Original Article

Significance of Angiotensin II Receptor Blocker Lipophilicities and Their Protective Effect against Vascular Remodeling

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Although the lipophilicities of the various angiotensin II receptor blockers (ARBs) are very different, the relationship between lipophilicity and the protective effect against vascular remodeling is unclear. In this study, we compared the protective effects of a highly lipophilic ARB, telmisartan, and an ARB with low lipophilicity, losartan, on vascular function and oxidative stress in stroke-prone spontaneously hypertensive rats (SHR-SP). SHR-SP received oral placebo, 1 mg/kg telmisartan, or 10 mg/kg losartan for 2 weeks. The blood pressure (BP) in SHR-SP was significantly higher than that in Wistar-Kyoto (WKY) rats before treatment, and the BP was reduced equally in telmisartan- and losartan-treated SHR-SP compared to placebo-treated SHR-SP. Acetylcholine-induced vasorelaxation in isolated carotid arteries was significantly weaker in SHR-SP than in WKY rats, but in both telmisartan- and losartan-treated SHR-SP, acetylcholine-induced vasorelaxation was significantly higher than in placebo-treated SHR-SP. Moreover, acetylcholine-induced vasorelaxation in telmisartan-treated rats was significantly stronger than in losartan-treated SHR-SP. The expression of the endothelial nitric oxide synthase gene was significantly higher in telmisartan- and losartan-treated rats than in placebo-treated SHR-SP, and was significantly higher in telmisartan-treated rats than in losartan-treated rats. In contrast, the expression of the NAD(P)H oxidase subunit $p22^{phox}$ gene in telmisartan-treated SHR-SP was significantly lower than that in losartan-treated SHR-SP. Immunohistochemistry showed that angiotensin II expression in the aorta was significantly lower in telmisartan-treated SHR-SP than in losartan-treated SHR-SP. In conclusion, a highly lipophilic ARB, telmisartan, may be useful for preventing NAD(P)H oxidase activity, and thereby for conferring vascular protection. (*Hypertens Res* 2005; 28: 593–600)

***Key Words*: angiotensin II receptor blocker, lipophilicity, nitric oxide, NAD(P)H oxidase**

Introduction

Angiotensin II is formed from angiotensin I by angiotensin-converting enzyme (ACE) and non-ACE angiotensin II-forming enzymes, such as chymase. Angiotensin I is formed from angiotensinogen by renin. Angiotensin II plays an important role in increasing blood pressure (BP) by stimulating angiotensin II type 1 (AT_1) receptors. To prevent angiotensin II from acting, two types of agents have been developed: one type prevents angiotensin II formation and includes the ACE inhibitors and the renin inhibitors; the other type blocks the binding of angiotensin II to AT_1 receptors, and includes the angiotensin II receptor blockers (ARBs). ACE inhibitors were the first among these two types of agents to be developed and widely used in clinical practice. However, ACE inhibitors contribute not only to the inhibition of angiotensin II formation but also to bradykinin degradation, and thus are associ-

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ated with side effects, such as cough. On the other hand, ARBs do not affect bradykinin degradation, and therefore have fewer side effects than ACE inhibitors. Moreover, since ARBs block the effects of angiotensin II, one would also expect that they could decrease the risk of coronary artery disease, cardiac failure, renal dysfunction, and cerebral artery diseases (*1*). In fact, studies have shown that ARBs, like ACE inhibitors, do significantly reduce these risks, and that their mechanisms of action may involve the blocking of angiotensin II-related functions, such as by inducing growth factors and cytokines, in addition to their hypotensive effect.

Various ARBs have been widely used to treat hypertensive patients. Though the ARBs vary in their lipophilicities (*2*), the significance of the different lipophilicities of the various ARBs has hardly been discussed. In contrast, the significance of the different lipophilicities of the various ACE inhibitors has been discussed extensively (*3*–*6*). For example, it has been clearly shown that ACE inhibitors with high lipophilicity are more useful for inhibiting tissue ACE activity than ACE inhibitors with low lipophilicity, which resulted in different antihypertensive and tissue-protective effects (*3*–*6*). These reports suggest that different lipophilicities might result in different protective effects, even when the hypotensive effects are the same.

In general, the lipophilicity index is defined as the ratio of octanol to buffer, and the values of log *P* are: −2.45 with EXP 3174 (an active metabolite of losartan); −0.96 with candesartan; −0.95 with valsartan; +1.48 with irbesartan; and +3.20 with telmisartan (*2*). Thus, the ARB with the lowest lipophilicity is EXP 3174, and the ARB with the highest lipophilicity is telmisartan. In the present study, we compared the effects on vascular remodeling in stroke-prone spontaneously hypertensive rats (SHR-SP) of an ARB with high lipophilicity (telmisartan, 1 mg/kg per day) and an ARB with low lipophilicity (losartan, 10 mg/kg per day) at doses which showed equal hypotensive effects based on our preliminary study (data not shown).

Methods

Animals

Twelve-week-old male Wistar-Kyoto (WKY) rats ($n=8$) and SHR-SP ($n=24$) were obtained from Japan SLC Inc. (Shizuoka, Japan). The experimental procedures were in accordance with the Guide for the Care and Use of Laboratory Animals (Animal Research Laboratory, Osaka Medical College).

SHR-SP were given placebo ($n=8$), 1 mg/kg telmisartan ($n=8$), or 10 mg/kg losartan ($n=8$) daily for 2 weeks. Systolic BP (SBP) was monitored by tail-cuff plethysmography (BP-98; Softron Co., Tokyo, Japan). After placebo or ARBs were administered for 2 weeks, the body weights of the rats were measured. The animals were anesthetized with 35 mg/kg of sodium pentobarbital intraperitoneally, and then blood and tissue samples were obtained.

Plasma Renin Activity (PRA) and Angiotensin II Concentration

PRA was determined using an SRL renin kit (TFB Co., Tokyo, Japan). Angiotensin II concentration was measured using an enzyme immunoassay kit (Peninsula Laboratories Inc., Belmont, USA).

Acetylcholine-Induced Vasorelaxation in Isolated Rat Arteries

Isolated rat carotid arteries were cut into helical strips, 10 mm in length and 1.0 mm in width. The artery strip was placed on a myograph under a resting tension of 1.0 g. The bathing medium was Tyrode's solution consisting of 137 mmol/l NaCl, 2.7 mmol/l KCl, 1.8 mmol/l $CaCl_2$, 1.1 mmol/l $MgCl_2$, 0.42 mmol/l NaH_2PO_4, 12 mmol/l $NaHCO_3$ and 5.7 mmol/l glucose, pH 7.4. The medium was maintained at 37°C and was bubbled continuously with 5% CO_2 in oxygen. Vasoconstriction to 50 mmol/l KCl was first obtained, and then the bathing medium was washed out. Relaxation with acetylcholine was assessed after contraction to a steady-state tension using 1 μmol/l norepinephrine.

Reverse Transcription (RT)–Polymerase Chain Reaction (PCR)

The total RNA of the aorta was extracted using Trizol reagent (Life Technologies, Rockville, USA) and dissolved in 0.1% diethyl pyrocarbonate-treated water. RT to cDNA was accomplished by analyzing 5 μg of the total RNA sample with SuperScript II reverse transcriptase and oligo$(dT)_{12–18}$ primer (Invitrogen, Carlsbad, USA). The reaction was carried out in the presence of first-strand buffer, 1 mmol/l dNTPs and 20 mol/l dithiothreitol, at 42°C for 50 min. The PCR mixture contained 1 μl of the cDNA reaction mixture, 20 pmol/l primers, PCR buffer, 0.4 mmol/l dNTPs, and 2.5 U *Taq* polymerase. The reaction was carried out with a RoboCycler (Stratagene, La Jolla, USA). The sequences of the oligonucleotide primers for PCR were as follows: an endothelial nitric oxide synthase (eNOS) sense primer, 5′-GGCATCACCAG GAAGAAGAC-3′, and antisense primer, 5′-CGAACACA CAGAACCTGACC-3′, were used for the amplification of eNOS; a $p22^{phox}$ sense primer, 5′-GCTCATCTGTCTGCTG GAGTA-3′, and antisense primer, 5′-ACGACCTCATCTGT CACTGGA-3′, were used for the amplification of $p22^{phox}$; and a β-actin sense primer, 5′-CCAAGGCCAACCGC GAGAAGATGAC-3′, and antisense primer, 5′-AGGG TACATGGTGGTGCCGCCAGAC-3′, were used for the amplification of β-actin for the calibration of sample loading. The PCR products were separated by electrophoresis on 2% agarose gel stained with ethidium bromide, and the samples were then visualized by ultraviolet transillumination.

Table 1. Effects of Telmisartan and Losartan on Body Weight, Heart Weight and Ratio of Heart Weight to Body Weight

Parameters	Groups	Pretreatment	24 h after last p.o. administration
Body weight (g)	WKY rats	312±2.8**	348±6.1**
	Placebo	250±3.2	281±11
	Telmisartan	250±3.1	285±8.7
	Losartan	247±3.1	283±10
Heart weight (g)	WKY rats	—	0.91±0.01**
	Placebo	—	1.20±0.03
	Telmisartan	—	1.06±0.08**,#
	Losartan	—	1.12±0.01**
Heart weight/body weight (mg/g)	WKY rats	—	2.62±0.04**
	Placebo	—	4.29±0.11
	Telmisartan	—	3.70±0.03**,#
	Losartan	—	3.94±0.07**

WKY rats, Wistar-Kyoto rats. **$p<0.01$ *vs.* placebo, #$p<0.05$ *vs.* losartan.

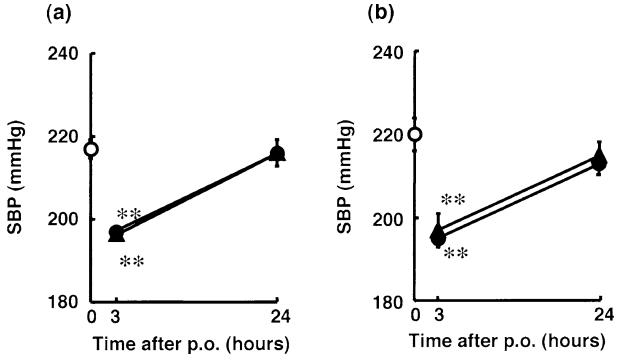

Fig. 1. *Blood pressure at 3 and 24 h after the first (a) and last (b) doses of telmisartan (closed circles) and losartan (closed triangles) and blood pressure at 12 (a) and 14 weeks of age (b) in placebo-treated SHR-SP (open circles).* **p < *0.01* vs. *placebo-treated SHR-SP.*

Immunohistochemistry

Immunostaining with antibodies against angiotensin II (IgG Co., Nashville, USA) was used to stain the tissue as described previously (*7*). The immunostain-positive area was quantified with an image analysis system (model VM-30; Olympus Optical Co., Tokyo, Japan).

Statistical Methods

Data measurements were taken in a blinded fashion. Data are expressed as the mean±SEM. Statistical analyses were performed using 1-way ANOVA followed by a post-hoc analysis (Fisher's test). Values of $p<0.05$ were considered to indicate statistical significance.

Results

Body Weight and Heart Weight

The effects of telmisartan and losartan treatments on body weight and heart weight are shown in Table 1. The body weights were not significantly different among the groups. On the other hand, the ratio of heart weight to body weight in the placebo-treated SHR-SP was significantly greater than in WKY rats. The ratio in both the telmisartan- and losartan-treated SHR-SP was significantly lower than in the placebo-treated SHR-SP. Furthermore, the ratio in the telmisartan-treated SHR-SP was significantly lower than that in the losartan-treated SHR-SP.

Blood Pressure

The effects of telmisartan and losartan on SBP are shown in Fig. 1. The SBP before telmisartan was 217±2.2 mmHg and that before losartan was 217±1.9 mmHg. The SBP values 3 h after the first doses of telmisartan and losartan were significantly decreased compared with the pretreatment values, but these values gradually recovered within 24 h. At 24 h after the first doses, there were no significant differences among the telmisartan-, losartan-, and placebo-treated groups. After the last dose, both ARBs exhibited significant hypotensive effects at 3 h, but not at 24 h, and no significant differences among the telmisartan-, losartan-, and placebo-treated groups were observed. Overall, telmisartan and losartan had similar hypotensive effects.

PRA and Angiotensin II Concentration

Both the PRA and the angiotensin II concentration at 3 and 24 h after the last doses were significantly lower in the telmisar-

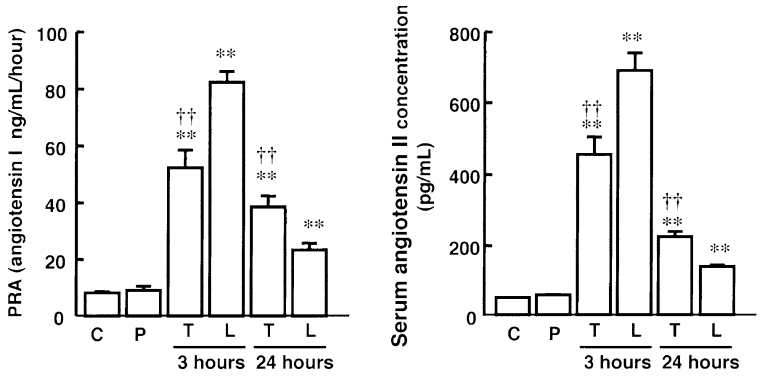

Fig. 2. *PRA and angiotensin II concentration in WKY rats (C), and placebo (P)-, telmisartan (T)-, and losartan (L)-treated SHR-SP.* **p < *0.01* vs. *placebo-treated SHR-SP.* ††p < *0.01* vs. *losartan-treated SHR-SP.*

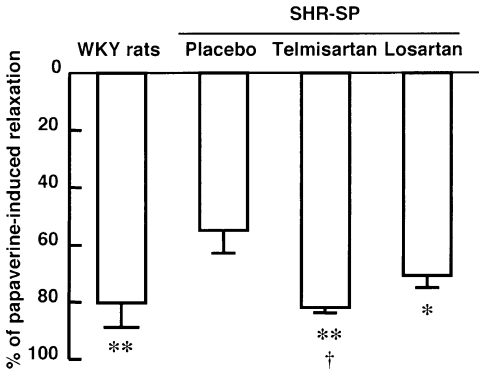

Fig. 3. *Acetylcholine-induced vasorelaxation in noradrenaline-precontracted carotid arteries in WKY rats, and placebo-, telmisartan-, and losartan-treated SHR-SP. The results are given as the percentages of the maximal relaxation for papaverine.* *p < *0.05 and* **p < *0.01* vs. *the placebo-treated SHR-SP.* †p < *0.05* vs. *losartan-treated SHR-SP.*

tan- and losartan-treated groups than in the placebo-treated SHR-SP (Fig. 2). However, at 3 h after the last dose, these levels in the telmisartan-treated SHR-SP were significantly lower than those in the losartan-treated SHR-SP, whereas at 24 h the levels in the telmisartan-treated SHR-SP were higher than those in the losartan-treated SHR-SP (Fig. 2).

Vascular Responses

In all rats, acetylcholine-induced vasorelaxation was observed (Fig. 3). The vasorelaxation in the placebo-treated SHR-SP was significantly lower than that in the WKY rats (Fig. 3). Vasorelaxation in the telmisartan- and the losartan-treated SHR-SP was significantly greater than that in the placebo-treated SHR-SP. Of note, vasorelaxation in the telmisartan-treated SHR-SP was significantly greater than that in the losartan-treated SHR-SP (Fig. 3).

Expressions of eNOS and p22^{phox}

The expression of eNOS in the aortas of SHR-SP is shown in Fig. 4. The expression of eNOS in the aortas of placebo-treated SHR-SP and WKY rats was very weak, though the eNOS expression in WKY rats tended to be lower than that in SHR-SP. On the other hand, the eNOS expressions in both the telmisartan- and the losartan-treated SHR-SP were significantly higher than those in the placebo-treated SHR-SP and the WKY rats. However, eNOS expression in the telmisartan-treated SHR-SP resulted in a significantly greater induction than that seen in the losartan-treated SHR-SP (Fig. 4).

In contrast, a significant induction of p22^{phox} expression was observed in the placebo-treated SHR-SP rather than in the WKY rats. However, p22^{phox} expression in both the telmisartan- and the losartan-treated SHR-SP was significantly lower than that in the placebo-treated SHR-SP (Fig. 5). Nevertheless, p22^{phox} expression in the telmisartan-treated SHR-SP was significantly lower than that in the losartan-treated SHR-SP (Fig. 5).

Immunohistochemistry

Anti-angiotensin II antibody-positive cells in the aortas of WKY rats were observed only on the intimal side of the medial lesions, but these cells in the aortas of placebo-treated SHR-SP were observed not only on the intimal side but also over the whole medial lesion, including the adventitial side (Fig. 6). The anti-angiotensin II antibody-positive cells in both the telmisartan- and the losartan-treated SHR-SP were fewer in number than in the placebo-treated SHR-SP (Fig. 6). Positive cells in the aortas of the telmisartan-treated SHR-SP, as in the WKY rats, were observed only on the intimal side, but those in the losartan-treated SHR-SP, as in the placebo-treated SHR-SP, were observed over the whole medial lesion (Fig. 6). The ratios of anti-angiotensin II antibody-positive cells to total cells in both the telmisartan- and the losartan-treated SHR-SP were significantly lower than in the placebo-treated SHR-SP (Fig. 6). This ratio in the telmisartan-treated

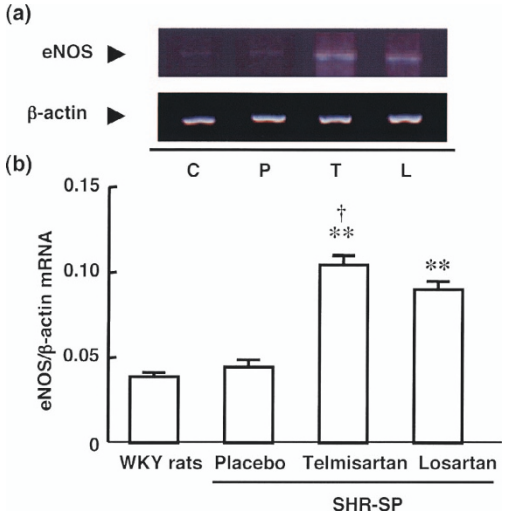

Fig. 4. *(a) Typical photographs of eNOS and β-actin expressions in aortas obtained from WKY rats (C), and placebo (P)-, telmisartan (T)-, and losartan (L)-treated SHR-SP. (b) Ratios of eNOS expression to β-actin in aortas obtained from WKY rats, and placebo-, telmisartan-, and losartan-treated SHR-SP.* **p < *0.01* vs. *placebo-treated SHR-SP.* †p < *0.05* vs. *losartan-treated SHR-SP.*

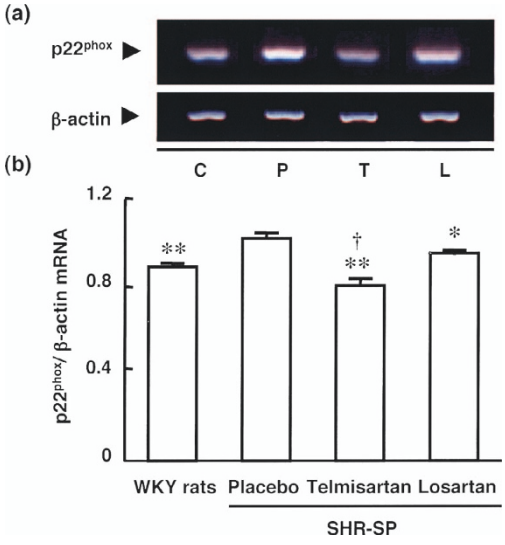

Fig. 5. *(a) Typical photographs of p22^{phox} and β-actin expressions in aortas obtained from WKY rats (C), and placebo (P)-, telmisartan (T)-, and losartan (L)-treated SHR-SP. (b) Ratios of p22^{phox} expression to β-actin in aortas obtained from WKY rats, and placebo-, telmisartan-, and losartan-treated SHR-SP.* *p < *0.05 and* **p < *0.01* vs. *the placebo-treated SHR-SP.* †p < *0.05* vs. *losartan-treated SHR-SP.*

SHR-SP was the same as that in the WKY rats, and the ratio in the telmisartan-treated SHR-SP was significantly lower than that in the placebo-treated SHR-SP. On the other hand,

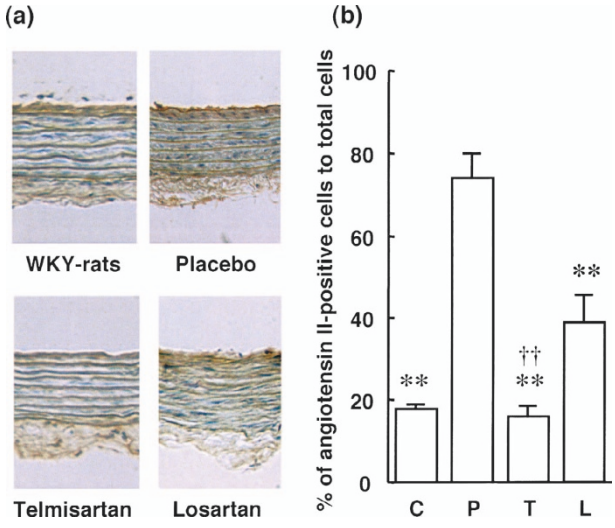

Fig. 6. *(a) Typical photographs of anti-angiotensin II antibody-stained aortas in WKY rats, and placebo-, telmisartan-, and losartan-treated SHR-SP. (b) Ratio of anti-angiotensin II antibody-stained cells to total cells in WKY rats (C), and placebo (P)-, telmisartan (T)-, and losartan (L)-treated SHR-SP.* **p < *0.01* vs. *the placebo-treated SHR-SP.* ††p < *0.01* vs. *the losartan-treated SHR-SP.*

although the ratio in the losartan-treated SHR-SP was significantly lower than that in the placebo-treated SHR-SP, the ratio in the losartan-treated SHR-SP was significantly higher than that in the telmisartan-treated SHR or the WKY rats (Fig. 6).

Discussion

In the present study, we evaluated the protective effects against vascular remodeling of telmisartan, an ARB with high lipophilicity, and losartan, an ARB with low lipophilicity. Oxidative stress caused by angiotensin II has been thought to play an important role in the development and progression of vascular remodeling, and the expression of the NAD(P)H oxidase subunit p22^{phox} is regarded as a typical marker of oxidative stress (*8*–*11*). For example, an increase of p22^{phox} expression reflects an increase in NAD(P)H oxidase activity, which is well known to be closely related to oxidative stress caused by angiotensin II in the vascular tissue of hypertensive rats (*8*, *9*). In the aortas of SHR-SP, p22^{phox} expression was significantly higher than in the aortas of WKY rats in our study, as has also been previously reported (*10*). Brosnan *et al*. (*11*) demonstrated that the expression of p22^{phox} in the aortas of irbesartan-treated SHR-SP was significantly lower than in vehicle SHR-SP. We also observed a significant reduction of p22^{phox} expression in the aortas of telmisartan- and losartan-treated SHR-SP compared with placebo-treated SHR-SP. However, a highly lipophilic ARB, telmisartan, significantly

suppressed the expression of $p22^{phox}$ compared to an ARB with low lipophilicity, losartan, despite the two ARBs exhibiting the same degree of BP lowering. One possible explanation for the present finding that $p22^{phox}$ expression was lower in the telmisartan-treated SHR-SP may be the different lipophilicities of the two ARBs. NAD(P)H oxidase activity, evaluated using isolated mononuclear leukocytes *in vitro*, was found to be significantly reduced by treatment with a more highly lipophilic ACE inhibitor, such as quinapril, but not with ACE inhiitors having lower lipophilicity, such as enalapril and lisinopril (*12*). Similarly, more highly lipophilic angiotensin II-blocking agents may be able to more easily penetrate into the tissues or the cells. This would result in a greater reduction of $p22^{phox}$ in the vascular tissues by telmisartan treatment than by losartan treatment.

In clinical studies, ARBs were expected to prevent cardiovascular events such as myocardial infarction in addition to suppressing BP in hypertensive patients. In fact, in the Evaluation of Losartan in the Elderly (ELITE) II trial, the Valsartan Heart Failure Trial (Val-HeFT), and the VALsartan In Acute myocardial iNfarcTion (VALIANT) trial, ARBs were shown to confer a level of protection against cardiovascular events almost equal to that of ACE inhibitors, which have shown more cardiovascular protection than any other antihypertensive agents in clinical studies (*13–15*). On the other hand, in the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial, the BP-lowering effect of amlodipine was greater than that of valsartan, and amlodipine was also found to be superior to valsartan in preventing cardiovascular events (*16*). This would suggest that a strong hypotensive effect may also be an important factor for preventing cardiovascular events. However, not only the degree of the hypotensive effect, but also its duration may be involved in preventing cardiovascular events, and the different half-lives of valsartan (9 h) and amlodipine (over 35 h) may play a role (*17*, *18*). Similarly, in the present study, the two ARBs not only had different lipophilicities (*i.e.*, telmisartan has high lipophilicity and losartan has low lipophilicity) but they also had very different durations of action. The half-life of telmisartan is approximately 24 h, while that of losartan is 2.1 h and that of EXP3147 (an active metabolite of losartan) is approximately 6.3 h (*19*, *20*). However, in the present study, we used losartan at 10 times the dose of telmisartan, which resulted in both drugs having equal hypotensive effects throughout the experiment. Therefore, the difference noted between telmisartan and losartan with respect to the preventive effects of vascular damage in this study was not due to any hypotensive effects. Jinno *et al*. (*21*) reported that treatment with 0.5 mg/kg or 3 mg/kg of olmesartan did not affect the BP in normotensive mice, but that treatment with 3 mg/kg olmesartan, but not 0.3 mg/kg olmesartan, significantly reduced $p22^{phox}$ expression. Therefore, this would suggest that the different degree of $p22^{phox}$ expression inhibition between telmisartan and losartan found in the present study was likely independent of BP reduction.

In the present study, acetylcholine-induced vasorelaxation, which is used as an index of endothelial function, was significantly lower in SHR-SP than in WKY rats, as has also been previously reported (*22*). Endothelial dysfunction is directly affected by nitric oxide (NO) bioavailability, and its dysfunction is associated not only with hypertension but also with vascular remodeling. It is thought that endothelial dysfunction is induced in hypertension by the reduction of eNOS expression and an increase of oxidative stress in the vasculature. However, the reduction of NO bioavailability has been related to increased oxidative stress rather than to decreased eNOS expression. In the present study, we did not observe a significant difference in eNOS expression between SHR-SP and WKY rats, although eNOS expression in SHR-SP tended to be higher than that in WKY rats. Although a relative deficiency in NO has been associated with hypertension, data as to the regulation of eNOS expression in SHR-SP are not consistent, in that decreased, increased, and unchanged eNOS expression have been reported (*23–26*). Although the underlying causes of these discrepancies are unknown, it is possible that they may be related to the use of different age groups of SHR-SP in these experiments. For example, in SHR-SP, baseline eNOS expression in 8- to 12-week-old rats was increased, that in 12- to 16-week-old rats was unchanged, and that in 31-week-old rats was decreased (*23–25*). In spontaneously hypertensive rats (SHR), it has been reported that eNOS expression in younger age groups was increased, while eNOS expression was decreased in older age groups (*27*, *28*). Together with the present results, these findings indicate that endothelial dysfunction may not be directly affected by eNOS expression. We also observed that eNOS expression in SHR-SP was significantly increased with telmisartan and losartan treatment compared to placebo treatment, but that the degree of increase was significantly greater with telmisartan treatment than with losartan treatment. Although there was a greater increase in eNOS expression with telmisartan treatment than with losartan treatment, this may have been partly due to a greater improvement of endothelial function with telmisartan, which would have limited the contribution of eNOS expression.

On the other hand, in the present study, the expression of $p22^{phox}$ was significantly higher with telmisartan treatment than with losartan treatment. Hamilton *et al*. (*10*) have reported that treatment with inhibitors of NAD(P)H oxidase improved endothelial function of isolated blood vessels not only in SHR-SP but also in humans. NAD(P)H oxidase is known to be activated by mechanical forces and angiotensin II (*29*, *30*). In human vascular smooth muscle cells (VSMCs), the binding of angiotensin II to AT_1 receptors leads to a phosphorylation of $p47^{phox}$, initiating the translocation of this subunit to the cell membrane and assembly of the enzyme complex (*31*). Angiotensin II also increases the expression of all NAD(P)H oxidase subunits, including $p22^{phox}$, which was evaluated in the present study (*32*). Previously, we reported that ACE activity in the aorta was significantly higher in

SHR-SP than in WKY rats, although plasma ACE activity was lower in SHR-SP (*33*). In genetically hypertensive models, such as SHR and SHR-SP, expressions of ACE and angiotensin II concentration in the vasculature are upregulated and angiotensin II action against blood vessels is strengthened (*34*, *35*). In the present study, we observed a significant increase of anti-angiotensin II antibody-positive cells in placebo-treated SHR-SP compared with WKY rats, suggesting an increase of angiotensin II formation in SHR-SP. On the other hand, both telmisartan and losartan treatments resulted in a reduction of anti-angiotensin II antibody-positive cells. This finding suggests that both telmisartan and losartan block angiotensin II binding to AT_1 receptors, and that this results in a decrease of angiotensin II effects, such as NAD(P)H oxidase expression in the vasculature. Moreover, the fact that telmisartan blocks the binding of angiotensin II to vascular AT_1 receptors more strongly than does losartan could result in the lower $p22^{phox}$ expression by telmisartan, and this difference between the two ARBs may have been involved in the finding that improvement of endothelial function by telmisartan treatment was significantly greater than that by losartan treatment.

Cardiac hypertrophy was observed in all SHR-SP, but the hypertrophy in the telmisartan-treated SHR-SP, but not in the losartan-treated SHR-SP, was significantly lower than in the placebo-treated SHR-SP. Our findings agree with Wagner *et al*. (*36*), who reported that telmisartan, but not losartan, reduced cardiac hypertrophy, despite the similar BP reduction between the two drugs. Therefore, since the hypotensive effects seen with telmisartan and losartan are similar, they cannot account for the differences seen in the reduction of cardiac hypertrophy. Although we have not studied the mechanism of cardiac hypertrophy reduction, it is possible that the higher lipophilicity of telmisartan may be a contributing factor for reducing cardiac hypertrophy. In the present study, both the PRA and angiotensin II concentration were significantly higher in the losartan-treated group than in the telmisartan-treated group at 3 h after the last doses, but they were significantly higher in the telmisartan-treated group than in the losartan-treated group at 24 h after the last doses. In general, increases of PRA and angiotensin II concentration after ARB treatment were observed, and were reflected in the tissue angiotensin II blockade. Therefore, the findings of the present study may be dependent on the longer duration of tissue angiotensin II blockade caused by telmisartan than by losartan. In SHR, there was a significant positive correlation between left ventricular weight and tissue angiotensin II concentration, which is related to lipophilicity (*37*). We recently reported that an ACE inhibitor with high lipophilicity, trandolapril, but not an ACE inhibitor with low lipophilicity, enalapril (both of which produced the same hypotensive effect), reduced cardiac hypertrophy (*6*). Izumi *et al*. (*38*) reported that an increase of mitogen-activated protein kinases, which are activated by AT_1 receptor stimulation, contributed to cardiac hypertrophy in SHR-SP. Therefore, the differences in lipophilicity among ARBs may also be involved in the different levels of protection against cardiac hypertrophy conferred by these agents.

In conclusion, ARBs with different lipophilicities show different protective effects against vascular remodeling in SHR-SP. Although it is accepted that all ARBs show antihypertensive effects and vascular protective effects, different ARBs may exhibit different vascular protective effects in various experimental models and clinical studies. Therefore, further studies are needed to assess the significance of lipophilicity among ARBs.

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