fatty (OLETF) rats; glucose tolerance

Obesity and obesity-linked type 2 diabetes are increasing throughout the world. Obesity and weight gain are caused by the unbalance of lipid anabolism and lipid catabolism, and are associated with heart disease, diabetes, and hypertension. Insulin resistance is a major risk factor in the progression of type 2 diabetes and it occurs by lipid accumulation in the liver.1) The liver is the principal organ responsible for the catabolism and anabolism of fatty acid depending on the physiological conditions. Under the starved condition, fatty acids derived from adipose tissue are oxidized by β-oxidation to form ketone bodies and acetate as the final products.2) Free acetate produced in the liver is provided to the extrahepatic tissues as fuel in a similar way to the physiological role of ketone bodies.2,3) Acetate is activated by acetyl-CoA synthetase (AceCS) to produce acetyl-CoA, an essential metabolic intermediate that is utilized in various metabolic processes including the TCA cycle, fatty acid synthesis and cholesterol synthesis.4–9) On the other hand, under the fed condition, an intake of excess carbohydrate leads to the activation of several glycolytic and lipogenic enzymes, including liver pyruvate kinase (L-PK), acetyl-CoA carboxylase (ACC), and fatty acid synthase (FAS), and consequently results in increased fat storage. The carbohydrate-responsive element (ChRE)-binding protein (ChREBP) is a recently discovered transcription factor responsible for glucose-induced transcription of L-PK.10) In response to high glucose, ChREBP is dephosphorylated to be localized in nuclei and activate transcription of the L-PK gene.11) Studies of ChREBP-/− mice and its hepatocytes have indicated that ChREBP coordinately regulates the genes required for converting glucose to fatty acids in the liver.12,13) ChREBP has recently been shown to be inactivated in cultured hepatocytes with the incubation of fatty acids, including acetate, octanoate, and palmitate. Those fatty acids increased the AMP/ATP ratio and activated AMP-activated protein kinase (AMPK).14) Phosphorylation of ChREBP by AMPK resulted in the inhibition of its DNA-binding activity and decreased its transcription activity. AMPK is a multi-subunit protein kinase which has been found to play a central role in lipid metabolism.15–22) AMPK is activated by a high AMP/ATP ratio in the cytosol which occurs under heat shock, hypoxia, and starvation. Acetate incorporated in the hepatocytes is converted to acetyl-CoA with the formation of AMP by the catalytic action of AceCS, resulting in the higher ratio of AMP/ATP in the cytosol.

Abbreviations: OLETF, Otsuka Long-Evans Tokushima Fatty; LETO, Long-Evans Tokushima Otsuka; ChREBP, carbohydrate-responsive element-binding protein; AceCS, acetyl-CoA synthetase; ACC, acetyl-CoA carboxylase; ME, malic enzyme; G6PD, glucose 6-phosphate dehydrogenase; L-PK, liver pyruvate kinase; FAS, fatty acid synthase; ACL, ATP citrate lyase; LCACD, long-chain acyl-CoA dehydrogenase; 3KACT, 3-ketoacyl-CoA thiolase; SREBP-1, sterol regulatory element-binding protein-1; AMPK, AMP activated protein kinase

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Acetate has been reported to be readily absorbed in the intestines.\textsuperscript{23,24} We hypothesized that orally injected acetate would be absorbed and excreted into the blood stream, and easily incorporated in tissues. We investigated in this study whether orally administered acetate would contribute to the suppression of lipogenesis in the liver and consequent reduction of lipid accumulation in the adipose tissue of OLETF rats, which are a genetic model of animals showing spontaneous development of non-insulin-dependent diabetes mellitus (NIDDM), and exhibit hyperglycemic obesity with hyperinsulinemia and insulin resistance similar to that in humans.\textsuperscript{25} We report here that acetate had a potential function to decrease body mass, fat accumulation and glucose tolerance, and consequently improve obesity-linked type 2 diabetes of OLETF rats.

Materials and Methods

Acetate administration experiment. Four-week-old male Otsuka Long-Evans Tokushima Fatty (OLETF) rats and Long-Evans Tokushima Otsuka (LETO) rats as a non-diabetic control were obtained from Otsuka Pharmaceutical Co., Ltd. (Tokushima, Japan) and fed on a normal laboratory diet (CE2, Clea, Tokyo, Japan) for 1 week to stabilize the metabolic conditions. The rats were housed individually in an air-conditioned room at approximately 25 °C with alternating 12-h periods of light and dark (lighting, 8:00–20:00). All the animals were allowed free access to water and the appropriate diet. The OLETF rats were randomly assigned to two groups: water-injected and acetate-injected. The water-injected group was given distilled water at 5 ml/kg of body weight, and the acetate-injected group was given 5.2 mg/kg BW (1% (v/v) acetate of 5 ml/kg of body weight) at 9:30 and 10:30 daily 5 days a week for 6 months. The initial body weights of the LETO, water-administered OLETF, and acetate-administered OLETF rats were 83 ± 16, 119 ± 7, and 103 ± 20 g, respectively. The food consumption and body weight were recorded every day. At 15 and 30 weeks of age, the rats were anesthetized, and blood was taken from the jugular vein; at 31 weeks of age, an oral glucose tolerance test was performed, and at 32 weeks of age, an oral glucose tolerance test was performed on rats that had been fasted overnight, before glucose (2 g/kg) was administered per os. Blood was collected from the tail vein immediately before and 30, 60, 90 and 120 min after the administration to determine the plasma glucose levels. The plasma glucose concentrations were measured by an ACCU-Chek Compact instrument (Roche Diagnostics).

Preparation of the cRNA probe for Northern blotting. The cDNA fragments for rat acetyl-CoA carboxylase (ACC), malic enzyme (ME), glucose 6-phosphate dehydrogenase (G6PD), liver pyruvate kinase (L-PK), fatty acid synthase (FAS), ATP citrate lyase (ACL), long-chain acyl-CoA dehydrogenase (LCAD), 3-ke-toacyl-CoA thiolase (3KACT), and sterol regulatory element-binding protein-1 (SREBP-1) were obtained by the polymerase chain reaction from first-strand cDNA from rat liver mRNA that had been isolated with an mRNA isolation kit (Roche, Germany) from total RNA of rat liver. First-strand cDNA was prepared by using Superscript II transcriptase primed with oligo-dT. The PCR primers used were as follows. ACC: 5′-GTTTGGCCCTTTCACATGAGTCT-3′; and 3′ primer, 5′-GTGGGGATACCTGAGTTGAG-3′; ME: 5′ primer, 5′-TCTTGCATGCCAGCAATACAGT-3′; and 3′ primer, 5′-TATCCGAGACAGCAAGAGG-3′; G6PD: 5′ primer, 5′-GGGATCCCTAGAGGGAAGTTGTT-3′; and 3′ primer, 5′-GGTCATGCGTGATCTGGT-3′. L-PK: 5′ primer, 5′-GAAGGTTGTAACCTGAA-3′; and 3′ primer, 5′-ACAGGTCTCCACAAGGAAACTGC-3′. FAS: 5′ primer, 5′-GACCCCTGTGGTGGTGTAGGAAC-3′; and 3′ primer, 5′-CTTGAGTGTCCTCCAGCT-3′. ACL: 5′ primer, 5′-TGATCTGGAGGTGTCACAGAA-3′; and 3′ primer, 5′-GT-CAGCTCTGGACCTGGAAAA-3′. LCAD: 5′ primer, 5′-CCTAAAGGTTCTGGAGTTGATGG-3′; and 3′ primer, 5′-GTGACACGCTTGGTTTACATGC-3′. 3KACT: 5′ primer, 5′-AGAAAGACTGCGACAGATGC-3′; and 3′ primer, 5′-TATCCACTAGCTGACG-CTTTA-3′. SREBP-1: 5′ primer, 5′-CAAAACACAGAGACATCGAGACGCCC-3′; and 3′ primer, 5′-CACTGGTTCCCTCCAGCT-3′. The polymerase chain reaction was performed with Taq DNA polymerase (Takara Shuzo Co., Shiga, Japan). Forty-one cycles of amplification were made by using the following program: 94 °C, 1 min; 66 °C, 1 min; and 72 °C, 2 min. The amplified products were subcloned into the pGEM-T Easy vector (Promega, Madison, WI, USA). These plasmid DNAs were used for DIG-RNA labeling with the DIG labeling system (Roche, Germany), and the cRNA probes were used as probes for Northern blotting.

Northern blotting. Total RNA was extracted from each tissue by using Isogen (Nippon Gene, Toyama, Japan). The RNA was dissolved in diethylpyrocarbonate-treated water and quantified by its absorbance at 260 nm. Total extracted RNA was denatured with formaldehyde and electrophoresed in 1% agarose gel con-
taining formaldehyde, the amount of loaded RNAs being checked by staining the 28 and 18 S rRNA bands with ethidium bromide. After capillary transfer to a nylon membrane (Roche, Germany) and UV crosslinking, the membrane was hybridized overnight at 68 °C with each DIG-labeled cRNA probe recognizing ACC, ME, G6PD, L-PK, FAS, ACL, LCACD, 3KACT, and SREBP-1. The filter was washed twice with 2 × SSC and 0.1% SDS at room temperature, washed twice further with 0.1 × SSC and 0.1% SDS at 68 °C for 30 min, incubated with a blocking solution and anti-DIG antibody-conjugated alkaline phosphatase for 30 min at room temperature, and then detected by using CDP-Star (Roche, Germany) to expose to an X-ray film. The amount of each transcript was quantified with an image analyzer (Gel Print 2000i, Genomic Solutions, Tokyo, Japan) and is expressed as the relative intensity. Each membrane was reprobed with β-actin to ensure that the changes observed did not reflect any unequal loading of the samples.

Histological analysis of the liver. Small pieces of liver were fixed with a 10% formalin neutral buffered solution (Wako Chemical Co., Japan) and embedded in paraffin. Sections (8 µm) were cut and stained with hematoxylin and eosin. Other pieces of the liver were quickly frozen. Cryostat sections 7–10 µm thick were obtained, and stained with Oil red O. Images were captured with a CCD camera (Olympus Optical, Tokyo) at a magnification of ×200.

AMP, ADP, and ATP assays. The removed livers were frozen quickly in liquid nitrogen, lyophilized, homogenized with ice-cold 0.5 N perchloric acid, neutralized and centrifuged. The concentrations of AMP, ADP and ATP in each liver extract were determined by a reverse-phase HPLC analysis.

Immunoblotting. The rat liver samples were cut with scissors into small pieces, suspended in 20 mM potassium phosphate (pH 7.4), and homogenized in potter-Elvehjem equipment. The homogenate was centrifuged (20,000 × g, 10 min) to remove the tissue debris. An aliquot (30 µg of protein) of each liver extract from the OLETF and LETO rats was applied to 12% SDS acrylamide gel electrophoresis and transferred to an Immobilon-P membrane (Millipore, Osaka, Japan). An immunoblot analysis was performed by using the ECL Western blotting detection system (GE Healthcare, NJ, USA). Membrane sheets were first incubated with the antibody against phosphopeptides based on the amino-acid sequence surrounding Thr 172 of the α-subunit of human AMPK (Cell Signaling, MA, USA) for 1 h at room temperature, then washed several times and incubated with biotinylated goat anti-rabbit IgG, and subsequently with streptavidin-conjugated horseradish peroxidase according to the protocol supplied by the manufacturer. We also determined the protein level of AMPKα by using a specific antibody for the α subunit of AMPK.

Other analyses. Blood samples were obtained from the jugular vein under feeding conditions. Plasma glucose, triglyceride, and cholesterol were respectively measured by the Glucose CII-Test, Triglyceride E-Test, and Cholesterol E-Test kits (Wako Pure Chemicals, Osaka, Japan). Plasma insulin and leptin were respectively measured by ELISA Insulin (Morinaga, Yokohama, Japan) and ELISA Rat Leptin kits (Morinaga, Yokohama, Japan). Plasma acetate level was determined by F-kit acetate (Roche, Germany).

Statistical analysis. Each data value is presented as the mean ± SE. The water-administered OLETF rats and LETO rats, as well as the water-administered OLETF rats and acetate-administered OLETF rats were respectively compared by an unpaired Student’s t test. Statistical significance is defined as p < 0.05–0.001.

Results

Effect of acetate on the weight gain and glucose tolerance

The body weight change was lower in LETO rats than in the water-administered OLETF rats. After administering acetate to the OLETF rats from 5 weeks to 9 weeks of age, they began to show a lower weight gain than that of the water-injected group, and at the age of 30 weeks, the average body weight was significantly lower in the LETO and acetate-injected OLETF rats than in the water-injected OLETF rats (Fig. 1A, Table 1). The total food intake of the LETO, water-administered OLETF, and acetate-administered OLETF rats was 3741 ± 91, 5791 ± 210 and 4933 ± 51 g, respectively. The food efficiency was not significantly different between the water-administered OLETF rats and LETO rats, although it was significantly lower in the acetate-injected OLETF than in the water-injected group (Fig. 1B). The plasma glucose, triglyceride, cholesterol, insulin and leptin levels were significantly lower in the LETO and acetate-administered OLETF rats than in the water-administered OLETF rats (Table 1). The abdominal fat content of the LETO and acetate-administered OLETF rats at 32 weeks of age was also lower by about 80% and 70%, respectively, than in the water-administered OLETF rats. Figure 2 shows the change in plasma glucose concentration measured by OGTT in the water- and acetate-administered OLETF rats at 31 weeks of age. The plasma glucose levels in the LETO and acetate-administered OLETF rats were significantly lower than that in the water-administered OLETF rats.

Effect of acetate on the mRNA expression of lipogenic enzymes

To examine the effect of acetate administration on lipogenesis in the liver, the mRNA levels of lipogenic
Effect of Acetate on the Body Weight Change of OLETF Rats.

Acetate (5.2 mg/kg BW) was orally administered to OLETF rats for 6 months. The food efficiency was calculated as the body weight change (g) divided by the food intake (g). Each data value is expressed as the mean ± SE of 3–4 rats.

In respect of the lipolytic genes, the LCACD, 3KACT, and SREBP-1 mRNA levels were not significantly different between the water- and acetate-administered OLETF rats (Fig. 3B).

Effect of acetate on the hepatic lipid accumulation

A histological analysis indicated that the water-administered OLETF rats accumulated higher levels of hepatic lipid, although the acetate-administered OLETF rats had a lower hepatic lipid accumulation than the water-administered OLETF rats (Fig. 4).

Effect of acetate on the change in AMP/ATP ratio and phosphorylation of AMPK in the liver

A dose of acetate at each concentration of 2.6, 5.2, and 10.5 mg/kg BW to SD rats stimulated the plasma acetate concentration within 1 min after the injection, although the level returned to the basal level within 10 min after the injection (Fig. 5A). We determined the adenine nucleotide concentration in perchloric acid extracts of the liver after intragastric injection of 10.5 mg/kg BW of acetate. The AMP content of the liver increased about 3-fold within 0.5 min after injecting the acetate (Fig. 5B and C). An injection of 5.2 mg/kg BW of acetate also stimulated the AMP level in the

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Table 1. Phenotypic Comparison of the Water- and Acetate-Administered OLETF with the LETO Rats

<table>
<thead>
<tr>
<th></th>
<th>OLETF-water</th>
<th>OLETF-acetate</th>
<th>LETO</th>
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<tbody>
<tr>
<td></td>
<td>15</td>
<td>30</td>
<td>15</td>
</tr>
<tr>
<td>Body weight (g)</td>
<td>549 ± 13</td>
<td>741 ± 27</td>
<td>453 ± 23&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Abdominal fat weight (g)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>—</td>
<td>68.3 ± 8.6</td>
<td>—</td>
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<tr>
<td>Plasma glucose (mg/dl)</td>
<td>228.7 ± 16.3</td>
<td>290.9 ± 30.3</td>
<td>216.2 ± 24.8</td>
</tr>
<tr>
<td>Plasma triglycerides (mg/dl)</td>
<td>169.1 ± 17.2</td>
<td>400.5 ± 15.7</td>
<td>69.7 ± 39.8&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Plasma cholesterol (mg/dl)</td>
<td>102.1 ± 6.1</td>
<td>139.8 ± 7.9</td>
<td>78.3 ± 7.7&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Plasma insulin (ng/ml)</td>
<td>13.1 ± 2.1</td>
<td>14.8 ± 2.5</td>
<td>6.7 ± 2.4&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Plasma leptin (ng/ml)</td>
<td>20.9 ± 4.3</td>
<td>61.4 ± 17.6</td>
<td>8.9 ± 4.0&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
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Acetate (5.2 mg/kg BW) was orally administered to OLETF rats for 6 months. At 15 and 30 weeks of age, blood was taken from the jugular vein. Each data value is expressed as the mean ± SE of 3–4 rats. <sup>a</sup>p < 0.05, <sup>b</sup>p < 0.01, <sup>c</sup>p < 0.001; compared with the water-injected OLETF rats.

<sup>*<sup>Abdominal fat content was measured at 32 weeks of age.

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Fig. 1. Effect of Acetate on the Body Weight Change of OLETF Rats.

A, Body weight change. B, Food efficiency. Acetate (5.2 mg/kg BW) was orally administered to OLETF rats for 6 months. At 15 and 30 weeks of age, blood was taken from the jugular vein. Each data value is expressed as the mean ± SE of 3–4 rats. <sup>*<sup>p < 0.05; <sup>**<sup>p < 0.01; <sup>***<sup>p < 0.001; compared with the water-injected OLETF rats.

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Fig. 2. Effect of Acetate on the Plasma Glucose Level during the Oral Glucose Tolerance Test (OGTT).

OGTT was performed on the OLETF rats administered with water or acetate (5.2 mg/kg BW) and LETO rats at 31 weeks of age after a 20-h fast. Glucose (2 g/kg) was administered orally. Each data value is expressed as the mean ± SE of 3–4 rats. <sup>*<sup>p < 0.05; <sup>**<sup>p < 0.01; <sup>***<sup>p < 0.001; compared with the water-injected OLETF rats.

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Fig. 3. Improvement of Obesity and Glucose Tolerance by Acetate.
liver, the amount being half as much as that with the 10.5 mg/kg BW of acetate injection (data not shown). An increase in the AMP/ATP ratio would induce phosphorylation of AMPK, following the AMPK activation. Phosphorylated AMPK in the liver of the water-and acetate-injected OLETF rats was determined by western blotting. In the acetate-injected OLETF rats, the protein level of phosphorylated AMPK was higher than that in the water-injected group (Fig. 5D).

**Discussion**

Acetate is an endogenous metabolite of fatty acid \( \beta \)-oxidation in liver mitochondria under the starved condition. Acetate formed in the liver is excreted into the blood stream and utilized as a biological fuel in the extrahepatic tissues under the starved condition. However, under the fed condition, orally administered acetate was immediately taken up from the intestine, and excreted into the blood stream (Fig. 5A). The acetate was then absorbed by tissues including the liver, and would have been activated to acetyl-CoA with the concomitant formation of AMP by the catalytic activity of AceCS in the cytosol. The increase in AMP concentration led to an increase in the AMP/ATP ratio, following the phosphorylation of AMPK, which is its active form, in the liver.
AMPK acts as the key metabolic “master switch” and regulates a number of enzymes involved in lipid homeostasis.\textsuperscript{15–22} It has been reported that the activation of AMPK led to the inactivation of acetyl-CoA carboxylase by phosphorylation, blocking fatty acid synthesis, and by decreasing intracellular malonyl-CoA, permitting the activation of carnitine palmitoyl-CoA transferase I and fatty acid oxidation to generate energy and enhance energy expenditure system.\textsuperscript{17,18} It has recently been reported that carbohydrate-responsive element-binding protein (ChREBP) was also phosphorylated by AMPK.\textsuperscript{14} ChREBP, a newly discovered transcription factor, plays an essential role in glucose-induced L-PK gene transcription by binding to the carbohydrate-responsive element of the L-PK promoter.\textsuperscript{10} Furthermore, ChREBP has been revealed to activate the transcription of genes involving lipogenesis, including ACC, ME, G6PD, FAS, ACL as well as L-PK.\textsuperscript{12} Kawaguchi et al.

**Fig. 4.** Histological Sections of the Liver from LETO, Water-Administered OLETF, and 5.2 mg/kg BW of Acetate-Administered OLETF Rats.

A, Hematoxylin and eosin staining (×200 magnification). B, Oil red O staining (×200 magnification).

**Fig. 5.** Stimulation of AMP/ATP Ratio in the Liver after an Oral Administration of Acetate.

The effect is shown of an acetate injection on (A) the plasma acetate concentration, (B) adenine nucleotide content in the liver, and (C) AMP/ATP ratio. Acetate at concentrations of 2.6, 5.2, and 10.5 mg/kg BW were orally injected into 10-week-old male SD rats (body weight, 350–450 g; \( n = 5–7 \) for each point). Blood samples were obtained from the jugular vein at each time point indicated after injecting individual rats. The liver was excised at each time point indicated after injecting 10.5 mg/kg BW of acetate into an individual rat, frozen, lyophilized, and then the nucleotides were extracted. Each data value is expressed as the mean ± SE of 5–7 rats. \(* p < 0.05; ** p < 0.01; *** p < 0.001; \) compared with the 0 min point for the control rats. (D) Phosphorylation of AMPK\(\alpha\) and total protein level of AMPK\(\alpha\) are shown in the liver of the water- or acetate-injected OLETF rats and LETO rats at 32 weeks of age. The liver was excised 24 hr after injecting water or acetate.
have shown that the administration of a variety of fatty acids, including acetate, octanoate and palmitate, to hepatocytes overexpressing ChREBP resulted in an inhibition of the glucose activation of L-PK gene expression. The mechanism for ChREBP inhibition by fatty acids appears to have been mediated by the phosphorylation of ChREBP by AMPK. The phosphorylation of ChREBP by AMPK resulted in the inhibition of its DNA-binding activity and decreased transcription activation of the L-PK gene. As expressed in Fig. 6, fatty acid was synthesized from excess carbohydrate in the liver. Glucose incorporated in the liver is metabolized by glycolysis to pyruvate, a process requiring the action of pyruvate kinase. After pyruvate has been formed in the cytosol, pyruvate enters the mitochondria to form citrate, which leaves the mitochondria to generate cytosolic acetyl-CoA, and malonyl-CoA is then generated to finally synthesize fatty acid. The ingested acetate activates AMPK by increasing the AMP/ATP ratio in the liver, the phosphorylation of ChREBP then occurring, and the transcripts of lipogenic genes might be decreased.

Acetate administration protected the OLETF rats against obesity. Acetate contributed to lowering the accumulation of abdominal fat and protected from the accumulation of lipid in the liver. Under lipogenic conditions, the synthesis of several lipogenic enzymes, including ACC, FAS, ACL, ME, G6PD and LPK, is induced. The transcripts of lipogenic genes in the liver were decreased in the acetate-administered OLETF rats. The observation that acetate administration did not affect the expression of SREBP-1 would reflect the results of the previous report that the reduced lipogenic enzyme expression in ChREBP-/- mice had been a direct effect of ChREBP rather than a secondary response mediated by reduced SREBP-1 expression. An accumulation of excess lipid in the liver or skeletal muscle disturbs insulin signaling. So the effect of acetate on the marked reduction of lipid content in the adipose tissue and liver might contribute to improving glucose tolerance and insulin resistance as the secondary effect on OLETF rats. The direct effect of acetate on anti-diabetes should be investigated further for OLETF rats. Indeed, an amelioration of hyperglycemia in diabetic KK-A(y) mice through the activation of hepatic AMPK by acetate has been recently reported.

The data obtained here prompt the suggestion that acetate had a profound anti-obese and anti-diabetic function in animal models of obesity and type 2 diabetes.

Acknowledgments

We thank Dr. Masaaki Mori of the Department of Nursing at Okayama Prefectural University for his technical advice. We also thank Ms. Sachiko Kanoh, Ms. Emi Ota, Ms. Rie Kimura, and Ms. Makiko Yamato of the Department of Nutritional Science at Okayama Prefectural University for their technical assistance. This work was supported in part by grant-aid for scientific research from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

References


