Overexpression of human adiponectin in transgenic mice results in suppression of fat accumulation and prevention of premature death by high-calorie diet

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Am J Physiol Endocrinol Metab 293: E210–E218, 2007. First published March 27, 2007; doi:10.1152/ajpendo.00645.2006.—Adiponectin, a physiologically active polypeptide secreted by adipocytes, shows insulin-sensitizing, anti-inflammatory, and antiatherogenic properties in rodents and humans. To assess the effects of chronic hyperadiponectinemia on metabolic phenotypes, we established three lines of transgenic mice expressing human adiponectin in the liver. When maintained on a high-fat/high-sucrose diet, mice of two lines that had persistent hyperadiponectinemia exhibited significantly decreased weight gain associated with less fat accumulation and smaller adipocytes in both visceral and subcutaneous adipose tissues. Macrophage infiltration in adipose tissue was markedly suppressed in the transgenic mice. Expression levels of adiponectin receptors were not altered in skeletal muscle or liver. Circulating levels of endogenous adiponectin were elevated, whereas fasting glucose, insulin, and leptin levels were reduced compared with control mice. In the hyperadiponectinemic mice daily food intake was not altered, but oxygen consumption was significantly greater, suggesting increased energy expenditure. Moreover, high-calorie diet-induced premature death was almost completely prevented in the hyperadiponectinemic mice in association with attenuated oxidative DNA damage. The transgenic mice also showed longer life span on a conventional low-fat chow. In conclusion, transgenic expression of human adiponectin blocked the excessive fat accumulation and reduced the morbidity and mortality in mice fed a high-calorie diet. These observations may provide new insights into the prevention and therapy of metabolic syndrome in humans.

adipocyte; macrophage; life span; 8-hyrox-2-deoxyguanosine

RESTRICTION OF CALORIC INTAKE retards age-related changes and extends the maximum life span in mammals (22, 37). The longevity is associated with a reduction in steady-state oxidative damage to proteins, lipids, and DNA in animals subjected to restricted caloric intake (13). These decreases in oxidative damage may be attributable to a decrease in the mitochondrial free radical generation rate in various tissues (4). Conversely, obese rats fed a high-calorie diet ad libitum have a shorter life span than their lean counterparts fed a low-calorie diet (36). The excessive production of oxidative stress resulting from high caloric intake may play a role in the premature death.

Metabolic syndrome associated with obesity is a growing cause of morbidity and mortality in humans (16, 18). Accumulating evidence has revealed that a reduction in the serum level of adiponectin, a bioactive peptide secreted by adipocytes, is involved in the development of metabolic syndrome and the acceleration of atherosclerosis. The serum level of adiponectin is decreased in patients with obesity (1), type 2 diabetes (17), and coronary artery disease (17), all of which are closely related to insulin resistance. Administration of adiponectin reduces plasma glucose and increases insulin sensitivity in mice (5, 11, 43).

A highly efficient expression strategy is required to generate transgenic (Tg) mice with hyperadiponectinemia, because the normal adiponectin concentration is extremely high compared with the concentrations of other hormones or cytokines. In the present study, we explored the long-term in vivo effects of hyperadiponectinemia by successfully establishing human full-length adiponectin Tg mice that exhibited significant hyperadiponectinemia for the first time. We used a construct containing a human adiponectin cDNA because the human peptide is known to act on mouse (6, 30) and is distinguishable from endogenous mouse adiponectin using specific assay systems. We hypothesized that the overexpression of adiponectin reduces oxidative DNA damage and extends life span and thus measures urinary excretion of 8-hydroxy-2-deoxyguanosine (8-OHdG), which is a reliable marker of in vivo oxidative DNA damage (10, 12, 21, 35).

MATERIALS AND METHODS

Generation of Tg mice. A human full-length adiponectin cDNA isolated by reverse transcription-PCR was subcloned into a multiple cloning site of pBluescript (Stratagene Japan, Tokyo, Japan). A fusion gene comprising the human serum amyloid P component promoter, which is highly specific to the liver (28, 34), and the cDNA encoding human full-length adiponectin was designed so that the adiponectin expression was targeted to the liver (29). We confirmed that the fusion gene had no errors by direct sequencing. A purified HindIII-Xhol fragment was microinjected into the pronucleus of fertilized C57BL/6N mouse (Clea, Tokyo, Japan) eggs, and viable eggs were transferred into the oviducts of pseudopregnant female ICR mice (Oriental Yeast, Tokyo, Japan) by use of standard techniques. Tg founder mice were identified by PCR of their tail DNA by using specific primers (5'‐gaatgcggctcattgtgtggtgtga‐3' and 5'‐aggactc‐gatcagttggtgtcatgta‐3') for the human full-length adiponectin cDNA.

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Mice with transgene expression were bred to C57BL/6N mice, and three independently derived lines of Tg mice, designated lines 3, 11, and 13, were established. All mice were treated in accordance with the guidelines for the care and use of laboratory animals of Kurume University School of Medicine and based on the National Institutes of Health Guidelines.

**Northern blot analysis.** To create probes for Northern blot analysis, PCR products amplified with primers 5'-tgcttggagtctccggctgtt-3' and 5'-agtattcgggctcaggatgctgtt-3' for human adiponectin, 5'-tgtacagagaagctgaca-3' and 5'-tctcagcatcaaggagacaggagacggcctcggctctg-3' for mouse adiponectin receptor 1, and 5'-aggtcctgatcagttggtgtcatggta-3' for mouse adiponectin receptor 2 were subcloned into the TA cloning system pCR2.1 (Invitrogen Japan, Tokyo, Japan) and then digested with EcoRI (Takara, Tokyo, Japan). Total RNA extracted by RNeasy Mini Kit (Qiagen, Valencia, CA) was electrophoresed in a formaldehyde-agarose gel, transferred to a nitrocellulose membrane (GE Healthcare Biosciences, Piscataway, NJ) in 20× saline sodium citrate, and immobilized by ultraviolet light. Probe labeling, prehybridization, hybridization, washing, and signal detection were carried out using an enhanced chemiluminescence (ECL) system (GE Healthcare Biosciences) according to the manufacturer’s recommended protocol.

**Diet studies.** Twenty-four male and 24 female wild-type (WT) mice, 24 male and 24 female mice in line 11, 16 male and 16 female mice in line 13, and six male mice in line 3 were randomly divided into two groups at the age of 6 wk. One group was fed the regular chow of 352 kcal/100 g containing 5% fat (fish oil, soybean oil, etc.), 52% carbohydrates, and 25% protein (Clea) throughout the experiment, whereas the other group was fed the regular chow for 2 wk and maintained on 592 kcal/100 g of a high-fat/high-sucrose (HF/HS) diet containing 70% fat (mainly lard), 14% sucrose, 3% other carbohydrates, and 13% protein (Oriental Yeast) from 8 wk of age.

**Energy balance studies.** Body weights were measured at 11 AM twice/wk, starting from 8 wk of age. Food consumption per 24 h was measured at 10 wk of age in male WT mice and Tg mice in each line (n = 6), and the average daily consumption was calculated. Before the measurement of food intake, each mouse was housed in an individual cage for 3 days. The oxygen consumption rate of six male WT mice, eight male mice in line 3, eight male mice in line 11, and four male mice in line 13 was evaluated using a metabolism measurement system (Model MK-5000; Muromachi-kikai, Tokyo, Japan) at 24°C as described previously (27).

**Assays.** The serum levels of human and mouse adiponectin of each group (n = 8) were measured with specific ELISA kits for human adiponectin (Otsuka, Tokushima, Japan) and mouse adiponectin (AdipoGen, Seoul, Korea), respectively, without detectable cross-reactivity (Fig. 1, A and B). Isoforms of circulating human adiponectin, i.e., high-, middle-, and low-molecular-weight forms, were analyzed by an enzyme immunoassay (Adiponectin Multimetric ELA; Daiichi, Tokyo, Japan). The mouse leptin and insulin levels were determined using ELISA kits obtained from Genzyme (Cambridge, MA) and Shibayagi (Gunma, Japan), respectively. The plasma glucose levels were measured by the glucose dehydrogenase method.

**Visceral and subcutaneous fat mass.** The entire omentum and mesentery fat pad covering the fat depots from the subgastric region to the cecal region were removed en bloc and weighed. Subcutaneous fat was also removed and weighed. The upper portion of the subcutaneous fat was the caudal border of the xiphoid process of the sternum, the lower portion was the urogenital organs, and the side portions were the dorsal and ventral midlines of the body (44).

**8-OHdG measurement.** Urine samples of each group (n = 8) were collected after an overnight fast and centrifuged at 2,000 g for 5 min to remove any suspended cell debris. The supernatants were used for determination of the 8-OHdG levels with a competitive ELISA kit (Japan Institute for the Control of Aging, Shizuoka, Japan).

**Western blot analysis.** Tissue sections of each group (n = 4) were lysed in ice-cold 0.5 mmol/l Tris-HCl buffer (pH 6.8) containing 2% sodium dodecyl sulfate, 6% β-mercaptoethanol, and 10% glycerol. The lysate was centrifuged for 30 min at 20,000 g at 4°C, and the supernatant was collected. After being heated at 100°C for 5 min, proteins were separated by 4–20% SDS-PAGE (Daiichi) and transferred to a nitrocellulose membrane (GE Healthcare Biosciences). The membrane was incubated with a polyclonal rabbit antibody raised against the NH2 terminus (GCRYADNDNSTFTGFLYHDTN) of human adiponectin at 4°C overnight. After being washed, the membrane was incubated with peroxidase-conjugated goat anti-rabbit IgG (Wako, Osaka, Japan) and then visualized using the ECL system.

**Histological analysis of adipose tissue.** Subcutaneous and visceral fat pads of each group (n = 3) were fixed in Bouin’s solution, embedded in paraffin, and sectioned. The sections were stained with hematoxylin and eosin (HE). Dieters of 100 adipocytes in each HE-stained specimen were measured using a micrometer (XY11; MeCan Imaging, Saitama, Japan). To detect macrophage infiltration, paraffin sections of visceral adipose tissue were immunostained by anti-mouse MAC-2 monoclonal antibody (Cedarlane, Burlington, ON, Canada) and rat secondary antibody combined with amino acid polymers and peroxidase (Cosmo Bio, Tokyo, Japan).

**Statistical analysis.** Data were expressed as means ± SE. Comparisons between two groups were performed with unpaired Student’s t-test and one-way ANOVA followed by the Bonferroni post hoc test when differences between more than two experimental groups were analyzed. The chi-square test was used to compare frequencies. A P.
value <0.05 was considered statistically significant. All analyses were performed using the SPSS statistical software package (version 11.5; SPSS, Chicago, IL).

RESULTS

Generation of Tg mice with hyperadiponectinemia. We established three lines of Tg mice (lines 3, 11, and 13) expressing human full-length adiponectin under the control of the serum amyloid P component promoter. Human adiponectin transcripts were expressed exclusively in the liver at high levels in lines 11 and 13 and at low levels in line 3 (Fig. 2A). No human adiponectin expression was detected in skeletal muscle, visceral fat, spleen, or brain (data not shown). Western blot analysis showed adiponectin protein in sera of Tg mice (Fig. 2B). Human adiponectin-specific ELISA exhibited serum levels of 1.6 ± 0.2, 115.2 ± 11.6, and 122.8 ± 7.5 μg/ml in 10-wk-old mice in lines 3, 13, and 11, respectively (Fig. 2D). Thus, Tg mice in lines 11 and 13 had significantly higher endogenous adiponectin levels than line 3 WT mice, suggesting a positive correlation between the serum levels of transgenically expressed adiponectin and those of endogenous adiponectin. Furthermore, mRNA levels of adiponectin receptor 1 and adiponectin receptor 2 in the liver and skeletal muscle from line 11 mice were almost identical to those of WT mice (Fig. 3, A and B). Because the Tg expression of adiponectin was minimal in

Table 1. Serum protein and liver function

<table>
<thead>
<tr>
<th></th>
<th>Total Protein, g/dl</th>
<th>Albumin, g/dl</th>
<th>Aspartate Aminotransferase, IU/l</th>
<th>Glutamic Pyruvic Transaminase, IU/l</th>
<th>γ-Glutamyl Transferase, IU/l</th>
<th>Alkaline Phosphatase, IU/l</th>
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<tbody>
<tr>
<td>WT (n = 6)</td>
<td>4.8±0.1</td>
<td>3.0±0.1</td>
<td>45±20</td>
<td>29±1</td>
<td>0.0±0.0</td>
<td>164±6</td>
</tr>
<tr>
<td>Line 11 (n = 6)</td>
<td>4.9±0.1</td>
<td>3.1±0.1</td>
<td>58±17</td>
<td>17±2</td>
<td>0.2±0.1</td>
<td>170±18</td>
</tr>
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Values represent means ± SE. WT, wild type. All mice were 16 wk of age and supplied with regular chow ad libitum.
Fig. 3. Northern blot analysis of adiponectin receptor 1 mRNA (A) and receptor 2 mRNA (B) using 20 μg total RNA each from the liver or the skeletal muscle of male WT and line 11 mice aged 10 wk. These Northern blots were performed at least 3 times with essentially the same results. There was no apparent difference in expression levels of adiponectin receptor 1 or adiponectin receptor 2 between WT and line 11 mice.

line 3, we further analyzed phenotypes of Tg mice in lines 11 and 13.

Body weight of mice fed the regular or high-calorie diet. When the mice were supplied with the regular chow ad libitum, no significant difference was observed in body weight among WT mice in lines 11 and 13 and WT mice up to the age of 45 wk (Fig. 4, A and C). A remarkable difference in weight was observed when the mice were fed the HF/HS diet from 8 wk of age. WT mice showed a rapid difference in weight was observed when the mice were fed the HF/HS diet up to the age of 45 wk (Fig. 4, A).

We also measured the body weight of six male mice in line 3, in which only a trace amount of human adiponectin was expressed, up to the age of 45 wk. No significant difference was obtained for the weights at each age between WT and line 3 on the regular chow or on the HF/HS diet (Fig. 4, A and B).

Fat distribution, adipocyte size, and organ weight. Male WT and Tg mice were fed the HF/HS diet from 8 wk of age and killed at 20 wk of age to assess their fat distribution and adipocyte size. Both visceral and subcutaneous fat accumulations were significantly greater in WT mice and Tg mice in line 3 than in Tg mice in lines 13 and 11 (Fig. 5A). The adipocyte diameters of visceral fat in WT and line 11 mice were 164.6 ± 7.4 and 54.9 ± 2.4 μm, respectively (P < 0.0001, Fig. 5B), and those of subcutaneous fat were 155.3 ± 6.1 and 38.3 ± 1.4 μm, respectively (P < 0.0001). The weights of the liver, kidneys, heart, spleen, and digestive tracts did not differ significantly between WT and Tg mice in lines 11 and 13 (Fig. 6, A).

Body weight of mice fed the regular or high-calorie diet. When the mice were fed the regular chow ad libitum, no significant difference was observed in body weight among WT, Tg, and three lines of Tg mice when the mice were fed the HF/HS diet (Fig. 4, B and D). Moreover, differences in body weight between line 11 and line 13 on the HF/HS diet reached statistical significance from 20 wk of age. We also measured the body weight of six male mice in line 3, in which only a trace amount of human adiponectin was expressed, up to the age of 45 wk. No significant difference was obtained for the weights at each age between WT and line 3 on the regular chow or on the HF/HS diet (Fig. 4, A and B).

Glucose, leptin, and insulin levels. No significant difference was observed in fasting plasma glucose levels among WT mice and Tg mice in lines 11 and 13. In contrast, when maintained on the high-calorie diet, Tg mice in lines 11 and 13 had lower fasting plasma glucose levels than WT mice and Tg mice in line 3 at the age of 20 wk. Line 11 mice fed the regular chow showed comparable levels of leptin and insulin with WT mice (Fig. 6, B and C). On the high-calorie diet, however, 20-wk-old Tg mice in lines 11 and 13 exhibited significantly lower levels
of leptin than age-matched WT mice (Fig. 6B). Serum insulin levels were also significantly lower in Tg mice in lines 11 and 13 than in WT mice (Fig. 6C). Levels of leptin and insulin were lower in line 11 than in line 13, in accordance with the higher human adiponectin concentration in line 11.

Food intake and oxygen consumption. Daily food intake was measured at 10 wk of age when the body weights did not differ significantly among WT mice and Tg lines (Fig. 7A). We found no significant difference in food ingestion among the four groups on either the regular chow or the high-calorie diet. To elucidate the mechanism underlying the antiobesity effect under the high-calorie condition, we measured the daily oxygen consumption rate of 10-wk-old male mice fed the HF/HS diet. The oxygen consumption rate proved to be greater in hyperadiponectinemic Tg mice (lines 11 and 13) than in WT mice and mice in line 3 (Fig. 7B).

Suppression of macrophage infiltration in adipose tissue. Macrophage was immunostained with monoclonal anti-mouse MAC-2 antibody in visceral adipose tissues of male WT mice and Tg mice in line 11 fed the regular chow or the HF/HS diet. Scattered foci of macrophage aggregates were observed around adipocytes in all three WT mice fed the HF/HS diet and in two of three WT mice fed the regular chow (Fig. 8). In contrast, MAC-2-expressing cells were not observed in adipose tissues from hyperadiponectinemic Tg mice, irrespective of diet content (n = 3 each).

Life span of hyperadiponectinemic mice. The observation that most WT mice fed the HF/HS diet died at ~1 yr of age prompted us to compare the life span between WT mice and Tg mice on the HF/HS diet. A survival rate analysis revealed that the life span was increased about twofold in male Tg mice in lines 11 and 13 compared with male WT mice (Fig. 9A). All 12
male mice in the WT group died before 82 wk of age, showing a gradual weight loss without glycosuria during their final few weeks, whereas 11 of 12 male mice in line 11 and seven of eight male mice in line 13 survived up to 100 wk of age ($P < 0.0001$).

The longevity was also increased in Tg mice in lines 11 and 13 fed the regular chow. When maintained on the conventional chow, 10 of 12 WT mice died before the age of 120 wk, whereas seven of 11 mice in line 11 and seven of eight mice in line 13 survived up to 120 wk ($P = 0.005$), and one mouse in line 11 and two mice in line 13 were still alive at the age of 155 wk (Fig. 9B).

**Urinary 8-OHdG excretion.** We measured the urinary levels of 8-OHdG, a product of DNA oxidation, at 20 wk of age.
There was no significant difference in the 8-OHdG levels between WT and line 11 mice on the regular chow. When WT mice were fed the HF/HS diet from 8 wk of age, they excreted high levels of 8-OHdG. However, the high-calorie diet-induced increase in urinary 8-OHdG was markedly suppressed in Tg mice in both line 13 and line 11.

DISCUSSION

Rodent models of chronic hyperadiponectinemia have not previously been available, probably due to the difficulty associated with exceeding the normal plasma level of adiponectin, which is the most abundant bioactive peptide in plasma. In the present study, we successfully established hyperadiponectinemic mice with transgenic expression of full-length human adiponectin in the liver and studied the metabolic phenotypes of the mice over a long period of time to evaluate the effects of persistent hyperadiponectinemia. It has been shown (6, 30) that human adiponectin is biologically active in mice. The major finding of this study is that the hyperadiponectinemic mice were almost completely protected against the body weight gain and premature death caused by the HF/HS diet.

Effects of adiponectin on body weights have been controversial. Some studies have shown that body weights were not changed in adiponectin knockout mice or rats with transient adiponectin overexpression (23–25, 32). However, Streeper et al. (33) recently showed that body weights of adiponectin knockout mice fed high fat were greater than those of control mice.

In this study, significant difference in body weight and in adipocyte size between Tg mice with high adiponectin expression (lines 11 and 13) and WT mice was observed only when mice were fed the HF/HS diet. Hence, the effect of adiponectin on weight gain may be, at least partly, dependent on the nutritional condition. Although the serum levels of human adiponectin were not significantly different between line 11 and line 13 at the age of 10 wk, Tg mice in line 11 showed higher human adiponectin levels than those in line 13 at the age of 20 wk. This may account for the differences in body weights, fat accumulations, and fasting levels of glucose, insulin, and leptin between line 11 and line 13.

In the hyperadiponectinemic mice, daily food intake was not altered, but oxygen consumption was significantly greater than in WT mice, suggesting that the less weight gain is attributable to increased energy expenditure. However, no significant difference was observed in oxygen consumption rate between line 11 and line 13. Hyperadiponectinemia might augment physical activity of mice, and the body weight difference between the lines on the HF/HS diet is possibly attributable to a difference in activity. It is not known whether the smaller size of adipocytes in adiponectin Tg mice can be explained merely by the altered energy balance. Adipocytes were apparently increased in number in hyperadiponectinemic Tg mice fed the HF/HS diet, raising the possibility that hyperadiponectinemia may be involved in the regulation of adipocyte number. Further studies are needed to define the precise role of adiponectin in adipocyte differentiation.

Recently, it has been demonstrated that macrophage accumulation in the adipose tissue of obese subjects may increase the production of proinflammatory cytokines and thereby contribute to the pathophysiological consequences of obesity (7, 38, 41). In this study we found scattered aggregates of MAC-2-expressing macrophages in adipose tissue from WT mice.
Surprisingly, MAC-2-positive cells were completely absent in the adipose tissue from the adiponectin Tg mice even when fed the HF/HS diet. Thus high levels of adiponectin may exert favorable effects on metabolism through the suppression of macrophage infiltration in adipose tissue. The anti-inflammatory effects of adiponectin could be associated with the regulation of adipocyte differentiation and fat accumulation.

Caloric restriction has proved to be a successful anti-aging strategy that significantly extends the life span and reduces age-related diseases in rodents (3). Conversely, high-calorie diet is associated with an increased risk of mortality in both humans and rodents. In the present study, WT mice, which lived for ~100 wk on the regular chow, showed a shorter life span of ~50 wk on the HF/HS diet. However, the high-calorie diet-induced premature death was almost completely prevented in Tg mice with hyperadiponectinemia. Moreover, the life span extension in lines 11 and 13 was also observed on the regular chow. Thus, in addition to the decreased fat accumulation, adiponectin itself may possess beneficial effects on the longevity regardless of adiposity and diet contents.

Since atherosclerotic lesions, which represent a common cause of mortality in obese humans, hardly develop in mice due to their extremely low levels of serum LDL cholesterol, we focused on the role of oxidative DNA damage. Oxidative DNA lesions are supposed to play central roles in the aging process as well as in the development of various diseases, including cancer, inflammation, and atherosclerosis (8, 14, 19, 39). Reactive oxygen species (ROS) induce several types of DNA damage. Although human adiponectin was shown to produce 8-OHdG, which is stable and excreted in the urine without being metabolized (42). Hence, urinary 8-OHdG serves as a reliable biomarker of oxidative DNA damage in vivo (15, 20, 26, 31, 40). As expected, the urinary levels of 8-OHdG were markedly elevated in 20-wk-old WT mice maintained on the HF/HS diet for 12 wk. However, the hyperadiponectinemic Tg mice showed distinctly lower levels of urinary 8-OHdG than WT mice despite equivalent intake of the HF/HS diet. Although 8-OHdG levels were not significantly different when maintained on the regular chow, attenuation of oxidative DNA damage may be a mechanism by which hyperadiponectinemia prevented premature death induced by the high-calorie diet.

Another interesting observation that may have potential pathophysiological implications is that the plasma level of endogenous mouse adiponectin was elevated in the human adiponectin Tg mice, indicating a lack of negative feedback regulation. The smaller size of adipocytes and the lack of macrophage infiltration in adipose tissue may be associated with the higher endogenous adiponectin levels. It may be plausible to suppose that transgenically expressed adiponectin efficiently exerts its beneficial effect through increasing total levels of circulating adiponectin.

In conclusion, Tg expression of human adiponectin in mice blocked the excessive accumulation of subcutaneous and visceral fat and prevented premature death especially induced by high-calorie diet probably through the attenuation of oxidative DNA damage. Although human adiponectin was shown to exert favorable effects in mice in vivo, the possibility remains that the use of human adiponectin cDNA might emphasize a facet of adiponectin actions due to potential interspecies differences. Nevertheless, the marked resistance of Tg mice against high-calorie diet-induced mortality and morbidity was likely to be attributable to the elevated level of human adiponectin. Thus the observations in mice with persistent hyperadiponectinemia may provide new insights into the prevention and therapy of metabolic syndrome in humans.

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