Antihypertensive Treatment Improves Endothelium-Dependent Hyperpolarization in the Mesenteric Artery of Spontaneously Hypertensive Rats

Uran Onaka, MD; Koji Fujii, MD, PhD; Isao Abe, MD, PhD; Masatoshi Fujishima, MD, PhD

Background — The vascular endothelium releases endothelium-derived hyperpolarizing factor (EDHF). The mesenteric arteries of 6- to 8-month-old spontaneously hypertensive rats (SHRs) exhibit an impairment of the hyperpolarization induced by acetylcholine via EDHF.

Methods and Results — We determined whether antihypertensive treatment can improve EDHF-mediated responses in SHRs. Beginning at age 8 to 9 months, the animals were treated with either enalapril (40 mg·kg⁻¹·d⁻¹) (SHR-Es) or a combination of hydralazine (25 mg·kg⁻¹·d⁻¹) and hydrochlorothiazide (7.5 mg·kg⁻¹·d⁻¹) (SHR-Hs) for 3 months. The control groups were age-matched SHRs (SHR-Cs) and Wistar Kyoto rats (WKYs). The two treatments lowered the blood pressure to comparable extents. The acetylcholine-induced hyperpolarization in the mesenteric artery of treated SHRs improved to a level comparable to that in WKYs (acetylcholine 10⁻⁴mol/L with norepinephrine 10⁻⁵mol/L: SHR-E, −14.4±1.8; SHR-H, −12.0±1.3; SHR-C, −7.2±1.2; and WKY, −13.3±2.3 mV). EDHF-mediated relaxation, as assessed by relaxation to acetylcholine resistant to N⁶-nitro-L-arginine in norepinephrine-contracted rings, was markedly improved in treated SHRs (maximal relaxation: SHR-E, 79.3±3.2%; SHR-H, 47.4±8.6%; SHR-C, 4.8±2.4%; and WKY, 45.1±6.0%). When the rings were contracted with 77 mmol/L KCl to eliminate EDHF response, no difference was found in relaxation to acetylcholine among the four groups. Similarly, the hyperpolarization and relaxation to levocromakalim, a K⁺ channel opener, were comparable among the groups.

Conclusions — Antihypertensive treatment improved EDHF-mediated hyperpolarization and relaxation in the mesenteric artery in SHRs, whereas NO-mediated relaxation did not appear to be modulated by drug therapy. Thus, alterations in the EDHF system may play a pivotal role in endothelial dysfunction and its improvement with drug therapy in SHRs.

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Key Words: endothelium-derived factors ♦ arteries ♦ hypertension ♦ drugs

Endothelial cells are important in the regulation of vascular tone by the release of relaxing factors such as NO²⁻¹³ and prostacyclin. Evidence suggests that the vascular endothelial cells release another diffusible factor that relaxes the underlying smooth muscle cells by producing membrane hyperpolarization.⁴⁻⁸ This substance, called EDHF,⁵⁻⁷⁻⁸ is thought to hyperpolarize membranes by opening the K⁺ channels.⁶⁻⁹⁻¹⁰ Recent studies suggest that EDHF may be a cytochrome P450–derived arachidonic acid metabolite in certain arteries¹¹⁻¹²; however, confirmation is still required.¹³

Hypertension has been shown to be associated with an impairment of endothelium-dependent relaxation both in humans¹⁴⁻¹⁶ and in animal models of experimental hypertension.¹⁷⁻²¹ The mechanisms seem to vary.¹⁷⁻²⁰⁻²³⁻²⁴ We previously reported a severe impairment of the ACh-induced hyperpolarization and relaxation via EDHF in the mesenteric arteries of 6- to 8-month-old SHRs.¹⁰⁻²⁵ Considering the importance of the endothelium in the control of vascular tone,²⁶ we thought that it was important to determine whether endothelial dysfunction in hypertension is reversible or preventable. It has been shown that acute treatment with perindoprilat, an ACE inhibitor, potentiates endothelium-dependent hyperpolarization to bradykinin in the canine and human coronary arteries in vitro.²⁷ Although several studies found that endothelial function was improved by drug therapy,¹⁸⁻¹⁹⁻²¹⁻²²⁻²⁸⁻³¹ none evaluated the effects of chronic antihypertensive treatment on EDHF-mediated hyperpolarization per se.

The present study tested whether antihypertensive treatment can restore the impaired EDHF-mediated hyperpolarization and relaxation in the mesenteric arteries of SHRs. For this purpose, we treated 8- to 9-month-old SHRs with either the ACE inhibitor enalapril or a combination of hydralazine and hydrochlorothiazide for 3 months.

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Methods

Handling of Animals
This study was approved by the Committee on the Ethics of Animal Experimentation of the Faculty of Medicine, Kyushu University. Male SHR/Imz and age-matched WKY/Imz rats were purchased from the Disease Model Cooperative Research Association, Kyoto, Japan. Rats were fed a standard rat chow and had free access to tap water. At the age of 8 to 9 months, SHRs were assigned to one control (SHR-C) and two treatment groups. The SHR-E group was treated with enalapril (Sigma Chemical Co) 40 mg/kg, whereas the SHR-H group was treated with a combination of hydralazine (Sigma) 25 mg/kg and enalapril (Sigma)-treated SHR. SHR-C was untreated control SHR. SHR-H was hydralazine-/hydrochlorothiazide-treated SHR. WKY = Wistar Kyoto rat.

Electrophysiological Experiments
Briefly, conventional glass capillary microelectrodes filled with 3 mol/L KCl and 20 mmol/L KCl. Indomethacin is an inhibitor of cyclooxygenase, and L-NNA is an inhibitor of NO synthase. All agents were applied 60 minutes before the challenge with NE and were present throughout the experiments. The rings were contracted with 10−4 mol/L NE; in preliminary experiments, this dose of NE produced near-maximum contraction in each group. After the contractions had reached a steady level, the relaxant effects of ACh were studied by adding the drug in increasing concentrations, from 10−9 to 10−3 mol/L.

In some preparations, rings were contracted with 77 mmol/L KCl solution in the presence of 10−3 mol/L indomethacin and the relaxing response to ACh was observed. Relaxation in response to levcromakalim and sodium nitroprusside (Sigma) was studied in rings contracted with 10−3 mol/L NE in the presence of 10−2 mol/L indomethacin. The extent of relaxation was expressed as the percentage of the initial contraction evoked by the contractile agonist.

Acute Effects of ACE Inhibitor
In addition, the acute effect of captopril (Sigma), an ACE inhibitor, on the endothelium-dependent hyperpolarization and relaxation to ACh in the mesenteric arteries of SHR-Cs was investigated. ACh (10−6 mol/L)–induced hyperpolarization was obtained before and after the application of captopril (10−5 mol/L). In a separate set of experiments, after preincubation with indomethacin (10−3 mol/L) and L-NNA (10−4 mol/L), ACh-induced relaxation was studied in rings contracted with 10−3 mol/L NE in the presence or absence of captopril (10−3 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 levcromakalim in 90% ethanol. All drugs were further diluted 1000 times or more in Krebs solution to produce the final bath concentrations. The solvents used to dissolve the drugs did not affect electrical and mechanical responses in the final bath concentrations.

Statistics
Results are given as mean±SEM. Concentration-response curves of hyperpolarization and relaxation were analyzed by two-way ANOVA followed by Scheffe’s test for multiple comparisons. The concentrations of agonists causing half-maximal responses (EC50 value) were also calculated for hyperpolarizations and relaxations using a nonlinear regression analysis. The EC50 values were expressed as the negative logarithm of the molar concentration (pD2 values). Other variables were analyzed by one-way ANOVA followed by Scheffe’s test for multiple comparisons or paired Student’s t test. A level of P<0.05 was considered statistically significant.

Results
Systolic Blood Pressure, Heart Rate, and Body Weight
Systolic blood pressure, heart rate, and body weight of SHRs and WKYs before and at the end of the treatment period were

<table>
<thead>
<tr>
<th>SHR-E</th>
<th>SHR-H</th>
<th>SHR-C</th>
<th>WKY</th>
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**Select Abbreviations and Acronyms**

ACh = acetylcholine  
EDHF = endothelium-derived hyperpolarizing factor  
L-NNA = Nω-nitro-L-arginine  
NE = norepinephrine  
SHR = spontaneously hypertensive rat  
SHR-C = untreated control SHR  
SHR-E = enalapril-treated SHR  
SHR-H = hydralazine-/hydrochlorothiazide-treated SHR  
WKY = Wistar Kyoto rat
shown in Table 1. Before the initiation of treatment, the systolic blood pressure was significantly higher in the SHRs than in the WKYs. Antihypertensive treatment with enalapril or with a combination of hydralazine and hydrochlorothiazide significantly lowered the blood pressure of SHRs to a level comparable to that of WKYs. No significant difference was noted in the blood pressure of SHR-Es and SHR-Hs during the treatment period.

Heart rate was increased significantly by combined treatment with hydralazine and hydrochlorothiazide. Body weight was significantly greater in WKYs than in SHRs both before and after treatment. Body weight did not differ among the SHR groups throughout the study period.

Resting Membrane Potential in Mesenteric Arteries

The resting membrane potential of smooth muscle cells of the mesenteric artery was significantly less negative in SHR-Cs (-43.9±2.0 mV) than in WKYs (-49.8±0.6 mV, P<0.05). The resting membrane potential in SHR-Es (-49.8±1.3 mV) was more negative than that in SHR-Cs (P<0.05) but did not differ from that in WKYs. Although the resting membrane potential also tended to be more negative in SHR-Hs (-46.1±1.3 mV) than in SHR-Cs, the difference did not reach statistical significance.

Endothelium-Dependent Hyperpolarization in Mesenteric Arteries

Representative tracings and a summary of the data of the oscillatory response, was comparable among the four groups (data not shown).

\[ pD_2 \text{ indicates negative logarithm of molar concentration of the drug causing half-maximal hyperpolarization; Max, maximal hyperpolarization to drugs. Values are mean±SEM. There were 6 to 11 rats in each group.} \]

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

<table>
<thead>
<tr>
<th>Blood Pressure, mm Hg</th>
<th>Heart Rate, bpm</th>
<th>Body Weight, g</th>
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</thead>
<tbody>
<tr>
<td>Before</td>
<td>After</td>
<td>Before</td>
</tr>
<tr>
<td>SHR-C</td>
<td>246±5†</td>
<td>259±4†</td>
</tr>
<tr>
<td>SHR-E</td>
<td>252±5†</td>
<td>143±8†</td>
</tr>
<tr>
<td>SHR-H</td>
<td>242±6†</td>
<td>163±6†</td>
</tr>
<tr>
<td>WKY</td>
<td>155±5*</td>
<td>158±3*</td>
</tr>
</tbody>
</table>

Values are mean±SEM. There were 10 or 11 rats in each group. *P<0.01 vs SHR-C; †P<0.01 vs WKY; ‡P<0.05 vs before.

### TABLE 2. Hyperpolarizations to ACh and Levcromakalim in the Mesenteric Artery of SHRs and WKYs

<table>
<thead>
<tr>
<th>Acetylcholine</th>
<th>Levcromakalim</th>
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<tbody>
<tr>
<td>pD2</td>
<td>Max, mV</td>
</tr>
<tr>
<td>SHR-C</td>
<td>7.1±0.1</td>
</tr>
<tr>
<td>SHR-E</td>
<td>6.9±0.1</td>
</tr>
<tr>
<td>SHR-H</td>
<td>6.8±0.1</td>
</tr>
<tr>
<td>WKY</td>
<td>7.1±0.1</td>
</tr>
</tbody>
</table>

pD2 indicates negative logarithm of molar concentration of the drug causing half-maximal hyperpolarization; Max, maximal hyperpolarization to drugs. Values are mean±SEM. There were 6 to 11 rats in each group. *P<0.05 vs SHR-C; †P<0.05 vs WKY.
significantly improved the ACh-induced relaxation compared with the response in SHR-Cs (Figure 3A and 3B and Table 3); the relaxation in SHR-Es was comparable to that in WKYs. Treatment with hydralazine and hydrochlorothiazide also tended to improve ACh-induced relaxation, and the response in SHR-Hs was comparable to that in WKYs in the presence of indomethacin (Figure 3B, Table 3).

In SHR-Cs, incubation with $10^{-4}$ mol/L L-NNA virtually abolished the relaxation in rings pretreated with indomethacin (Figure 3C, Table 3). However, in SHR-Es, SHR-Hs, and WKYs, substantial relaxation remained after exposure to both indomethacin and L-NNA. This residual relaxation was abolished by a high-KCl solution ($20$ mmol/L). Antihypertensive treatment with a combination of hydralazine and hydrochlorothiazide markedly improved the L-NNA–resistant relaxation to ACh, to a level comparable to that in WKYs (Figure 3C, Table 3). Enalapril treatment led to an even more pronounced improvement in L-NNA–resistant relaxation to ACh.

When rings pretreated with indomethacin were contracted with $77$ mmol/L KCl to eliminate EDHF-mediated hyperpolarization, no difference was found in the relaxation produced in response to ACh among the four groups (Figure 4) ($p_D_2$ values: SHR-C, $6.6\pm0.1$; SHR-E, $6.7\pm0.1$; SHR-H, $6.4\pm0.2$; WKY, $6.4\pm0.1$; $P$=NS. Maximal relaxation (%): SHR-C, $59.1\pm4.8$; SHR-E, $61.7\pm5.3$; SHR-H, $64.3\pm2.5$; WKY, $66.7\pm3.7$; $P$=NS). This relaxation was abolished by further incubation with $10^{-4}$ mol/L L-NNA.

**Endothelium-Independent Hyperpolarization and Relaxation in Mesenteric Arteries**

Levcromakalim produced a comparable degree of hyperpolarization in the mesenteric arteries in all groups (Table 2). The levcromakalim-induced relaxation in rings precontracted with $10^{-5}$ mol/L NE was similar among the four groups (Table 3).

Relaxations to sodium nitroprusside, an NO donor, in rings precontracted with $10^{-5}$ mol/L NE also did not differ among the four groups (Table 3).

**Acute Effects of ACE Inhibitor**

ACh ($10^{-5}$ mol/L)–induced hyperpolarization in the mesenteric arteries of SHR-Cs was not affected by the in vitro treatment with captopril ($10^{-5}$ mol/L) (control, $-6.0\pm2.0$ mV; in the presence of captopril, $-5.3\pm1.8$ mV; $n$=5; $P$=NS). Likewise, in SHR-Cs, captopril ($10^{-5}$ mol/L) treatment did not improve relaxation to ACh in rings precontracted with NE ($10^{-5}$ mol/L) in the presence of indomethacin ($10^{-5}$ mol/L) and L-NNA ($10^{-4}$ mol/L) (maximum relaxation: without captopril, $7.8\pm2.4$%; in the presence of captopril, $6.3\pm2.2$%; $n$=5; $P$=NS).

**Discussion**

The present study clearly demonstrated that antihypertensive treatment improved the EDHF-mediated hyperpolarization and relaxation in the mesenteric arteries of SHRs. Although
enalapril as well as a combination of hydralazine and hydrochlorothiazide favorably influenced endothelial function, the effects of enalapril tended to be more pronounced. The NO-mediated relaxation appeared to be preserved in the mesenteric arteries and was not modulated by antihypertensive treatment. The levocromakalim-induced hyperpolarization and relaxation were comparable among the SHR and WKY groups regardless of treatment.

**Effects of Antihypertensive Treatments on EDHF-Mediated Hyperpolarization**

Previous studies have suggested that endothelium-dependent hyperpolarization in response to ACh in the rat mesenteric artery is not mediated by NO or prostacyclin but presumably is mediated by EDHF. Also, EDHF-mediated hyperpolarization contributes to endothelium-dependent relaxation. We previously showed that ACh-induced hyperpolarization and relaxation via EDHF are markedly impaired in the arteries of 6- to 8-month-old SHRs compared with age-matched WKYs. Van de Voorde et al reported an impairment of endothelium-dependent hyperpolarization in response to carbachol in the aortas of rats with renal hypertension. Endothelium-dependent hyperpolarization decreases with increasing age, even in normotensive rats.

The underlying mechanisms by which drug therapy improved the EDHF-mediated hyperpolarization are not known from the present study, but we can speculate about several mechanisms. Because hyperpolarization in response to levocromakalim, a direct activator of ATP-sensitive K⁺ channels, was not modulated by antihypertensive treatment, alteration in smooth muscle properties may not be involved. However, because the K⁺ channels responsible for hyperpolarization may differ with ACh and levocromakalim, this possibility cannot be totally dismissed. In isolated canine and human coronary arteries, hyperpolarization elicited by bradykinin, which is mediated by EDHF, was augmented in the presence of perindoprilat, an ACE inhibitor. It is possible that such an acute effect of the ACE inhibitor contributed to the improvement of ACh-induced hyperpolarization after chronic treatment. This seems unlikely, however, because treatment was withdrawn before the experiments, and the preincubation of isolated vessels with the ACE inhibitor captopril did not affect ACh-induced hyperpolarization in SHR-Cs.

Because two different regimens improved ACh-induced hyperpolarization to a level similar to that in WKYs, this improvement may be at least partially attributable to their blood pressure–lowering effects. However, a significant difference compared with SHR-Cs was attained in the SHR-E group but not in the SHR-H group despite a comparable reduction in blood pressure by both treatments. This raises the possibility that enalapril may exert beneficial effects in part via a mechanism unrelated to blood pressure control. Consistent with this notion, in the TREND study, 6-month treatment with the ACE inhibitor quinapril in normotensive patients with coronary artery disease improved their endothelial function without affecting their blood pressure. Furthermore, Clozel et al demonstrated that treatment of SHRs with cilazapril but not with hydralazine improved endothelial function of the carotid arteries.

Subendothelial thickening of the vessel wall has been documented in arteries of SHRs. Such thickening could potentially limit the transit of EDHF. One possible mechanism by which drug therapy improves endothelial function may be reversal of subendothelial thickening. Indeed, ACE inhibitors have been shown to reverse cardiovascular structural changes effectively. Further studies are required to elucidate underlying mechanisms of the impaired EDHF-

### Table 3. Relaxations to ACh, Sodium Nitroprusside, and Levocromakalim in the Mesenteric Arteries of SHRs and WKYs

<table>
<thead>
<tr>
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<th>Acetylcholine</th>
<th>Sodium Nitroprusside</th>
<th>Levocromakalim</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>pD₂</td>
<td>Max, %</td>
<td>pD₂</td>
</tr>
<tr>
<td>SHR-C</td>
<td>6.6±0.2</td>
<td>16.9±5.7†</td>
<td>7.4±0.2</td>
</tr>
<tr>
<td>SHR-E</td>
<td>6.9±0.2</td>
<td>71.8±10.9*</td>
<td>7.7±0.3</td>
</tr>
<tr>
<td>SHR-H</td>
<td>6.9±0.1</td>
<td>40.8±9.5</td>
<td>7.2±0.1</td>
</tr>
<tr>
<td>WKY</td>
<td>7.3±0.3</td>
<td>67.0±10.0*</td>
<td>7.3±0.2</td>
</tr>
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</table>

*pD₂ indicates negative logarithm of molar concentration of the drug causing half-maximal relaxation in the norepinephrine (10⁻⁵ mol/L)-precontracted arterial rings; Max, maximal relaxation to drugs; and ND, not determined. Values are mean±SEM. There were 7 to 9 rats in each group. *P<0.05 vs SHR-C; †P<0.05 vs WKY; †‡P<0.05 vs SHR-H.

Figure 4. Concentration-response curves of relaxation to ACh in rings precontracted with 77 mmol/L KCl in presence of 10⁻⁶ mol/L indomethacin in endothelium-intact mesenteric arterial rings of SHR-Cs, SHR-Es, SHR-Hs, and WKYs. Values are mean±SEM. There were 7 to 9 rats in each group.
mediated hyperpolarization in SHRs and its improvement by drug therapy.

Effects of Antihypertensive Treatments on EDHF-Mediated Relaxation

Most studies in animal models have demonstrated a favorable influence of antihypertensive treatment on endothelial function, although the benefits have varied considerably, depending on the antihypertensive drugs used. Studies in humans have given less consistent results, but some found improvement in endothelial function after short- or long-term drug treatments.

ACH-induced relaxation in the rat mesenteric artery is determined by the balance of NO, EDHF, and endothelium-derived contracting factor. The present study demonstrated that 3 months of antihypertensive treatment in SHRs improved endothelium-dependent relaxation in response to ACh in mesenteric arteries precontracted with NE. The relaxation, especially in the SHR-C group, was enhanced by incubation with indomethacin, confirming that some impairment in SHRs is due to the simultaneous release of cyclooxygenase-dependent endothelium-derived contracting factor. However, the most marked improvement was observed in the relaxation that remained after the exposure to a combination of indomethacin and L-NNA. The latter is a potent inhibitor of NO synthase. This relaxation was abolished by further incubation with high KCl, suggesting that this relaxation is mediated by EDHF. Accordingly, the improvement of this component of relaxation most likely reflects the improved EDHF-mediated hyperpolarization.

The EDHF-mediated relaxation in enalapril-treated SHRs was significantly better than that in SHRs treated with hydralazine and hydrochlorothiazide. In the electrophysiologic experimental, enalapril tended to improve the ACh-induced hyperpolarization to a greater extent than did the combined treatment with hydralazine and hydrochlorothiazide, which may partly explain the greater EDHF-mediated relaxation in enalapril-treated SHRs.

It is not known why EDHF-mediated relaxation in enalapril-treated SHRs exceeded that in WKYs, despite the comparable degree of ACh-induced hyperpolarization in the two groups. Hyperpolarization may induce relaxation in part by closure of voltage-dependent Ca2+ channels. Vascular tone has been shown to depend on voltage-dependent Ca2+ influx to a greater extent in SHRs than in WKYs. It follows that a given hyperpolarization might lead to greater relaxation in SHRs. However, this does not fully explain the difference between enalapril-treated SHRs and WKYs, because the relaxation induced by levocarnalamil did not differ among the study groups. Furthermore, enalapril treatment has been shown to correct such an abnormality in Ca2+ handling in arteries of SHRs. Treatment with ACE inhibitors may reduce the contractile response to agonists, thereby mechanically augmenting the relaxation. However, the maximal active tension generated by 10-3 mol/L NE did not differ among the four study groups (unpublished data). Finally, we cannot completely exclude the possibility that ACh-induced hyperpolarization may indeed be larger in SHR-Es than in WKYs under the conditions used in the tension experiment.

Kähönen et al showed that NO synthase inhibition inhibited the relaxation response to ACh less effectively in rings of quinapril-treated, 17-week-old SHRs precontracted with NE than in those of untreated SHRs, suggesting a greater role of EDHF in relaxation of treated SHRs. Takase et al also showed that long-term treatment with a calcium antagonist or ACE inhibitor prevented endothelial dysfunction in NO-deficient hypertension, most likely by a mechanism independent of NO production. It should be mentioned that antihypertensive treatment in our study was initiated at age 8 to 9 months, much later than in other animal studies. We previously showed that EDHF-mediated hyperpolarization and relaxation in SHRs are preserved at 5 to 6 weeks of age but are impaired at 6 to 8 months. Nakashima and Vanhoutte showed that ACh-induced hyperpolarization was comparable in SHRs and WKYs up to 20 to 24 weeks of age but was significantly less in SHRs at 40 to 50 weeks. These findings suggest that the impairment of EDHF-mediated hyperpolarization in SHRs becomes evident after hypertension is established. Thus, our study design may have allowed us to elucidate the restoration rather than the preservation of the EDHF-mediated responses with drug therapy.

NO-Mediated Relaxation in SHRs

In the present study, when vessels were precontracted with a high-KCl solution, which eliminates ACh-induced hyperpolarization, relaxation in response to ACh was almost identical among the treated-SHR, untreated-SHR, and WKY groups. Because this relaxation was abolished by L-NNA, it could be solely attributable to NO. Therefore, the NO-mediated relaxation response to ACh may be preserved in mesenteric arteries of SHRs and may not be modulated by antihypertensive treatment. This possibility is somewhat unexpected but may be consistent with some of the previous publications.

Kähönen et al also found that relaxation in response to ACh in KCl-contracted mesenteric arterial rings was similar among SHRs, quinapril-treated SHRs, and WKYs. Lüscher and Vanhoutte and our group showed that in the aorta, where the contribution of EDHF to relaxation is of minor importance, the relaxation in response to ACh was comparable in SHRs and WKYs during cyclooxygenase blockade. Furthermore, Hayakawa et al showed that the level of NO metabolites in the perfusate of isolated kidneys did not differ in SHRs and WKYs. Conversely, their group reported decreased release of NO in other types of hypertensive rats (stroke-prone SHRs and deoxycorticosterone acetate–salt rats). In addition, several investigators found a beneficial effect of antihypertensive treatment on NO-mediated responses, such as in the coronary arteries and renal resistance arteries of SHRs. These findings suggest that mechanisms of endothelial dysfunction and its modulation by drug therapy in experimental hypertension are heterogeneous according to the type of hypertension and the vascular bed studied.

Clinical Relevance

Several studies have demonstrated the existence of an EDHF system in human blood vessels. Nakashima et al showed that bradykinin elicits endothelium-dependent hyperpolarization-
tion, which is resistant to both indomethacin and NO synthase inhibition, in coronary arteries excised from heart transplant patients. Petersson et al reported substance P–induced, endothelium-dependent hyperpolarization in the human cerebral artery. In addition, several studies revealed that part of the endothelium-dependent relaxation to various agonists in isolated human blood vessels (such as coronary, omental, and cerebral arteries) is resistant to a combined blockade of cyclooxygenase and NO synthase but is eventually abolished by a high-K solution, suggesting a possible role of EDHF in the relaxation. It remains to be seen whether alteration in the EDHF-mediated response is involved in endothelial dysfunction in hypertension and its improvement by drug therapy in humans.

In conclusion, the present study demonstrated that antihypertensive treatment restored impaired EDHF-mediated hyperpolarization and relaxation in mesenteric arteries of SHR. NO-mediated relaxation appeared to be preserved in this preparation and was not modulated by drug therapy. Alterations in the EDHF system may contribute to both endothelial dysfunction and its improvement by drug therapy in this model. The possibility that ACE inhibitors may be more beneficial in reversing endothelial dysfunction than other classes of antihypertensive drugs warrants further investigation.

Acknowledgment

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