Original Article

Olmesartan Medoxomil, an Angiotensin II Receptor Blocker Ameliorates Insulin Resistance and Decreases Triglyceride Production in Fructose-Fed Rats

Kenta OKADA, Tsutomu HIRANO, Jianmin RAN, and Mitsuru ADACHI

Although angiotensin II receptor blockers (ARBs) have been recommended as a first line of anti-hypertensive agents in patients with diabetes, it remains unclear whether ARBs have a favorable effect on insulin action and triglyceride (TG) metabolism, both of which are impaired in type 2 diabetes. In this study we addressed this issue by investigating how a newly developed ARB, olmesartan medoxomil, influenced insulin sensitivity and TG metabolism in fructose-fed rats, a representative animal model of insulin resistance. Olmesartan was administered as a 0.01% drinking solution *ad libitum* to rats either fed normal chow or fructose-enriched chow (60%) for 21 days. Olmesartan treatment markedly decreased both systolic and diastolic blood pressure in both chow-fed and fructose-fed animals. The area under the curve of insulin (AUCI) was substantially greater in fructose-fed rats in the intravenous glucose tolerance test, and olmesartan treatment significantly reduced the AUCI. Olmesartan significantly improved the insulin sensitivity index in fructose-fed rats assessed by Bergman's minimal model without affecting insulin-independent glucose disposal. Olmesartan significantly decreased plasma TG and non-esterified fatty acid levels in fructose-fed rats without affecting lipoprotein lipase mass. The TG secretion rate determined by the triton WR1339 technique was two-fold higher in fructose-fed rats, but olmesartan restored the TG secretion to a normal rate. Olmesartan did not affect plasma parameters, insulin sensitivity or TG metabolism in chow-fed rats. Olmesartan ameliorates insulin resistance and overproduction of TG in fructose-fed rats, and these effects appear to be independent of its hypotensive action. (*Hypertens Res* 2004; 27: 293–299)

Key Words: olmesartan medoxomil, insulin resistance, triglyceride metabolism, fructose-fed rat

Introduction

Glucose intolerance, hypertension and dyslipidemia, a triad of established risk factors for cardiovascular diseases, are often clustered in individuals with insulin resistance and its compensatory hyperinsulinemia. Although hypertension is associated with glucose intolerance and dyslipidemia, the exact mechanisms behind these associations remain largely unknown. Angiotensin II, a potent vasoconstrictor, plays an important role in the development of hypertension (1), and

there has been accumulating evidence that angiotensin II directly impairs insulin action (2–4). In turn, several studies have demonstrated that angiotensin I converting enzyme inhibitors (ACEIs), suppressors of angiotensin II production, can improve insulin resistance (5, 6). Angiotensin II receptor blockers (ARBs) and ACEIs have both been recommended as first lines of anti-hypertensive treatment in patients with diabetes, but it remains uncertain whether ARBs exert as favorable an effect on insulin action as ACEIs. Insulin resistance/hyperinsulinemia leads to a condition of hypertriglyceridemia by stimulating triglyceride (TG) production in the

From the First Department of Internal Medicine, Showa University School of Medicine, Tokyo, Japan.

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Address for Reprints: Tsutomu Hirano, M.D., First Department of Internal Medicine, Showa University School of Medicine, 1–5–8 Hatanodai, Shinagawa-ku, Tokyo 142–8666, Japan. E-mail: hirano@med.showa-u.ac.jp

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liver and suppressing lipoprotein lipase, a key enzyme for TG hydrolysis (7). It remains poorly understood whether ARB has a favorable effect on TG metabolism in hypertensive subjects with insulin resistance. In this study we sought to clarify this issue by investigating the effects of a newly developed ARB, olmesartan medoxomil, on insulin sensitivity and TG metabolism in fructose-fed rats, a representative animal model of insulin resistance.

Methods

Eight-week-old male Wistar rats (Charles River Japan, Tokyo, Japan) were divided into two groups, one group fed standard rat chow containing 60% vegetable starch, 5% fat, and 24% protein (Oriental Yeast Co., Tokyo, Japan), and the other group fed fructose-rich chow containing 60% fructose, 5% fat and 20% protein (Oriental Yeast Co.) for a feeding period of 5 weeks. Each group was given drinking water with or without 0.01% olmesartan medoxomil (CS-866; Sankyo Co, Tokyo, Japan) for the last 21 days of the 5-week period. Our decision to commence the olmesartan treatment on the 15th day was based on our finding in preliminary experiments that the degree of hyperinsulinemia and hypertriglyceridemia stabilized 2 weeks after the start of fructose feeding. All rats were kept in individual cages on a rotating 12-h light-dark cycle with free access to food and water. On the day of the experiment, food was removed at 9:00 AM but the drinking water remained available, and the experiment was started at 2:00 PM (5 h-fasting state). In three rats, we measured the plasma concentration of olmesartan by high performance liquid chromatography (HPLC) (8) at the very start of the experiments. All procedures were performed in accordance with the "Guide for the Care and Use of Laboratory Animals" of Showa University, and were approved by the Animal Care and Use Committee of that institution.

Blood Pressure (BP) and Heart Rate (HR) Measurement

Systolic BP (SBP), diastolic BP (DBP) and HR were recorded in completely conscious rats using indirect tail-cuff equipment (Natsume Seisakusho Co., Tokyo, Japan). Rats were preheated on a 37°C plate for 20 min, and then the BP and HR were each measured 5 times; the mean values were taken as the individual BP or HR for each rat.

Triglyceride Secretion Rate (TGSR)

TGSR was determined by the Triton WR1339 method, as described in detail previously (9). Rats were anesthetized with an intraperitoneal injection of 50 mg/kg sodium pentobarbital, a dose of 500 mg/kg of Triton WR1339 was intravenously injected, and blood samples were taken before and at 60 and 90 min after injection. TGSR was calculated from the increments of the plasma TG concentration per minute, multiplied by plasma volume (estimated as 4% of the body

weight). The result was expressed as mg/min/100 g body weight.

Lipoprotein Lipase (LPL) Mass in Postheparin Plasma

Postheparin blood samples were obtained 15 min after the injection of heparin (100 U/kg) into the femoral vein of the anesthetized rats. Plasma was collected by low-speed centrifugation at 4°C and stored at -20°C until utilization. LPL mass was assayed by the ELISA method (Daiichi Kagaku Co., Ltd., Tokyo, Japan) (10), a method that cross-reacts with rat LPL.

Intravenous Glucose Tolerance Test (IVGTT)

Glucose (0.5 g/kg, as a 50% solution in water) was bolusly injected into anesthetized rats *via* a femoral vein. Blood samples (0.2 ml for each time point) were drawn from tail vein into microtubes containing heparin at -5, 5, 10, 30, 60, and 90 min. Plasma was separated by centrifugation at 4°C, and stored at -20°C for subsequent measurement of glucose and insulin. The area under the curve of glucose (AUCG) and insulin (AUCI) were calculated by an intrapezoid method.

Frequently Sampled Intravenous Glucose Tolerance Test (FSIVGTT)

As there were no significant differences in glucose and insulin levels between chow-fed rats with and without olmesartan in IVGTT (shown later), FSIVGTT was performed to evaluate the insulin sensitivity index (SI) and glucose effectiveness (SG) by Bergman's minimal model method (11) in sub-groups of rats in both the chow-fed and fructose-fed groups with and without olmesartan. One hour before the experiment, rats were anesthetized with pentobarbital, and a catheter filled with heparin was placed into a femoral vein. Glucose solution (50%, a dose of 0.5 g/kg) was bolusly injected at the basal state, and then blood samples (0.15 ml for each time point) were taken at -5, 2, 4, 6, 8, 10, 12, 14, 16, 19, 22, 30, 40, 60, 90, and 120 min. All samples were treated with the same procedure used in IVGTT, as described above. SI and SG in the minimal model approach of Bergman (11) represent insulin-dependent and insulin-independent glucose disposal abilities *in vivo*, respectively. The program was written in Turbo C 2.0 (Borland International, Scotts Valley, USA) on the DOS operating system (Microsoft, USA). The Marquardt-Levenberg method is used for nonlinear least-square estimation of the parameters, the values at 2–6 min after the glucose injection are zero-weighted, and the step size for integration is 1 min. The plasma glucose disappearance rate constant (K_g) is calculated as the slope of the least-square regression line representing the natural logarithm of the glucose concentration between 4 and 16 min.

Table 1. General Profiles In Chow-Fed And Fructose-Fed Rats Treated with or without Olmesartan

	<i>n</i>	Body weight (g)	Food intake (g/day)	Water intake (ml/day)	Olmesartan intake (mg/kg/d)	HR (/min)
Chow	13	445 ± 30	27.3 ± 1.9	42.7 ± 8.5		351 ± 30
Chow with olmesartan	13	452 ± 19	30.8 ± 3.6	44.0 ± 3.8	11.4 ± 1.0	355 ± 35
Fructose	23	446 ± 40	16.6 ± 6.6 *	48.8 ± 1.8		376 ± 24
Fructose with olmesartan	27	465 ± 25	17.2 ± 2.6 *	50.0 ± 3.5	10.0 ± 0.6	387 ± 40

Data are expressed as mean ± SD. * $p < 0.05$ vs. the chow group without olmesartan. HR, heart rate.

Fig. 1. Systolic and diastolic blood pressure (SBP and DBP) in chow-fed and fructose-fed rats treated with or without olmesartan. * $p < 0.05$ and ** $p < 0.01$ vs. the chow group without olmesartan, ## $p < 0.01$ vs. the fructose group without olmesartan.

Fig. 2. Glucose and insulin levels during IVGTT. * $p < 0.05$ vs. the chow group without olmesartan, # $p < 0.05$ vs. the fructose group without olmesartan.

Biochemical Assays

Plasma levels of glucose, total cholesterol (TC), TG, non-esterified fatty acid (NEFA) and high density lipoprotein cholesterol (HDL-C) were measured in duplicate spectrophotometrically with standard commercial kits (Wako Pure Chemical Industries, Osaka, Japan). Plasma insulin concentration was determined using a specific insulin ELISA kit for rats (Morinaga, Yokohama, Japan).

Statistical Analysis

Results are expressed as the mean ± SD. One-way ANOVA was used to evaluate differences of means between different groups. Statistical significance was accepted at $p < 0.05$.

Results

Final body weights were similar between fructose-fed and chow-fed rats. Food intake was significantly lower in fructose-fed rats than in chow-fed rats. Olmesartan treatment did

Table 2. Intravenous Glucose Tolerance Test in Chow-Fed and Fructose-Fed Rats Treated with or without Olmesartan

	<i>n</i>	FPG (mg/dl)	FPI (μ U/ml)	AUCG (mg/dl $\times$ min $\times 10^4$)	AUCI (μ U/ml $\times$ min $\times 10^4$)
Chow	8	144.25 $\pm$ 31.53	34.09 $\pm$ 21.56	0.82 $\pm$ 0.15	0.27 $\pm$ 0.04
Chow with olmesartan	8	147.21 $\pm$ 25.12	42.50 $\pm$ 16.97	0.81 $\pm$ 0.06	0.26 $\pm$ 0.03
Fructose	14	163.18 $\pm$ 28.20	136.45 $\pm$ 12.10**	0.81 $\pm$ 0.14	0.43 $\pm$ 0.20**
Fructose with olmesartan	16	153.68 $\pm$ 43.89	91.97 $\pm$ 29.30##	0.76 $\pm$ 0.11	0.29 $\pm$ 0.10 [#]

Data are expressed as mean $\pm$ SD. ** $p < 0.01$ vs. the chow group without olmesartan, [#] $p < 0.05$ and ## $p < 0.01$ vs. the fructose group without olmesartan. FPG, fasting plasma glucose; FPI, fasting plasma insulin; AUCG, area under the curve of glucose; AUCI, area under the curve of insulin.

Fig. 3. Glucose and insulin profiles during the frequently sampled intravenous glucose tolerance test (FSIVGTT).**Table 3. Frequently Sampled Intravenous Glucose Tolerance Test Assessed by the Bergman's Minimal Model**

	Chow	Fructose	Fructose with olmesartan
<i>n</i>	6	6	6
AUCG (mg/dl $\times$ min $\times 10^4$)	2.00 $\pm$ 0.26	2.40 $\pm$ 0.31	2.28 $\pm$ 0.33
AUCI (μ U/ml $\times$ min $\times 10^4$)	0.45 $\pm$ 0.14	1.92 $\pm$ 0.45**	1.40 $\pm$ 0.33##
SI (μ U/ml/min $\times 10^{-4}$)	17.29 $\pm$ 8.79	1.31 $\pm$ 1.17**	4.48 $\pm$ 1.40 [#]
SG (/min $\times 10^{-2}$)	4.50 $\pm$ 1.19	4.50 $\pm$ 1.29	4.63 $\pm$ 0.94
K_g (%/min)	4.80 $\pm$ 0.66	4.25 $\pm$ 0.58	5.00 $\pm$ 0.69

Data are expressed as mean $\pm$ SD. ** $p < 0.01$ vs. the chow group without olmesartan, [#] $p < 0.05$ and ## $p < 0.01$ vs. the fructose group without olmesartan. AUCG, area under the curve of glucose; AUCI, area under the curve of insulin; SI, insulin sensitivity index; SG, glucose effectiveness; K_g , glucose disappearance rate constant.

not affect body weight or food consumption in either chow-fed or fructose-fed rats (Table 1). The doses of olmesartan administered were comparable between the chow-fed and fructose-fed animals (Table 1). The plasma concentration of olmesartan after ingestion of 0.5 mg/kg olmesartan was measured in 3 rats; the maximum plasma concentration was 75.4 ± 0.4 ng/ml, which fell within the safe range (the toxic dose is above 100 mg/kg for male rats) (8).

SBP was significantly higher in fructose-fed rats than in chow-fed rats (138 ± 11 vs. 126 ± 7 mmHg; $p < 0.05$). DBP tended to be higher in fructose-fed rats, but the difference was not statistically significant (100 ± 9 vs. 93 ± 11 mmHg)

(Fig. 1). In both chow-fed and fructose-fed rats, treatment with olmesartan substantially lowered both SBP and DBP (Fig. 1) without affecting the HR (Table 1).

IVGTT

Although glucose levels were comparable, the fasting insulin concentration was markedly higher in fructose-fed rats than in chow-fed rats. Treatment with olmesartan significantly lowered the high concentration of insulin in fructose-fed rats. Figure 2 depicts changes in glucose and insulin in the four groups tested in the IVGTT. Insulin levels remained elevated

Table 4. Plasma Lipid Levels and Lipoprotein Lipase in Chow-Fed and Fructose-Fed Rats Treated with or without Olmesartan

	<i>n</i>	TC (mg/dl)	TG (mg/dl)	HDL-C (mg/dl)	NEFA (mEq/l)	LPL (ng/ml)
Chow	8	73 ± 5	101 ± 17	41 ± 2	0.90 ± 0.11	106 ± 38
Chow with olmesartan	8	72 ± 3	136 ± 33	39 ± 1	0.88 ± 0.24	94 ± 21
Fructose	14	85 ± 10	280 ± 85**	39 ± 4	2.03 ± 0.87**	131 ± 9
Fructose with olmesartan	16	97 ± 11	189 ± 89##	40 ± 5	1.33 ± 0.33 [#]	128 ± 34

Data are expressed as mean ± SD. ** $p < 0.01$ vs. the chow group without olmesartan, [#] $p < 0.05$ and ## $p < 0.01$ vs. the fructose group without olmesartan. TC, total cholesterol; TG, triglyceride; HDL-C, high density lipoprotein cholesterol; NEFA, non-esterified fatty acid; LPL, lipoprotein lipase.

Fig. 4. Triglyceride secretion rate (TGSr) in chow-fed and fructose-fed rats treated with or without olmesartan. ** $p < 0.01$ vs. the chow group without olmesartan, ## $p < 0.01$ vs. the fructose group without olmesartan.

after the glucose administration in the fructose-fed rats, and these elevated levels were decreased by olmesartan treatment. The AUCI was substantially greater in fructose-fed rats, and was also significantly decreased by olmesartan treatment (Table 2). Olmesartan did not affect fasting insulin or AUCI in chow-fed rats (Table 2).

FSIVGTT (Bergman's Minimal Model)

Figure 3 depicts changes in plasma glucose and insulin levels in FSIVGTT. Table 3 indicates parameters obtained by assessment of Bergman's minimal model. Fructose-fed rats showed marked hypersecretion of insulin in FSIVGTT, and treatment with olmesartan significantly attenuated this hypersecretion. AUCG was not altered by fructose feeding or olmesartan treatment. Fructose-fed rats showed severe insulin resistance as evaluated by SI. Olmesartan treatment in-

creased SI 3.4-fold in fructose-fed rats. Fructose feeding did not affect the SG value, which reflects insulin-independent glucose disposal, and olmesartan did not affect SG. The K_g was comparable among all four groups.

Plasma Lipid Levels and TG Metabolism

Fructose-fed rats had significantly higher fasting levels of TG and NEFA than chow-fed rats, but the levels of TC and HDL-C were comparable between the two groups (Table 4). Olmesartan treatment significantly decreased the high concentrations of TG and NEFA in fructose-fed rats (Table 4), but did not lower either TG or NEFA in chow-fed rats. TGSr was 2-times higher in fructose-fed rats than in chow-fed rats (0.14 ± 0.06 vs. 0.08 ± 0.05 mg/min/100 g body weight) (Fig. 4). Olmesartan treatment attenuated the high TGSr to within the normal range (0.07 ± 0.03 mg/min/100 g body weight) in fructose-fed rats (Fig. 4). As with plasma TG concentration, the TGSr showed no change whatsoever in the chow-fed rats treated with olmesartan (0.07 ± 0.05 mg/min/100 g body weight). Olmesartan exerted no effect on the postheparin LPL mass in either fructose-fed rats or chow-fed rats (Table 4).

Discussion

Recent experimental studies have suggested that angiotensin II impairs the action of insulin (2–4). If so, the inhibition of angiotensin II can be expected to improve insulin sensitivity. Several studies have demonstrated that the inhibition of angiotensin II production by ACEI improves insulin resistance in hypertensive patients (5, 6, 12). However, ACEI increases bradykinin concentration, a process that might be more closely associated with insulin sensitivity (13) than the angiotensin II suppression. The effect of ARB on insulin action remains controversial. Though several clinical trials failed to demonstrate any losartan-induced improvement in insulin sensitivity in hypertensive or normotensive subjects (14–16), Paolisso *et al.* (17) succeeded in demonstrating a losartan-induced improvement in insulin sensitivity in insulin-resistant hypertensive patients. In a study using the euglycemic glucose clamp technique, Higashiura *et al.* (18) demonstrated

that ACEI (temocapil) and ARB (olmesartan) both improved insulin resistance in fructose-fed rats. Recently, Umeda *et al.* (19) reported that ARB ameliorated insulin resistance and hyperleptinemia in sucrose-fed spontaneously hypertensive rats. Similarly, we found that olmesartan significantly ameliorated insulin sensitivity in fructose-fed rats as determined by Bergman's minimal model. This minimal model assessment can be used to determine insulin-independent glucose disposal (SG) as well as insulin-sensitive glucose disposal (SI). We found that only insulin-dependent glucose disposal was impaired in fructose-fed rats, and olmesartan selectively improved this without affecting insulin-independent glucose metabolism. Olmesartan treatment did not affect insulin sensitivity in chow-fed rats. Given that olmesartan markedly decreased the BP in both fructose-fed and chow-fed rats, the improvement of insulin sensitivity in fructose-fed rats is not likely to be associated with the hypotensive action of olmesartan. Taking these findings in sum, we hypothesize that ARB exhibits its stimulating action on insulin sensitivity only in an insulin-resistant state. This might explain why losartan improved insulin sensitivity only in insulin-resistant hypertensive subjects. Similarly, Henriksen *et al.* (20) reported that irbesartan improved insulin sensitivity in obese Zucker rats having severe insulin resistance.

In our study, olmesartan was administrated to rats as 0.01% of a drinking solution, which corresponds to a high-dose olmesartan treatment according to the dose-response studies of Mizuno *et al.* (21). Nonetheless, the plasma concentrations of olmesartan were within the treatable range (22). Not having performed a dose-response study, we have yet to establish whether a lower dose of olmesartan can improve insulin sensitivity. This issue should be examined in further studies.

Several possible mechanisms may explain the ARB-induced improvement of insulin sensitivity. First, ARB has the action of vasodilation, which increases the blood flow in skeletal muscle and activates the glucose transporter and its translocation to plasma membrane (18). Second, ARB selectively increases insulin-sensitive type fiber in the skeletal muscles (23). Third, ARB suppresses the activity of the sympathetic nervous system, and thereby decreases the blood flow in skeletal muscle and antagonizes the action of insulin (24). However, further evidence will be required to explain why the ARB-induced amelioration of insulin sensitivity is manifested only in an insulin-resistant state.

In the present study, we found that olmesartan significantly improved hypertriglyceridemia induced by a high fructose diet. Fructose feeding causes overproduction of TG in the liver (25) and a defect in TG catabolism due to altered composition and nature of very-low-density lipoprotein particles (26). Olmesartan remarkably suppressed TGSR without affecting LPL concentration in fructose-fed rats. To the best of our knowledge, this is the first study to suggest that the TG-lowering effect of ARB is primarily attributable to the suppression of TG production. The following mechanisms have

been proposed as explanations for the overproduction of TG observed in fructose-fed animals: fructose moiety stimulates lipogenesis in the liver (27); fructose feeding causes insulin resistance in the liver, which diminishes insulin-induced apolipoprotein B degradation in hepatocytes and thereby increases very low density lipoprotein (VLDL) assembly (28, 29); and fructose feeding causes insulin resistance in adipose tissues, which blunts insulin's anti-lipolytic effect and thereby increases the flux of fatty acid into the liver. The NEFA level was significantly increased in fructose-fed rats, possibly due to the increased mobilization of fatty acids by adipose tissue or increased TG level in the plasma circulation. Olmesartan significantly reduced the high NEFA levels in the fructose-fed rats, and this NEFA-reductive effect may be responsible for the suppression of TG production. LPL is a key enzyme for TG catabolism, and this enzyme is insulin-dependent (30). However, fructose feeding did not decrease LPL mass in postheparin plasma, which was consistent with our previous report on LPL activity (31, 32). This result also suggests that olmesartan-induced reduction of TG is solely due to the suppression of TG production. As with glucose metabolism, olmesartan elicited no effects on plasma lipid levels and TG kinetics in the chow-fed rats. Thus, we can reasonably assume that the amelioration of lipid metabolism by olmesartan is largely dependent on the simultaneous improvement of insulin resistance. Kim *et al.* (33) recently reported that a TG-lowering agent, bezafibrate, improved hypertension and insulin resistance. If so, there is another possibility—namely, that the decrease of TG level by olmesartan treatment is associated with improvement of insulin resistance. The suppressive effect of olmesartan on TG production was stronger than the ameliorative effect of TG on insulin sensitivity in fructose-fed rats. This also implies the possibility that olmesartan directly affects lipid metabolism, which subsequently improves insulin sensitivity.

In conclusion, we demonstrated that olmesartan improves insulin sensitivity and overproduction of TG in fructose-fed rats independently of its hypotensive action. The favorable effects of olmesartan on glucose and lipid metabolism may be helpful in the treatment of hypertension, especially in subjects with insulin resistance.

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