Hypertension
JOURNAL OF THE AMERICAN HEART ASSOCIATION
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Hypertension 2006;48;51-57; originally published online May 22, 2006;
DOI: 10.1161/01.HYP.0000225402.69580.1d
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Telmisartan Prevents Obesity and Increases the Expression of Uncoupling Protein 1 in Diet-Induced Obese Mice

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Abstract—The aim of the present study was to clarify the effect of telmisartan, an angiotensin II receptor blocker, on the development of obesity and related metabolic disorders in diet-induced obese mice. Treatment with telmisartan dissolved in drinking water at a dosage of 5 mg/kg per day for 14 days attenuated the diet-induced weight gain without affecting food intake in diet-induced obese mice compared with controls using nontreated water. Telmisartan treatment decreased the weight of visceral adipose tissue and the triglyceride content in the liver and skeletal muscle. In addition, hyperglycemia, hyperinsulinemia, and hypertriglyceridemia in diet-induced obese mice all improved with telmisartan treatment. Furthermore, telmisartan treatment increased adiponectin mRNA in visceral white adipose tissue and was associated with a concomitant change in the serum adiponectin level. In contrast, the treatment reduced the serum level of resistin. Finally, telmisartan treatment increased the mRNA expression of uncoupling protein 1 in brown adipose tissue and was accompanied by an increase in oxygen consumption. In conclusion, telmisartan treatment might prevent the development of obesity and related metabolic disorders by altering the levels of adiponectin, resistin, and uncoupling protein 1 in diet-induced obese mice. Our results indicate that telmisartan can be used as a therapeutic tool for metabolic syndrome, including visceral obesity. (***Hypertension*****. 2006;48:51-57.)**

Key Words: obesity ■ hypertension, obesity ■ metabolism ■ insulin resistance ■ adipose tissue

The renin–angiotensin system (RAS) is expressed in adipose tissue.[1,2] Recent studies have revealed the importance of the RAS as a pathogenetic factor in the development of obesity and related metabolic disorders, including insulin resistance.[3,4] Marked increases in the plasma concentration of angiotensin II (Ang II) have been observed in diet-induced obese (DIO) rats.[5] Based on this background, the use of Ang II receptor blockers (ARBs), which are antihypertensive medications, has received a great deal of attention as a therapeutic tool for obesity-related metabolic disorders.

Vitale et al demonstrated that telmisartan, an ARB, can improve insulin sensitivity and reduce the incidence of type 2 diabetes in patients with hypertension.[6] In rats fed a high-fat, high-carbohydrate diet, orally administered telmisartan has been shown to reduce weight gain and improve the high levels of serum glucose, insulin, and triglyceride (TG).[7] Peroxisome proliferator-activated receptor (PPAR)-γ has been assumed to be one of the targets for the metabolic effects of telmisartan, which is structurally similar to a PPAR-γ agonist.[7] In fact, telmisartan treatment in vitro augmented the PPAR-γ activity.[7,8] These results provided evidence that telmisartan exerts its pharmacological effect on adipocytes.

Adipose tissue is an endogenous source of circulating lipids as well as the site of the production and secretion of several hormones and cytokines, including adiponectin and resistin.[9,10] Recent studies have demonstrated that these adipose-derived signaling molecules are likely to play a key role in the complex network modulating obesity and related disorders, including insulin resistance and inflammation.[11,12] In a previous study, adiponectin was found to reduce body adiposity by affecting the mRNA expression of uncoupling proteins (UCPs) in brown adipose tissue (BAT), white adipose tissue (WAT), and skeletal muscle.[13] In particular, UCP1 in BAT is a crucial factor of energy expenditure, and the expression of the molecule is regulated by humoral and neuronal factors.[14] These findings suggest that adiponectin and UCP1 may be related to the pathogenesis of obesity-related metabolic disorders and that the signaling network composed of adipocytokines and UCP1 may play an important role in the pharmacological effect of telmisartan on obesity-related metabolic disorders.

To address this issue using DIO diabetic mice, we investigated the effects of telmisartan on the following: food intake; body weight changes; serum metabolic parameters such as glucose, insulin, and TG; adiposity in WAT; UCP1 expression in BAT; oxygen consumption; and the respiratory quotient. The goal of the present study was to confirm the usefulness of telmisartan as a therapeutic tool for obesity and related metabolic disorders.

Received February 27, 2006; first decision March 9, 2006; revision accepted April 21, 2006.
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Hypertension **is available at http://www.hypertensionaha.org** **DOI: 10.1161/01.HYP.0000225402.69580.1d**

Methods

Animals

Mature male mice (C57Bl/6N; Seac Yoshitomi, Fukuoka, Japan) (n=8 or 14 for each group) were housed in a light-, temperature-, and humidity-controlled room (12-hour light:12-hour dark cycle, lights on/off at 0700/1900 hour; 21±1°C; 55±5% relative humidity). The mice were allowed free access to standard laboratory food (CLEA Japan, Tokyo, Japan), 60% high-fat food (Cat. No. D12492: 20% protein, 20% carbohydrate, and 60% fat, 5.2 kcal/g; Research Diet, Tokyo, Japan), and water. The high-fat food contained soybean oil (25/773.85 g) and lard (245/773.85 g). All animals were treated in accordance with the Oita University Guidelines for the Care and Use of Laboratory Animals based on the National Institutes of Health (NIH) Guide for the Care and Use of Laboratory Animals.

Telmisartan Preparation

Telmisartan (Yamanouchi Pharm, Tokyo, Japan) was dissolved in phosphate-buffered saline (PBS) containing ethyl-cellulose (adjusted pH 6.8 to 7.4). Each solution was prepared on the day it was administered.

Chronic Telmisartan Treatment

Mice were selected and divided into treatment groups. High-fat food was administered for 6 weeks to mice that were 8 to 14 weeks old. Telmisartan was applied to the drinking water at a dosage of 5 mg/kg per day, and controls received untreated water for 14 consecutive days (last 2 weeks). The cumulative food intake was measured every 24 hours (once daily) for each of the 14 days of treatment. Body weight, histology of epididymal-WAT (epi-WAT), subcutaneous-WAT (sub-WAT), BAT UCP1, and epi-WAT adiponectin and resistin mRNA expression levels were measured in all animals at the end of the 14-day treatment period. WAT was dissected from epididymal fat located in the upper region of the testis as visceral fat (epi-WAT) and subcutaneous fat from the right femoral area (sub-WAT).

Sampling for Measurements

The mass of body fat was measured to assess changes in body fat accumulation in mice. The excision of BAT that located subscapular was dissected. The tissues were removed, weighed, immediately frozen in liquid nitrogen (LN_2), and stored at −80°C until mRNA extraction. Blood was withdrawn from the jugular vein, and the serum was separated and immediately frozen at −20°C until assayed. Levels of serum glucose, insulin, TG, and free fatty acids were measured using commercially available assay kits (Wako Chemical).

Histological Analysis

WAT samples were fixed with 10% formalin and embedded in paraffin. Twenty-micron sections were cut and stained with hematoxylin and eosin to examine the histology of the white adipocytes used in the analysis system (Olympus).

Triglycerides in Tissues

One hundred milligrams of skeletal muscle and liver were homogenized in 2 mL of a solution containing 150 mmol/L per liter NaCl, 0.1% Triton X-100, and 10 mmol/L/L Tris using a polytron homogenizer (NS-310E; Micro Tech Nichion) for 1 minute. The TG content was determined using a commercially available kit (Wako Chemical).

Indirect Calorimetry

The oxygen consumption and respiratory quotient were measured by indirect calorimetry using an open-circuit calorimetry system (Oxymax; Columbus Instruments Int. Corp). The respiratory quotient is the ratio of the volume of CO_2 produced to the volume of O_2 consumed. Locomotor activity (per 15 minutes) was measured by counting the number of times an animal broke a light beam (Sintekuno).

Real-Time Quantitative RT-PCR

UCP1, adiponectin, and resistin mRNA were amplified by PCR and quantified using real-time quantitative PCR as follows. Total cellular RNA was prepared from selected mouse tissues using TRIzol (Lifetech, Tokyo, Japan). The cDNA was synthesized from 150 ng of total RNA using a ReverTra-Dash reverse transcriptase kit (Toyobo). Primers were provided as preoptimized kits: adiponectin (cat. no. Mm00456425m1), resistin (cat. no. Mm00445641m1), and UCP1 (cat. no. Mm00494069m1). Primers for ribosomal RNA for use as internal controls were also provided as a preoptimized kit (cat. no. Hs99999901). Using an ABI PRISM 7000 sequence detector (Applied Biosystems), PCR amplification was performed in a 50-μL volume containing 100 ng cDNA template in PCR master mix (Roche). Target mRNA and ribosomal RNA values were calculated from standard curves obtained by amplification of 2-fold serial dilutions of cDNA from the tissues, and target mRNA amounts were normalized to ribosomal RNA. We verified that the cDNAs and ribosomal RNA were amplified with approximately the same efficiency. The results are expressed as the percent of ribosomal RNA–normalized target mRNA in experimental groups versus control groups. The results were analyzed using Sequence Detection Software (Applied Biosystems), as outlined in Perkin-Elmer's User Bulletin No. 2 (Perkin-Elmer).

Statistical Analysis

All data are expressed as the mean±SE. We used a repeated 2-way ANOVA with *a* post hoc Bonferroni test to analyze differences for multiple comparisons (StatView 4.0; SAS Inst.); a Mann–Whitney *U* test was used when appropriate.

Results

Effect of Telmisartan Treatment on Food Intake and Body Weight

Figure 1A shows the summation of the food intake during the 14-day period. There was no significant difference in the daily high-fat food consumption between telmisartan-treated (high-fat telmisartan, HFT) and non-treated (high fat, HF) animals ($P>0.1$). The change in body weight is shown in Figure 1B. Body weight gain in the HF group was significantly augmented compared with the control group fed a non-high-fat diet ($P<0.01$). Treatment with telmisartan (HFT) decreased the body weight compared with the non-treated HF group ($P<0.05$).

Effect of Telmisartan Treatment on Tissue Weight and WAT Morphology

Figure 2 shows the weight of the epi-WAT and sub-WAT removed from the mice. Both WAT weights in the HF group were higher than those in the control group ($P<0.05$ for each). Telmisartan treatment decreased both WAT weights compared with those in the non-treated HF group ($P<0.05$ for epi-WAT; $P<0.01$ for sub-WAT). Interestingly, the ratio of epi-WAT/sub-WAT was higher in the non-treated HF group than in the telmisartan-treated HFT group ($P<0.05$; Figure 2C). Figure 2D shows the morphology of the epi-WAT. Telmisartan treatment also decreased the weight of the liver but not the heart or kidney weight.

Effect of Telmisartan Treatment on Serum Parameters and the Expression of Adiponectin and Resistin mRNA in WAT

Serum glucose, insulin, TG, and free fatty acid levels increased in the HF group compared with the control ($P<0.01$

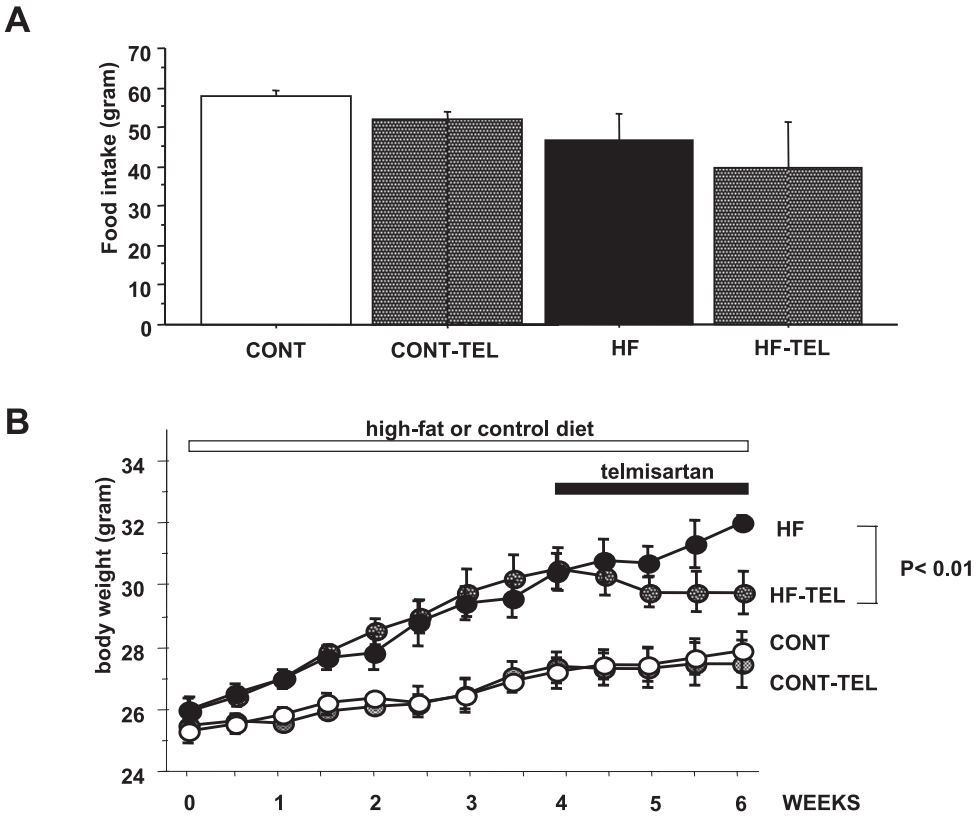

Figure 1. Effects of telmisartan on (A) cumulative food intake and (B) body weight change in diet-induced obese mice. The 4 groups of mice received the following: normal diet (CONT), normal diet with telmisartan (CONT-TEL), high-fat diet (HF), and high-fat diet with telmisartan (HF-TEL). Each value and vertical bar represents the mean±SE (n=8 for each group). Groups were compared by ANOVA with a post hoc Bonferroni test for independent samples.

for each group; Table). The changes in serum parameters were partially restored in the HFT group compared with the non-treated HF group ($P<0.05$ or $P<0.01$; Table). Liver and skeletal muscle TG contents were increased in the HF group compared with the control group ($P<0.01$ for each; Table). The changes in the TG content of each tissue were attenuated in the HFT group compared with the non-treated HF group ($P<0.05$ for each).

The levels of adiponectin mRNA and serum adiponectin were decreased in the HF group, and the levels of both were restored with telmisartan treatment. Conversely, the expression of resistin mRNA did not respond to high-fat diet or telmisartan; however, the serum level of resistin was increased in the HF group and was restored with telmisartan treatment.

The reduced serum adiponectin level in the HF group was also restored by treatment with pioglitazone, a full PPAR-γ agonist, and the non-PPAR-activating ARB candesartan. The elevated level of serum resistin in the HF group was also reduced by pioglitazone. In contrast, the level of serum resistin increased with candesartan treatment (data not shown).

Effect of Telmisartan Treatment on the Oxygen Consumption, Respiratory Quotient, and Expression of UCP1 mRNA in BAT

Treatment with telmisartan increased the UCP1 mRNA expression in BAT compared with the expression in the non-treated HF group, relative to the expression in the control group (HFT versus HF: 180.3±15.0% versus 130.2±11.3%, $P<0.05$; Figure 3). Telmisartan treatment increased the oxygen consumption compared with that in the non-treated controls at 01:00, 04:00, 10:00, 11:00, 13:00, 16:00, 17:00, 18:00, and 19:00 hours (Figure 4A), whereas telmisartan treatment decreased the respiratory quotient compared with that in the non-treated controls at 04:00, 11:00, 12:00, 13:00, 15:00, 16:00, 17:00, 19:00, and 20:00 hours (Figure 4B). The food intake and locomotor activity were not significantly changed by telmisartan treatment.

Discussion

The present study demonstrated that telmisartan reduces body weight without affecting food intake in DIO animals. The effect of telmisartan had been investigated previously,[7] but the organ contributing to this phenomenon had not been identified. The present study showed that telmisartan treatment reduces the tissue weight of WAT and the liver but does not affect other organs, such as the heart or kidneys. In particular, reduction of the adiposity of WAT and the liver may contribute to weight loss because the TG content in each tissue decreased after telmisartan treatment. An earlier study indicated that increased intramyocellular lipid represents an early abnormality in the pathogenesis of insulin resistance.[15] The removal of TG from the intraskeletal muscle in the present study improved hyperinsulinemia in DIO mice.

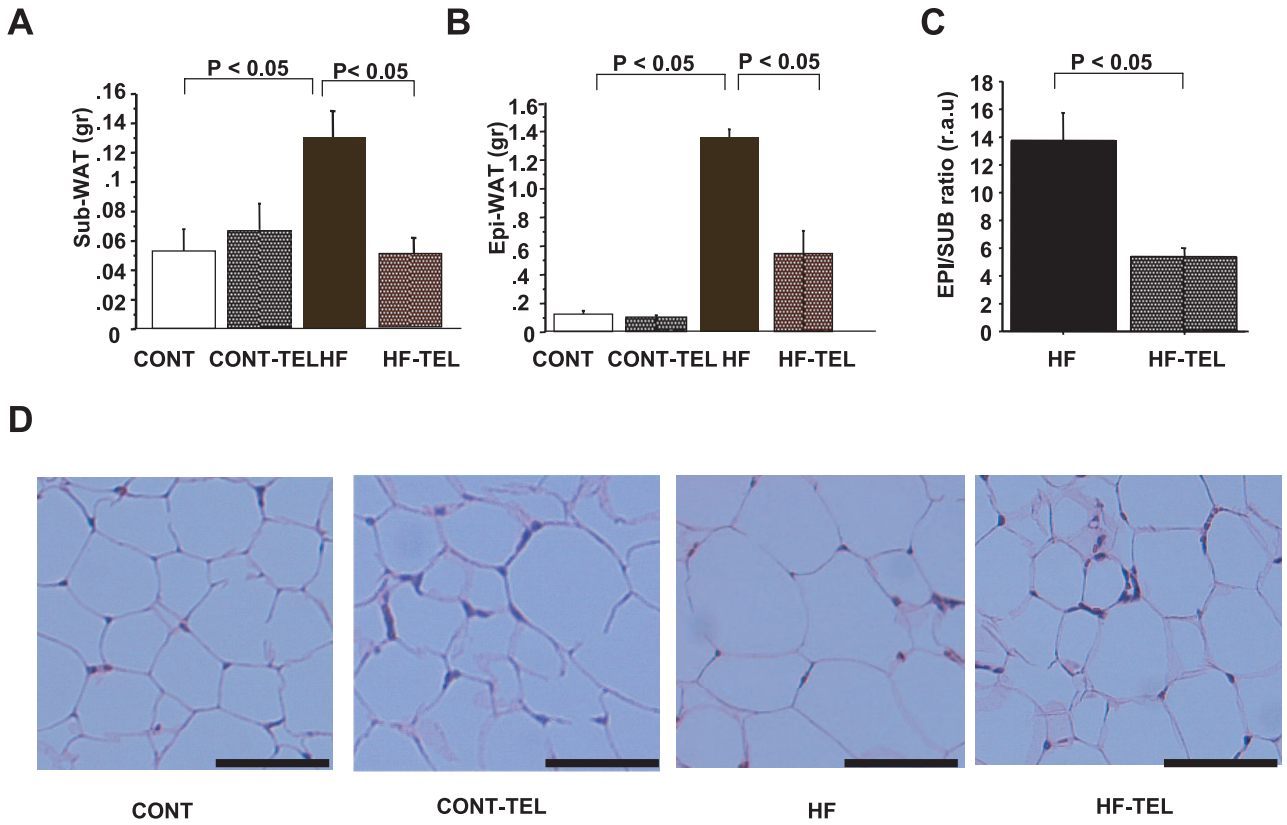

Figure 2. Effects of telmisartan on the weights of sub-WAT (A) and epi-WAT (B). The 4 groups of mice received the following: normal diet (CONT), normal diet with telmisartan (CONT-TEL), high-fat diet (HF), and high-fat diet with telmisartan (HF-TEL). (C) The weight ratio of epi-WAT/sub-WAT. (D) The morphology of epididymal WAT. Size bar denotes 100 μm. Each value and vertical bar represents the mean±SE (n=8 for each group). Groups were compared by ANOVA with a post hoc Bonferroni test for independent samples (A and B). Groups were compared using a Mann–Whitney *U* test (C).

The influence of telmisartan on adipose tissue is important because previous studies have suggested a direct effect of telmisartan on adipocytes.[7,16] In addition to the metabolic effects of telmisartan as a blocker of the Ang II receptor, its effects as a partial agonist of PPAR-γ must be considered. Telmisartan treatment in vitro has been shown to augment the expression of PPAR-γ as well as target genes, including adipocyte fatty acid–binding protein (aP2), adiponectin, and acetyl coenzyme A (CoA) carboxylase in murine and human adipocytes.[7] Our previous study showed that treatment with thiazolidine, a PPAR-γ agonist, reduced the hepatic TG content in Zucker fatty rats associated with a reduction of

Telmisartan and Metabolic Parameters. The Effect of Telmisartan on Serum Glucose, Insulin, TG, Free Fatty Acid, and Adipocytokine

Variable	CONT	CONT-TEL	HF	HF-TEL
Glucose, mg/dL	179±16	186±11	315±50*	257±33†
Insulin, ng/mL	0.9±0.1	0.7±0.1	1.4±0.2*	1.0±0.1†
TG, mg/dL	44±5.7	48±7.5	77±8.3*	58±3.3†
Free fatty acid, meq/L	0.3±0.1	0.4±0.04	1.2±0.2*	0.7±0.1†
Liver TG, mg/dL	16.3±2.1	15.3±1.9	37.5±3.9*	24.0±3.7†
Skeletal muscle TG, mg/dL	10.3±0.9	7.8±0.9	17.0±1.7*	12.3±1.2†
Adiponectin, mRNA/rRNA, r.a.u.%	100±11.4	91.5±7.8	59.5±5.1*	85.5±8.7†
Resistin, mrRNA/rRNA, r.a.u.%	100±4.5	102±8.7	70.7±10.7	74.5±8.6
Serum adiponectin, μg/mL	9.8±0.7	10.6±0.7	6.6±0.3*	10.9±1.2†
Serum resistin, ng/mL	7.6±1.0	5.6±0.6	18.2±1.7*	11.1±1.5†

The 4 groups of mice received the following: normal diet (CONT), normal diet with telmisartan (CONT-TEL), high-fat diet (HF), and high-fat diet with telmisartan (HF-TEL). Each value represents mean±SE (n=8 for each group). Groups were compared by ANOVA with a post hoc Bonferroni test for independent samples.

*$P<0.05$ vs the high-fat group; †$P<0.01$ vs the control group.

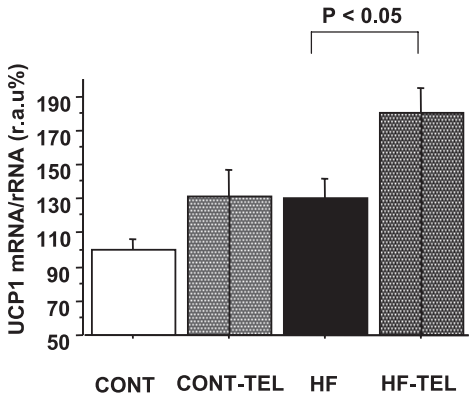

Figure 3. Effects of telmisartan on brown adipose tissue (BAT) uncoupling protein 1 (UCP1) mRNA in diet-induced obese mice. The 4 groups of mice received the following: normal diet (CONT), normal diet with telmisartan (CONT-TEL), high-fat diet (HF), and high-fat diet with telmisartan (HF-TEL). Each value and vertical bar represents the mean±SE (n=8 for each). Groups were compared by ANOVA with a post hoc Bonferroni test for independent samples.

hepatic lipogenic enzyme expression.[17] Given that PPAR-γ is a target for insulin-sensitizing agents,[18,19] the telmisartan-induced activation of PPAR-γ would be expected to improve insulin resistance in obese animal models. In the present in vivo studies using DIO animals, a reduction in higher levels of serum glucose and insulin was observed.

The present study demonstrated that telmisartan treatment in vivo causes changes in the serum levels of adiponectin and resistin, which are insulin-sensitizing and desensitizing adipocytokines, respectively.[10,11] Adiponectin has been shown to stimulate glucose utilization and fatty-acid oxidation by the activation of AMP-kinase.[20] The acceleration of fatty acid oxidation leads to the attenuation of TG synthesis and consequently prevents tissue TG accumulation. The effects of adiponectin may also contribute to the telmisartan-induced reduction of TG content in muscle tissues and probably in the liver.

Because telmisartan treatment did not affect food intake, the reduction in body adiposity of DIO animals in the present study might be attributable to effects on energy metabolism or lipolysis. Telmisartan treatment increased UCP1 mRNA in BAT in the present study, which is similar to the increased level of BAT UCP1 in mice lacking the Ang II type 1a receptor demonstrated in a previous study.[21] In addition, telmisartan treatment increased oxygen consumption and reduced the respiratory quotient compared with the values in nontreated controls in the present study. This decreased use of carbohydrate and increased use of fat to meet energy requirements is congruent with the observed decrease in body fat. Neither food intake nor locomotor activity was changed by telmisartan treatment in the present study. An oxygen consumption increase and/or respiratory quotient decrease with-

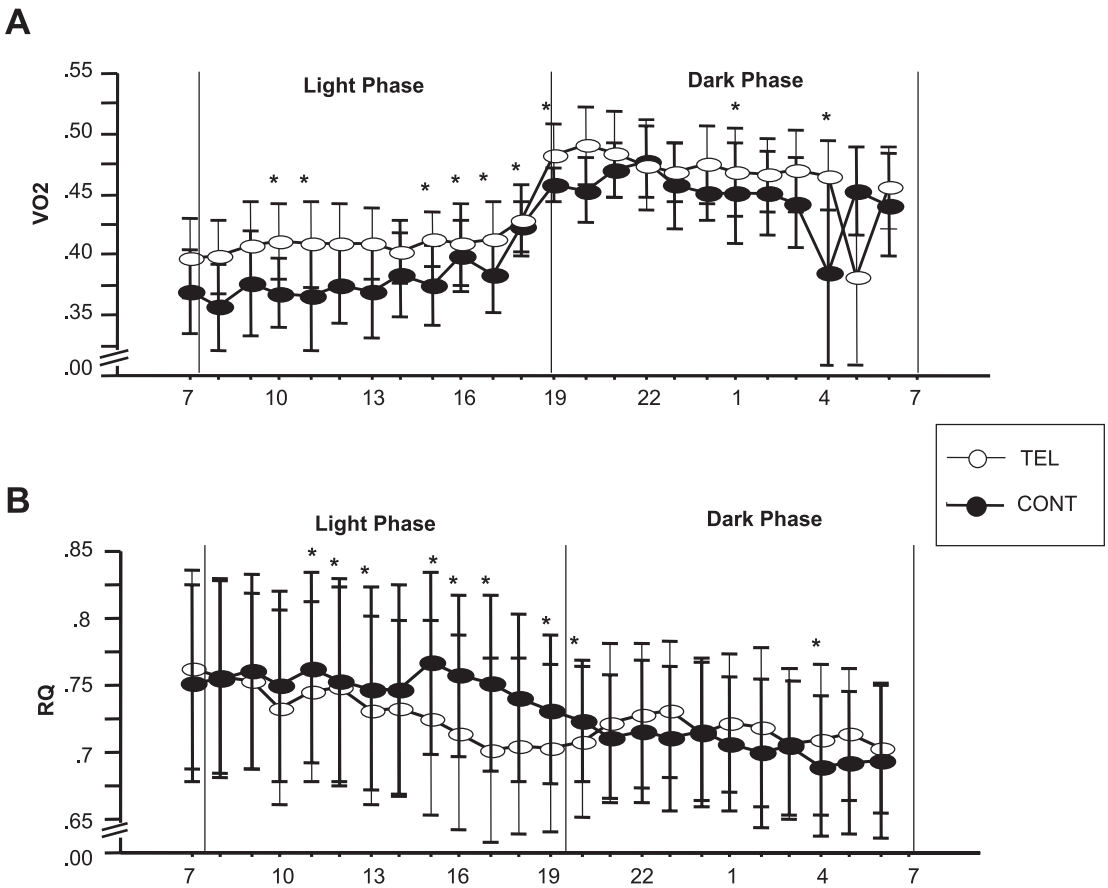

Figure 4. Effects of telmisartan on (A) oxygen consumption and (B) the respiratory quotient in diet-induced obese mice. The 2 groups received a high-fat diet (CONT) and a high-fat diet with telmisartan (TEL). Each value and vertical bar represents the mean±SE (n=14 for each group). The groups were compared by ANOVA with a post hoc Bonferroni test for independent samples.

out concomitant decreases in carbohydrate intake might reflect increased sympathetic activity.[22] These observations indicated the possibility that a change in UCP1, oxygen consumption, and the respiratory quotient by telmisartan treatment might regulate body adiposity by affecting energy metabolism. However, a contradictory observation that the administration of Ang II led to decreases in body adiposity has been made.[23] Thus, further study is needed to clarify the relationship between Ang II and body weight regulation.

Our results raise a question regarding the differential effects of telmisartan and thiazolidine, both PPAR-γ agonists. As shown in the present study, telmisartan was effective at reducing body weight and adiposity. However, in numerous previous studies, thiazolidine treatment failed to reduce body weight and adiposity and frequently increased body weight and/or adiposity.[24,25] In human studies using thiazolidine, a shift in the fat distribution from visceral to subcutaneous adipose tissue has been reported.[19] To confirm this possibility in DIO mice using telmisartan, we compared changes in the weights of visceral and subcutaneous adipose tissues; the ratio of the weight of epididymal/subcutaneous fat decreased with telmisartan treatment, suggesting no increase in subcutaneous fat in these mice. Thus, a differential responsiveness of epididymal and subcutaneous fat seems to determine the net influence of each PPAR-γ agonist on changes in body weight or adiposity.

Selective PPAR modulation is a new pharmacological approach based on selective receptor–cofactor interactions and target gene regulation. A recent study identifies telmisartan as a new selective PPAR modulator. The selective PPAR modulator activity of telmisartan could retain the metabolic efficacy of PPAR-γ activation while reducing adverse effects by concurrently blocking Ang II type 1 receptor activation.[26] This observation suggests that telmisartan may reduce the weight-promoting effects of PPAR-γ activation yet retain PPAR-mediated metabolic efficacy.

In summary, telmisartan treatment may prevent the development of obesity and related metabolic disorders by affecting the adiposity of WAT, the liver, and muscle tissue in DIO mice. Associated changes in UCP1, oxygen consumption, and the respiratory quotient may contribute to an improvement in these metabolic disorders. These results provide new insight into the therapeutic approach to metabolic syndrome based on obesity.

Perspectives

In the present study, telmisartan reduced the visceral adiposity and increased the expression of UCP1, which is a marker of energy expenditure, in DIO mice. These observations support the application of telmisartan as a therapeutic treatment for metabolic syndrome, including visceral obesity. In future studies, it will be interesting to compare the effects of different ARBs on metabolic syndrome.

Sources of Funding

This work was supported by Grants-in-Aid for Scientific Research 15406035 from the Japan Society for the Promotion of Science (2003–2005). This work was also supported in part by a grant from the Health and Labor Sciences Research Grants, Smoking Research Foundation, and Venture Business Laboratory in Oita University, and Health and Labor Sciences Research and Grant 16922171 from the Japan Society for the Promotion of Science.

Disclosures

None.

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