Angiotensin-Converting Enzyme Inhibitor Prevents Age-Related Endothelial Dysfunction

Kenichi Goto, Koji Fujii, Uran Onaka, Isao Abe, Masatoshi Fujishima

Abstract—Vascular relaxation via endothelium-derived hyperpolarizing factor (EDHF) declines in association with aging and also with hypertension, and antihypertensive treatment improves the endothelial dysfunction connected with hypertension. We tested whether the angiotensin-converting enzyme inhibitor improves EDHF-mediated responses in normotensive rats, with special reference to the age-related process. Wistar-Kyoto rats (WKY) were treated with either 20 mg · kg⁻¹ · d⁻¹ enalapril (WKY-E group) or a combination of 50 mg · kg⁻¹ · d⁻¹ hydralazine and 7.5 mg · kg⁻¹ · d⁻¹ hydrochlorothiazide (WKY-H group) from 9 to 12 months of age. Twelve-month-old WKY (WKY-O) and 3-month-old WKY (WKY-Y) served as controls (n=6 to 10 in each group). The 2 treatments lowered systolic blood pressure comparably. EDHF-mediated hyperpolarization to acetylcholine (ACh) in mesenteric arteries was significantly improved in WKY-E, but not in WKY-H, compared with WKY-O, and the hyperpolarization in WKY-E was comparable to that in WKY-Y (hyperpolarization to 10⁻⁵ mol/L ACh in the presence of norepinephrine: WKY-O, -14±2 mV; WKY-E, -22±3 mV; WKY-H, -15±2 mV; and WKY-Y, -28±0 mV). EDHF-mediated relaxation, as assessed by relaxation to ACh in norepinephrine-precontracted rings in the presence of indomethacin and NO synthase inhibitor, was also significantly improved in WKY-E, but not in WKY-H, to a level comparable to that in WKY-Y (maximum relaxation: WKY-O, 45±6%; WKY-E, 63±8%; WKY-H, 43±4%; and WKY-Y, 72±4%). Hyperpolarization and relaxation to levcromakalim, an ATP-sensitive K⁺ channel opener, were similar in all groups. These findings suggest that the angiotensin-converting enzyme inhibitor prevents the age-related decline in EDHF-mediated hyperpolarization and relaxation in normotensive rats, presumably through an inhibition of the renin-angiotensin system. (Hypertension. 2000;36:581-587.)

Key Words: endothelium-derived factor ▪ arteries ▪ aging ▪ drugs ▪ renin-angiotensin system

Endothelium-dependent relaxation, which may be accounted for by several factors, such as NO, prostacyclin, and endothelium-derived hyperpolarizing factor (EDHF),2-11 has been shown to be impaired with aging12,13 as well as by hypertension.7,14,15 Although the mechanisms for this impairment seem to be heterogeneous, we have shown that the decreased EDHF-mediated hyperpolarization partly accounts for the impaired endothelium-dependent relaxation to acetylcholine (ACh) in the mesenteric arteries of adult spontaneously hypertensive rats (SHR)7 and of aged normotensive Wistar-Kyoto rats (WKY).12 In addition, we have demonstrated that antihypertensive treatment with either the angiotensin-converting enzyme (ACE) inhibitor enalapril or a combination of hydralazine and hydrochlorothiazide restores the impaired EDHF-mediated response in SHR.16 Furthermore, in that previous study,16 enalapril tended to be more effective than the combination therapy despite a comparable reduction in blood pressure by both treatments. These observations have led us to consider that inhibition of the renin-angiotensin system may also be important in improving endothelial function.

ACE inhibitors are presently used not only in patients with hypertension but also in patients with other cardiovascular diseases, such as chronic heart failure and/or myocardial infarction. In the Trial on Reversing Endothelial Dysfunction (TREND) study,17 which was a randomized study conducted in normotensive patients with coronary artery disease, chronic treatment with the ACE inhibitor quinapril improved the epicardial arterial response to ACh. Therefore, it is conceivable that ACE inhibitors may have a favorable influence on endothelial function even in normotensive subjects. On the basis of these experimental and clinical findings, we hypothesized that chronic treatment with ACE inhibitors may improve EDHF-mediated hyperpolarization and relaxation in normotensive rats. Because EDHF-mediated hyperpolarization declines with aging,12 special attention was given to clarify a possible treatment effect on age-related changes in the response. For this purpose, we treated WKY with either enalapril (WKY-E) or a combination of hydralazine and hydrochlorothiazide (WKY-H) from 9 to 12 months of age. Age-matched 12-month-old WKY (WKY-O) and 3-month-old WKY (WKY-Y) both served as controls.
Methods

Handling of Animals

The present study was approved by the Committee on the Ethics of Animal Experimentation of Kyushu University. Male WKY/Izm (Disease Model Cooperative Research Association, Kyoto, Japan) were fed a standard rat chow and had free access to tap water. At the age of 9 months, WKY were assigned to either a control group (WKY-O) or to 1 of 2 treatment groups. The WKY-E were treated with 20 mg · kg⁻¹ · d⁻¹ enalapril (Sigma Chemical Co) for 3 months, and the WKY-H were treated with a combination of 50 mg · kg⁻¹ · d⁻¹ indomethacin (Sigma) and 7.5 mg · kg⁻¹ · d⁻¹ hydrochlorothiazide (Sigma) for 3 months. All drugs were given in the drinking water. Water intake was checked 3 times a week, and drug concentrations were adjusted to achieve the above daily doses. Untreated 3-month-old WKY also served as young controls (WKY-Y). There were 6 to 10 rats in each of the 4 groups. In addition, some of the 3-month-old WKY had been treated with 20 mg · kg⁻¹ · d⁻¹ enalapril when they were 8 to 12 weeks old (WKY-Y-E, n=4).

Systolic blood pressure was measured in conscious rats before and at the end of the treatment period. The drugs were withdrawn 2 days before the experiments. The rats were anesthetized with ether and killed by decapitation. The main branch of the mesenteric artery was excised and bathed in cold Krebs’ solution of the following composition (mmol/L): Na⁺ 137.4, K⁺ 5.9, Mg²⁺ 1.2, Ca²⁺ 2.5, HCO₃⁻ 15.5, H₂PO₄⁻ 1.2, Cl⁻ 134, and glucose 11.5. The artery was cut into rings of 3 and 1.2 mm for the electrophysiological and tension experiments, respectively.

Electrophysiological Experiments

Transverse strips cut along the longitudinal axis of the rings were placed in the experimental chamber with the endothelial layer up. Tissues were carefully pinned to the rubber base attached to the bottom of the 2-mL chamber and then superfused with 36°C Krebs’ solution aerated with 95% O₂ /5% CO₂ (pH 7.3 to 7.4) at a rate of 3 ml/min. After equilibration for at least 60 minutes, the membrane potentials of vascular smooth muscle cells were recorded, as described previously.² ¹² ¹⁶

Briefly, conventional glass capillary microelectrodes filled with 3 mol/L KCl and with tip resistances of 50 to 80 MΩ were inserted into the smooth muscle cells from the endothelial side. Criteria for successful insertion included the following: an abrupt drop in voltage when the microelectrode was impaled into the vascular smooth muscle cell, a stable membrane potential for at least 2 minutes, and a sharp return to zero potential on withdrawal of the electrode. Electrical signals were amplified through an amplifier (MEZ-7200, Nihon Koden), monitored on an oscilloscope (VC-11, Nihon Koden), and recorded with a pen recorder (RJG-4002, Nihon Koden).

ACh (Sigma) was applied either during the resting state of the membrane or under depolarization with 10⁻³ mol/L norepinephrine (NE, Sigma). Each dose of ACh was applied separately after an appropriate washout period. Levocromakalim (a gift from SmithKline Beecham Pharmaceuticals, Worthing, UK), a direct activator of ATP-sensitive K⁺ channels,¹⁰ was applied in a cumulative manner.

Isometric Tension Recording

Rings with intact endothelium were placed in the 5-mL organ chambers filled with 36°C Krebs’ solution aerated with 95% O₂ /5% CO₂ (pH 7.4). Two fine stainless-steel wires were placed through the bottom of the 2-mL chamber and then superfused with 36°C Krebs’ solution. The rings were placed in the experimental chamber with the endothelial layer up. Rings with intact endothelium were placed in the 5-mL organ chambers filled with the Krebs’ solution aerated with 95% O₂ /5% CO₂ (pH 7.4) at a rate of 3 ml/min. After equilibration for at least 60 minutes, the membrane potentials of vascular smooth muscle cells were recorded, as described previously.² ¹² ¹⁶

When the microelectrode was impaled into the vascular smooth muscle, a stable membrane potential was found for at least 60 minutes, and a sharp return to zero potential on withdrawal of the electrode. Electrical signals were amplified through an amplifier (MEZ-7200, Nihon Koden), monitored on an oscilloscope (VC-11, Nihon Koden), and recorded with a pen recorder (RJG-4002, Nihon Koden).

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Acute Effects of Angiotensin II

In some mesenteric arteries from WKY-Y, direct effects of angiotensin II (Sigma) on ACh-induced hyperpolarization and relaxation were examined under in vitro conditions. Relaxations to ACh in the presence or absence of 10⁻³ mol/L angiotensin II were examined in rings precontracted with 10⁻⁴ mol/L NE in the presence of indomethacin (10⁻³ mol/L) and L-NNA (10⁻⁴ mol/L).

Drugs and Solutions

The solutions containing 20 or 77 mmol/L KCl were obtained by equimolar replacement of NaCl by KCl in Krebs’ solution. Indomethacin was dissolved in 10 mmol/L Na₂CO₃; L-NNA, in 0.2 mol/L HCl; and levocromakalim, in 90% ethanol. All drugs were further diluted ≥1000 times in Krebs’ solution to produce the final bath concentrations.

Statistical Analysis

Results are given as mean±SEM. The concentration-response curves of hyperpolarization and relaxations were analyzed by 2-way ANOVA followed by the Scheffé test for multiple comparisons. The concentrations of agonists causing half-maximal responses (EC₅₀ value) were also calculated for hyperpolarizations and relaxations by nonlinear regression analysis. The EC₅₀ values were expressed as the negative logarithm of the molar concentration (pD₂ values). Other variables were analyzed by 1-way ANOVA followed by the Scheffé test for multiple comparisons or paired Student t test. A level of P<0.05 was considered statistically significant.

Results

Systolic Blood Pressure, Heart Rate, and Body Weight

The systolic blood pressure, heart rate, and body weight of WKY before and at the end of the treatment period are shown in Table 1. Chronic treatment with enalapril or a combination of hydralazine and hydrochlorothiazide lowered the blood pressure to a comparable extent.

Resting Membrane Potential in Mesenteric Arteries

The resting membrane potential of smooth muscle cells of the mesenteric artery did not differ among the study groups (WKY-O, −49.6±0.5 mV; WKY-E, −50.3±1.3 mV; WKY-H, −50.3±2.2 mV; and WKY-Y, −48.8±1.2 mV [P=NS for all]).

Endothelium-Dependent Hyperpolarization in Mesenteric Arteries

Dose-response curves of the hyperpolarization in response to ACh, applied in the resting state of the membrane, are shown in Figure 1. ACh-induced hyperpolarization was significantly smaller in WKY-O than in WKY-Y (P<0.05). Enalapril treatment (WKY-E) but not the combination of hydralazine and hydrochlorothiazide (WKY-H) led to a significant improvement in hyperpolarization compared with the control condition (WKY-O) (P<0.05), and the response attained in

NE. After the contractions had reached a steady level, the relaxant effects of ACh were studied by adding the drug in increasing concentrations, from 10⁻⁵ to 10⁻³ mol/L.

In some preparations, the rings were contracted with 77 mmol/L KCl solution in the presence of 10⁻³ mol/L indomethacin, and a relaxation response to ACh was observed. Relaxation in response to levocromakalim and sodium nitroprusside (Sigma) was studied in rings contracted with 10⁻⁴ mol/L NE in the presence of 10⁻³ mol/L indomethacin. The extent of the relaxation was expressed as the percentage of the initial contraction evoked by the contractile agonist.
WKY-E was comparable to that in WKY-Y (pD2 values: WKY-O, 7.1±0.1; WKY-E, 7.2±0.1; WKY-H, 7.1±0.1; and WKY-Y, 7.0±0.1 [P=NS for all]); maximal hyperpolarization: WKY-O, -10.2±1.3 mV [P<0.05 versus WKY-Y]; WKY-E, -15.9±1.4 mV [P<0.05 versus WKY-O]; WKY-H, -10.3±1.0 mV [P<0.05 versus WKY-Y]; and WKY-Y, -17.3±1.4 mV [P<0.05 versus WKY-O]).

Representative tracings and a summary of the data of ACh-induced hyperpolarization under conditions of depolarization with 10−5 mol/L NE in the presence of 10−5 mol/L indomethacin are shown in Figure 2. Vessels were preincubated with 10−5 mol/L indomethacin to eliminate the possible depolarizing actions of cyclooxygenase products known to be released under these conditions.14–16 The degree of depolarization (WKY-O), and no significant difference was observed between the responses in WKY-E and WKY-Y.

**Endothelium-Dependent Relaxation in Mesenteric Arteries**

In mesenteric arterial rings precontracted with 10−5 mol/L NE in the absence of indomethacin (10−5 mol/L), ACh produced a dose-dependent relaxation in all groups (Figure 3A, Table 2). The maximal relaxation was significantly smaller in WKY-O than in WKY-Y. Pretreatment with indomethacin augmented the relaxation in arteries from 12-month-old WKY groups, especially in WKY-O arteries (Figure 3A and 3B). In the presence of indomethacin, relaxations to ACh did not differ significantly among the 4 study groups, although the responses tended to be greater in WKY-Y.

The NO synthase inhibitor L-NNA (10−4 mol/L) significantly inhibited relaxations to ACh, but substantial relaxation remained after exposure to both indomethacin and L-NNA in all groups (Figure 3C, Table 2). This residual relaxation was abolished by a high-KCl solution (20 mmol/L). The L-NNA-resistant relaxation to ACh was significantly smaller in WKY-O than in WKY-Y. Enalapril treatment (WKY-E) but not the combination of hydralazine and hydrochlorothiazide (WKY-H) significantly improved the L-NNA-resistant relaxation to ACh to a level comparable to that in WKY-Y (Figure 3C, Table 2).

When rings pretreated with indomethacin were contracted with 77 mmol/L KCl to eliminate EDHF-mediated hyperpolarization,16,18 no difference was found in the relaxation produced in response to ACh among the 4 groups (pD2 values: WKY-O, 6.4±0.1; WKY-E, 6.1±0.2; WKY-H, 6.2±0.1; and WKY-Y, 6.5±0.1 [P=NS for all]); maximal relaxation: WKY-O, 63.0±3.2%; WKY-E, 52.3±8.1%; WKY-H, 56.6±2.2%; and WKY-Y, 63.9±1.1% [P=NS for all]). This relaxation was abolished by further incubation with 10−4 mol/L L-NNA (data not shown).

**TABLE 1.** Systolic Blood Pressure, Heart Rate, and Body Weight Before and After 3 Months of Treatment in the 4 Study Groups

<table>
<thead>
<tr>
<th></th>
<th>Blood Pressure, mm Hg</th>
<th>Heart Rate, bpm</th>
<th>Body Weight, g</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td>Before</td>
</tr>
<tr>
<td>WKY-O</td>
<td>151±5</td>
<td>155±4</td>
<td>411±18</td>
</tr>
<tr>
<td>WKY-E</td>
<td>155±3</td>
<td>126±5†</td>
<td>391±14</td>
</tr>
<tr>
<td>WKY-H</td>
<td>158±4</td>
<td>124±4†</td>
<td>373±17</td>
</tr>
<tr>
<td>WKY-Y</td>
<td>148±4</td>
<td>ND</td>
<td>370±7</td>
</tr>
</tbody>
</table>

Values are mean±SEM. ND indicates not determined. There were 7 to 10 rats in each group.

*P<0.01 vs WKY-O; †P<0.01 vs before; and ‡P<0.01 vs WKY-Y.
Endothelium-Independent Hyperpolarization and Relaxation
Levcromakalim produced a comparable degree of hyperpolarization in the mesenteric arteries in all groups (pD2 values: WKY-O, 6.8 ± 0.1; WKY-E, 6.8 ± 0.1; WKY-H, 6.8 ± 0.1; and WKY-Y, 7.0 ± 0.1 [P = NS for all]; maximal hyperpolarization: WKY-O, −26.1 ± 1.1 mV; WKY-E, −25.4 ± 1.7 mV; WKY-H, −26.2 ± 1.0 mV; and WKY-Y, −23.6 ± 0.2 mV [P = NS for all]). The levcromakalim-induced relaxation in rings precontracted with 10−5 mol/L NE was also similar among the 4 groups (Table 2).

The maximum relaxations to sodium nitroprusside, an NO donor, in rings precontracted with 10−5 mol/L NE did not differ among the 12-month-old WKY groups (Table 2), but the response was significantly smaller in WKY-O than in WKY-Y.

Effects of Enalapril Treatment on EDHF-Mediated Hyperpolarization and Relaxation in Young WKY
One-month treatment of 8-week-old WKY (WKY-Y-E) lowered systolic blood pressure from 148.0 ± 3.4 to 123.0 ± 5.0 mm Hg (n = 4, P < 0.05 for before versus after treatment). ACh-induced hyperpolarizations in mesenteric arteries in the absence or presence of NE in WKY-Y-E were not different from those in WKY-Y (pD2 values in the absence of NE: WKY-Y, 7.0 ± 0.1; WKY-Y-E, 6.7 ± 0.1 [P = NS]; maximal hyperpolarization in the absence of NE: WKY-Y, −17.3 ± 1.4 mV; WKY-Y-E, −16.8 ± 2.8 mV [P = NS]; hyperpolarization to 10−7 mol/L ACh in the presence of 10−5 mol/L NE: WKY-Y, −15.7 ± 2.3 mV; WKY-Y-E, −9.5 ± 1.7 mV [P = NS]; hyperpolarization to 10−5 mol/L ACh in the presence of 10−3 mol/L NE: WKY-Y, −28.3 ± 0.4 mV; WKY-Y-E, −25.0 ± 2.6 mV [P = NS]).
ACE inhibitor prevents age-related decline in EDHF-mediated hyperpolarization and relaxation in normotensive rats. In our previous study, EDHF-mediated responses in mesenteric arteries were attenuated in aged WKY (aged ≥24 months) compared with younger WKY. In the present study, EDHF-mediated hyperpolarization and relaxation were significantly smaller in untreated 12-month-old WKY than in 3-month-old WKY, suggesting that the age-related decline in the EDHF-mediated responses may already be evident at the age of ≈12 months in rats. The fact that chronic enalapril treatment eliminated the difference in the EDHF-mediated responses between young and older WKY suggests that the ACE inhibitor prevents the age-related deterioration in the EDHF responses.

In the present study, enalapril, but not a combination of hydralazine and hydrochlorothiazide, improved EDHF-mediated hyperpolarization and relaxation, despite a comparable reduction in blood pressure. These results suggest that inhibition of the renin-angiotensin system plays a major role in improving EDHF-mediated responses in normotensive rats and that blood pressure reduction alone is not sufficient for this effect. However, we cannot totally rule out the possibility that both renin-angiotensin system blockade and blood pressure lowering are required for the observed benefit.

The underlying mechanisms of the improvement in EDHF-mediated responses by ACE inhibitors remain unclear from the present findings alone. The improvement cannot be explained by the general improvement in the smooth muscle sensitivity to hyperpolarizing or vasodilatory stimuli, because hyperpolarization and relaxation to levcromakalim, a direct activator of ATP-sensitive K+ channels, and relaxation to nitroprusside, an NO donor, were not different for treated and untreated WKY. Furthermore, EDHF-mediated responses were significantly smaller in untreated 12-month-old WKY than in 3-month-old young WKY. These findings suggest that ACE inhibitors improve EDHF-mediated hyperpolarization and relaxation in normotensive rats, presumably through the prevention of the age-related impairment of the EDHF response, and that this beneficial effect may primarily be related to the inhibition of the renin-angiotensin system and not to the lowering of blood pressure per se.

In the rat mesenteric artery, ACh-induced hyperpolarization is mediated by EDHF, but not by NO or prostacyclins. On the other hand, ACh-induced relaxation in this preparation is determined by the balance of NO, EDHF, and endothelium-derived contracting factor, and the EDHF-mediated relaxation can be assessed by the relaxation under the combined blockade of cyclooxygenase and NO synthase. This is the first study to demonstrate that chronic treatment with the ACE inhibitor improves EDHF-mediated hyperpolarization and relaxation in normotensive rats. In our previous study, EDHF-mediated responses in mesenteric arteries were attenuated in aged WKY (aged ≥24 months) compared with younger WKY. In the present study, EDHF-mediated hyperpolarization and relaxation were significantly smaller in untreated 12-month-old WKY than in 3-month-old WKY, suggesting that the age-related decline in the EDHF-mediated responses may already be evident at the age of ≈12 months in rats. The fact that chronic enalapril treatment eliminated the difference in the EDHF-mediated responses between young and older WKY suggests that the ACE inhibitor prevents the age-related deterioration in the EDHF responses.

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be clarified whether the age-related decline in endothelial function and its improvement in response to ACE inhibitors are associated with vascular structural changes.

ACh-induced relaxations in rings contracted with NE in the presence of indomethacin but in the absence of NO synthase inhibitors may be accounted for by both NO and EDHF. In the present study, ACh-induced relaxation under this condition was not different among the study groups. Furthermore, the NO-mediated relaxation, which can be assessed by relaxation to ACh in rings precontracted with high KCl, was also comparable among the 4 groups, suggesting that the NO system in this particular preparation is preserved at least up to the age of the rats studied and is not modulated by drug therapy. It has been suggested that EDHF may serve as a backup system for NO. Even in WKY-O, ACh still evoked a certain amount of hyperpolarization, and we speculate that preserved NO-induced relaxation together with some hyperpolarization in WKY-O may manage to maintain a comparable relaxation to ACh under the above condition.

Several previous studies have examined the chronic effects of ACE inhibitors on endothelial function in normotensive rats. In a study by Kähönen et al., in which WKY were treated with quinapril from 7 to 17 weeks of age, no difference was found in the relaxation response to ACh in mesenteric arteries between treated and untreated rats in the presence or absence of NO synthase inhibitors. The difference in the results between their study and the present study might arise from the difference in the age of the rats; ie, in their study, even after the treatment period, the rats were only 17 weeks old, an age at which EDHF-mediated responses may well be preserved. This notion is also supported by the present observation that 1 month of treatment of young WKY with enalapril did not affect EDHF-mediated hyperpolarization and relaxation.

On the other hand, a 6-week treatment of Wistar rats with either enalapril or ramipril has been shown to improve endothelium-dependent relaxation in the aorta. However, EDHF-mediated relaxation was not assessed in these studies, and moreover, contribution of EDHF to relaxation is of minor importance in the rat aorta. Indeed, ramipril might improve the relaxation by enhancing NO availability after bradykinin accumulation. Atkinson et al. have examined the effects of long-term treatment (from 6 up to 30 months of age) with the ACE inhibitor perindopril on vasodilator responses in the perfused mesenteric vascular bed of normotensive rats. They found that such treatment prevents the decline in dilator response to carbachol; however, this decline is evident only in very old rats (30 months of age). Again, no information is available regarding the relative contribution of EDHF to the relaxation. Therefore, the present study is clearly distinct from previous studies in that the ACE inhibitor improves EDHF-mediated responses presumably by alleviating early endothelial dysfunction associated with aging process. The EDHF system functions in human arteries and may also decline with aging. It remains to be clarified whether the clinical benefits of ACE inhibitors are associated with any changes in the EDHF system. It also remains to be determined whether angiotensin II type 1 receptor antagonists or their combination with ACE inhibitors exerts effects similar to those of ACE inhibitors.

In conclusion, the present study has demonstrated that the treatment of normotensive rats with ACE inhibitors prevents the age-related decline in endothelium-dependent hyperpolarization and relaxation via EDHF, primarily through their specific actions on the renin-angiotensin system. The possibility that the early functional aging process of the vascular endothelium could be modulated by drugs that inhibit the renin-angiotensin system may warrant further investigation.

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