Angiotensin-Converting Enzyme Inhibition Improves Cardiac Function

Role of Bradykinin

Peter Gohlke, Wolfgang Linz, Bernward A. Schölkens, Ingo Kuwer, Susanne Bartenbach, Angela Schnell, Thomas Unger

Abstract The effect of chronic low- and high-dose treatment with the angiotensin-converting enzyme (ACE) inhibitor ramipril (0.01 and 1 mg/kg per day) on the development of hypertension and left ventricular hypertrophy as well as on functional and biochemical alterations of the heart was studied in stroke-prone spontaneously hypertensive rats treated prenatally and subsequently up to the age of 20 weeks. The contribution of endogenous bradykinin potentiation to the ACE inhibitor actions was assessed by cotreatment of rats with the bradykinin B2-receptor antagonist Hoe 140 (500 μg/kg per day SC) from 6 to 20 weeks of age. High- but not low-dose ACE inhibitor treatment prevented the development of hypertension and left ventricular hypertrophy. Chronic bradykinin receptor blockade did not attenuate the antihypertensive and antihypertrophic actions of ramipril. High-dose ramipril treatment improved cardiac function, as demonstrated by an increase in left ventricular pressure (29.9%), dP/dt_{max} (34.9%), and coronary flow (22.1%), without a change in heart rate. The activities of lactate dehydrogenase and creatine kinase and lactate concentration in the coronary effluent were reduced by 39.3%, 55.5%, and 66.7%, respectively. Myocardial tissue concentrations of glycogen and the energy-rich phosphates ATP and creatine phosphate were increased by 31.3%, 39.9%, and 73.7%, respectively, whereas lactate was decreased by 20.8%. Chronic low-dose ACE inhibitor treatment led to a pattern of changes in cardiodynamics and cardiac metabolism similar to that observed with the high dose. All ACE inhibitor-induced effects on cardiac function and metabolism were abolished by chronic bradykinin receptor blockade. Our results demonstrate that chronic ACE inhibitor treatment in stroke-prone spontaneously hypertensive rats improves cardiac function even at low doses that do not affect the development of hypertension and left ventricular hypertrophy. These effects of the ACE inhibitor are due to bradykinin potentiation. However, bradykinin does not seem to contribute to the antihypertensive and antihypertrophic actions of the ACE inhibitor in this model of hypertension. (Hypertension. 1994;23:411-418.)

Key Words • angiotensin-converting enzyme inhibitor • bradykinin • heart • rats, inbred SHR • ramipril

Angiotensin-converting enzyme (ACE) catalyzes the generation of angiotensin II (Ang II) from Ang I as well as the cleavage of bradykinin and other peptides to inactive fragments.1 ACE inhibitors, therefore, act not only through inhibition of Ang II formation but also through inhibition of bradykinin degradation. The relevance of a potentiation of endogenous bradykinin by chronic ACE inhibitor treatment has been largely underestimated in the past. With the development of the potent and long-acting bradykinin B2-receptor antagonist Hoe 140, it is now possible to study chronic actions of bradykinin, especially under conditions such as ACE inhibition when bradykinin levels are increased.2,3

In addition to their well-known antihypertensive and antihypertrophic effects, ACE inhibitors were shown to exert multiple actions relevant to cardiovascular control that were related in part to bradykinin potentiation. These include the prevention of neointima formation after endothelial denudation in rats,4 preservation of endothelial function in experimental atherosclerosis in rabbits,5 reduction of posts ischemic reperfusion arrhythmias in isolated working rat hearts,6 reduction of infarct size in dogs7 and rats,8 and prevention of the development of left ventricular hypertrophy in rats with aortic banding.9 Furthermore, in a recent study we have shown that chronic ACE inhibitor treatment induced myocardial capillary growth even at doses too low to affect the development of hypertension and left ventricular hypertrophy.10 In view of the fact that improved tissue perfusion can trigger capillary growth,11 this effect may be attributed to chronic bradykinin potentiation leading to improved myocardial perfusion, metabolism, and function. In the present study we investigated the effects of chronic high- and low-dose treatment with the ACE inhibitor ramipril on functional and biochemical cardiac parameters in stroke-prone spontaneously hypertensive rats (SHRSP) as well as the contribution of endogenous bradykinin potentiation to the actions of the ACE inhibitor. In particular, we tested the hypothesis that an ACE inhibitor-induced potentiation of endogenous bradykinin is involved in the improvement of myocardial perfusion, metabolism, and function that in turn could contribute to capillary proliferation in the heart.
Methods

Experiment 1: Effect of Chronic ACE Inhibitor Treatment on Cardiac Function and Metabolism in SHRSP

Male SHRSP bred at the Department of Pharmacology in Heidelberg since 1975 were used. The animals were treated in utero and subsequently up to 20 weeks of age with the ACE inhibitor ramipril at doses of 1 (n=7) and 0.01 (n=7) mg/kg per day. Control animals received vehicle (distilled water) (n=7). Drugs were added to the overnight drinking water and carefully adjusted to the individual drinking habits of the growing animals. Ramipril dosage during pregnancy and lactation was based on the body weight of the dams under the assumption of sufficient distribution of the drug into different compartments, including placenta and milk.

Blood pressure was measured by tail plethysmography with rats under light ether anesthesia at 2-week intervals. Measurements were begun when the animals were 6 weeks old.

At the end of the treatment period the animals were anesthetized with 200 mg/kg IP hexobarbitone, and the hearts were removed and perfused with Krebs-Henseleit buffer of the following composition (mmol/L): NaCl 113.8, NaHCO₃ 22, KCl 4.7, KH₂PO₄ 1.2, MgSO₄ 1.1, CaCl₂ 2.5, glucose 11, and Na-pyruvate 2. The solution was continuously gassed with 95% O₂-5% CO₂ to adjust to pH 7.4 and was maintained at 37°C. The perfusate did not recirculate, and the hearts were not stimulated.

A balloon was placed in the left ventricle closely fitting the ventricular cavity and was connected to an artificial systemic circulation. Left ventricular pressure was measured via a pressure transducer (Statham P 23 Db), which on differentiation yielded left ventricular dP/dt max and heart rate. Coronary flow was determined by an electromagnetic flow probe in the aortic cannula. All parameters were recorded on a Brush 2600 recorder. Data are presented as mean values over a 20-minute perfusion period.

For determination of lactate release, lactate dehydrogenase, and creatine kinase activities in the perfusate, samples were taken from the coronary effluent and analyzed spectrophotometrically. After the experiments glycogen, lactate, ATP, and creatine phosphate in the myocardial tissue were measured. Left ventricular weight was determined as a parameter for cardiac left ventricular hypertrophy.

Experiment 2: Effect of Chronic Bradykinin B₂-Receptor Blockade on the Actions of the ACE Inhibitor

SHRSP were treated in utero and subsequently up to 20 weeks of age with the following drug combinations: (1) 1 mg/kg per day ramipril plus 500 μg/kg per day Hoe 140 (n=12); (2) 0.01 mg/kg per day ramipril plus Hoe 140 (n=12); (3) distilled water vehicle plus 0.9% NaCl vehicle (n=6); and (4) distilled water vehicle plus Hoe 140 (n=6).

The bradykinin B₂-receptor antagonist Hoe 140 (d-Arg,[Hyp',Thi⁷,D-Tic⁹,Oic*-bradykinin) or vehicle (NaCl 0.9%) was applied chronically by subcutaneous infusion via osmotic minipumps beginning at the age of 6 weeks. Osmotic minipumps were changed every 2 weeks. In a recent study we have demonstrated that Hoe 140 at 500 μg/kg per day given by the same route effectively blocked the depressor response to exogenously applied bradykinin. The ACE inhibitors were added to the daily drinking water as described above.

At the end of the treatment period, cardiac functional and metabolic parameters as well as left ventricular weight were determined in an isolated working heart preparation as described in experiment 1.

Experiment 3: Effect of Chronic ACE Inhibitor Treatment on Cardiac Function and Metabolism in Normotensive Rats

Male 12-week-old Wistar rats (Mollegard) were used for the experiment. Animals were treated for 8 weeks with 1 mg/kg per day ramipril by gavage (n=7). Control animals received vehicle (distilled water) (n=7). At the end of the treatment period, cardiac function and metabolic parameters were determined in isolated working rat heart preparations as described in experiment 1.

Drugs

Ramipril and Hoe 140 were obtained from Hoechst AG.

Statistics

Data are reported as mean±SEM. Statistical analysis was performed by two-way ANOVA followed by appropriate post hoc tests (Crunch Interactive Statistical Package (CRISP)) between groups. A value of P<.05 was accepted as significant. Statistics on cardiac parameters were done on the original data. Conversion into percentage values was then performed to facilitate comparison between groups.

Results

Experiment 1: Effect of Chronic ACE Inhibitor Treatment on Cardiac Function and Metabolism in SHRSP

Oral treatment of SHRSP prenatally and subsequently up to 20 weeks of age with ramipril at the high dose of 1 mg/kg per day delayed and attenuated the development of hypertension and had a preventive effect on left ventricular hypertrophy, whereas SHRSP treated with the low dose of 0.01 mg/kg per day developed hypertension and left ventricular hypertrophy in parallel to the control group (Figs 1a and 2a).

Absolute control values for cardiac functional and metabolic parameters measured in isolated hearts from vehicle- and ramipril-treated SHRSP are summarized in Table 1.

Chronic oral treatment with the antihypertensive dose of ramipril increased left ventricular pressure (29.4%), dP/dt max (34.9%), and coronary flow (22.1%), with no change in heart rate. Enzyme activities of lactate dehydrogenase and creatine kinase as well as lactate concentration in the coronary effluent were reduced by 39.3%, 55.5%, and 66.7%, respectively. Myocardial tissue levels of glycogen, ATP, and creatine phosphate were increased by 31.3%, 39.9%, and 73.7%, respectively, and lactate was decreased by 20.8% (Fig 3, left).

Chronic oral treatment with the subantihypertensive dose of ramipril led to a pattern of changes in cardiodynamics and cardiac metabolism similar to that observed with the high dose (Fig 3, right). Left ventricular pressure, dP/dt max, and coronary flow were increased by 22.4%, 37.1%, and 24.8%, respectively, with no change in heart rate. Enzyme activities of lactate dehydrogenase and creatine kinase as well as lactate concentration in the coronary effluent were reduced by 42.8%, 41.7%, and 57.6%, respectively. Myocardial tissue levels of glycogen, ATP, and creatine phosphate were increased by 29.4%, 33.8%, and 82.8%, respectively, and lactate was decreased by 22.2% (Fig 3, right).
Converting Enzyme Inhibitors and Cardiac Function

Experiment 2: Effect of Chronic Bradykinin B2-Receptor Blockade on the Actions of the ACE Inhibitor

As in rats treated with ramipril alone (experiment 1), treatment with the high dose of 1 mg/kg per day ramipril plus the bradykinin antagonist Hoe 140 delayed and attenuated the development of hypertension and left ventricular hypertrophy (Figs 1b and 2b). Because blood pressure in vehicle-treated SHRSP in this group increased to higher levels (maximal increase, 275 ± 5 mm Hg) compared with vehicle-treated animals in experiment 1 (maximal increase, 251 ± 7 mm Hg), the blood pressure values from both experiments could not be compared directly. However, the degree of blood pressure reduction after treatment with high-dose ramipril plus Hoe 140 was similar to that in experiment 1, in which SHRSP were treated with ramipril alone (Fig 1a and 1b).

Chronic treatment of SHRSP with the low dose of 0.01 mg/kg per day ramipril plus the bradykinin antagonist Hoe 140 as well as chronic subcutaneous infusion of Hoe 140 alone did not alter the development of hypertension and left ventricular hypertrophy when compared with vehicle-treated control rats (Figs 1b and 2b).

Absolute values for cardiac functional and metabolic parameters measured in isolated hearts from vehicle- and ramipril-treated SHRSP are shown in Table 2. All ACE inhibitor-induced effects (high- and low-dose) on cardiac function and metabolism were prevented by chronic bradykinin B2-receptor blockade (Fig 3). The bradykinin B2-receptor antagonist Hoe 140 by itself had no effect on these parameters (Fig 4).

Experiment 3: Effect of Chronic ACE Inhibitor Treatment on Cardiac Function and Metabolism in Normotensive Rats

Oral treatment of normotensive Wistar rats for 8 weeks with 1 mg/kg per day ramipril had no effect on the cardiodynamic parameters of left ventricular pressure, dP/dt max, and coronary flow compared with vehicle-treated control animals (Table 3). Enzyme activities of lactate dehydrogenase and creatine kinase and lactate concentration in the venous effluent as well as myocardial tissue concentrations of glycogen, lactate, ATP, and creatine phosphate were not affected by ACE inhibitor treatment (Table 2). It should be noted, however, that the basal levels of functional and metabolic parameters in hearts from untreated Wistar rats and untreated SHRSP differed markedly: left ventricular pressure, dP/dt max, and coronary flow were lower; lactate dehydrogenase and creatine kinase activities as well as lactate concentration in the venous effluent were higher; and glycogen, lactate, ATP, and creatine phosphate concentrations in myocardial tissue were lower in SHRSP compared with Wistar rats (compare basal values for experiments 1 and 2 in Tables 1 and 2 versus vehicle-treated controls in Table 3; all differences significant at P < .05).

Discussion

In the present study we demonstrate that long-term treatment of SHRSP with the ACE inhibitor ramipril...
TABLE 1. Effect of Chronic Treatment with Ramipril on Cardiac Parameters of Isolated Perfused Hearts From Stroke-Prone Spontaneously Hypertensive Rats

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>10 μg/kg Ramipril</th>
<th>1 mg/kg Ramipril</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiodynamics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVP, mm Hg</td>
<td>67±3</td>
<td>82±3*</td>
<td>87±4*</td>
</tr>
<tr>
<td>dP/dt_{max}, mm Hg/s</td>
<td>219±198</td>
<td>293±207*</td>
<td>287±222*</td>
</tr>
<tr>
<td>CF, ml/g per min</td>
<td>11.3±0.9</td>
<td>14.1±1.3*</td>
<td>13.8±0.9*</td>
</tr>
<tr>
<td>HR, min⁻¹</td>
<td>190±4</td>
<td>193±5</td>
<td>185±5</td>
</tr>
<tr>
<td><strong>Venous effluent</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDH, mU/min per g wet wt</td>
<td>26±3</td>
<td>16±2*</td>
<td>17±3*</td>
</tr>
<tr>
<td>CK, mU/min per g wet wt</td>
<td>36±4</td>
<td>21±3*</td>
<td>16±2*</td>
</tr>
<tr>
<td>Lactate, μmol/min/g wet wt</td>
<td>0.33±0.03</td>
<td>0.14±0.02*</td>
<td>0.11±0.01*</td>
</tr>
<tr>
<td><strong>Myocardial tissue</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactate, μmol/g dry wt</td>
<td>22.1±1.5</td>
<td>17.2±1.3*</td>
<td>17.5±1.8*</td>
</tr>
<tr>
<td>Glycogen, μmol/g dry wt</td>
<td>113.8±5.2</td>
<td>147.3±5.7*</td>
<td>149.4±6.4*</td>
</tr>
<tr>
<td>ATP, μmol/g dry wt</td>
<td>14.8±1.7</td>
<td>19.8±1.9*</td>
<td>20.7±2.2*</td>
</tr>
<tr>
<td>CP, μmol/g dry wt</td>
<td>9.9±1.2</td>
<td>18.1±1.4*</td>
<td>17.2±1.9*</td>
</tr>
</tbody>
</table>

LVP indicates left ventricular pressure; dP/dt_{max}, differentiated left ventricular pressure; CF, coronary flow; HR, heart rate; LDH, lactate dehydrogenase; CK, creatine kinase; and CP, creatine phosphate.

*P<.05.

increases myocardial contractility and coronary flow, reduces the release of lactate dehydrogenase and creatine kinase into the coronary effluent, and increases myocardial tissue levels of glycogen and the energy-rich phosphates ATP and creatine phosphate. These changes in cardiodynamics and cardiac metabolism were observed even at a low dose of ramipril that did not affect blood pressure and left ventricular hypertrophy, and they could be prevented by chronic bradykinin B_{2}-receptor blockade. Thus, the observed cardiac effects of the ACE inhibitor were independent of blood pressure reduction and were mediated by ACE inhibitor-induced bradykinin potentiation.

In the present study we did not measure cardiac ACE activity. However, in previous studies in SHR using the same drug regimen as in the present study we could demonstrate a significant inhibition of cardiac ACE activity with the subantihypertensive dose of 10 μg/kg per day ramipril. The high dose of 1 mg/kg per day ramipril was only slightly more effective in inhibiting cardiac ACE activity. Furthermore, sustained myocardial ACE inhibition with low doses of ramipril (10 and 100 μg/kg per day)
was produced in experiments measuring the ACE activity in rat hearts excised at different times after single oral treatment. The results demonstrated a marked reduction of cardiac ACE activity for more than 24 hours after drug doses that were lower than those required for reduction of blood pressure in SHR. Thus, we feel it is justified to assume that cardiac ACE activity was inhibited by low-dose ramipril treatment in the present study.

Evidence that bradykinin is continuously formed in the heart has been provided by recent findings in isolated rat hearts perfused with Krebs-Henseleit buffer. In normoxic hearts, bradykinin was released into the venous effluent in rather high concentrations (0.85 ng/mL perfusate per gram wet weight). The addition of an ACE inhibitor increased the basal bradykinin release by increasing contractility and coronary flow. These effects were accompanied by reduced activities of lactate dehydrogenase and creatine kinase in the venous effluent and by increased myocardial levels of energy-rich phosphates and glycogen, whereas tissue levels of lactate were reduced. The observed alterations in cardiodynamic parameters usually occurred with bradykinin concentrations two to three orders of magnitude higher than those needed to induce metabolic changes. Low bradykinin concentrations were shown to elicit enzymatic and metabolic changes in the isolated working rat heart at concentrations of $10^{-10}$ to $10^{-12}$ mol/L, which lack cardiodynamic actions. Changes in cardiodynamic parameters usually occurred with bradykinin concentrations two to three orders of magnitude higher than those needed to induce metabolic changes. Low bradykinin concentrations were shown to affect nutritional flow across the capillary wall, leading to elevated glucose uptake and thus preserving cardiac glycogen stores. Glucose may have a number of beneficial effects on the heart, as suggested by earlier studies demonstrating that glucose influenced the transmembrane action potential in papillary muscles, prevented potassium loss during cardiac ischemia, reduced reperfusion arrhythmias as well as the release of lactate dehydrogenase when perfused in isolated rat hearts, and may act as a free-radical scavenger.

### Table 2. Effect of Chronic Cotreatment with Ramipril and Hoe 140 on Cardiac Parameters of Isolated Perfused Hearts From Stroke-Prone Spontaneously Hypertensive Rats

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control +NaCl SC</th>
<th>Control +Hoe 140 SC</th>
<th>10 µg/kg Ramipril +Hoe 140 SC</th>
<th>1 mg/kg Ramipril +Hoe 140 SC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiodynamics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVP, mm Hg</td>
<td>73.5±4</td>
<td>66.3±6</td>
<td>66.0±7</td>
<td>73.1±4</td>
</tr>
<tr>
<td>dP/dt max, mm Hg/s</td>
<td>2043±112</td>
<td>2339±98</td>
<td>2357±101</td>
<td>2325±121</td>
</tr>
<tr>
<td>CF, mL/g per min</td>
<td>12.2±0.8</td>
<td>12.0±0.9</td>
<td>11.3±1.0</td>
<td>13.1±1.2</td>
</tr>
<tr>
<td>HR, min⁻¹</td>
<td>210±6</td>
<td>215±5</td>
<td>196±7</td>
<td>200±4</td>
</tr>
<tr>
<td><strong>Venous effluent</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDH, µU/min per g wet wt</td>
<td>22±3</td>
<td>19±2</td>
<td>24±3</td>
<td>21±2</td>
</tr>
<tr>
<td>CK, µU/min per g wet wt</td>
<td>23±4</td>
<td>19±3</td>
<td>22±3</td>
<td>23±2</td>
</tr>
<tr>
<td>Lactate, µmol/min/g wet wt</td>
<td>0.23±0.06</td>
<td>0.26±0.04</td>
<td>0.31±0.07</td>
<td>0.29±0.05</td>
</tr>
<tr>
<td><strong>Myocardial tissue</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactate, µmol/g dry wt</td>
<td>20.0±1.8</td>
<td>19.0±1.7</td>
<td>20.9±1.6</td>
<td>22.0±2.4</td>
</tr>
<tr>
<td>Glycogen, µmol/g dry wt</td>
<td>115.4±6.2</td>
<td>108.6±7.1</td>
<td>119.3±7.1</td>
<td>117.6±8.0</td>
</tr>
<tr>
<td>ATP, µmol/g dry wt</td>
<td>15.2±1.1</td>
<td>16.0±1.3</td>
<td>15.8±1.0</td>
<td>17.4±1.2</td>
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<tr>
<td>CP, µmol/g dry wt</td>
<td>10.4±1.3</td>
<td>9.2±0.9</td>
<td>11.5±1.1</td>
<td>11.3±1.5</td>
</tr>
</tbody>
</table>

LVP indicates left ventricular pressure; dP/dt max, differentiated left ventricular pressure; CF, coronary flow; HR, heart rate; LDH, lactate dehydrogenase; CK, creatine kinase; and CP, creatine phosphate.
In isolated working rat hearts with postischemic reperfusion arrhythmias, pretreatment with ACE inhibitors at antihypertensive doses effectively prevented reperfusion arrhythmias and produced a fingerprint of changes in cardiodynamics and cardiac enzymatic and metabolic parameters almost identical to that observed with bradykinin. Again, these enzymatic and metabolic effects of the ACE inhibitor were observed in concentrations that did not alter basal cardiodynamics. Thus, in ischemic hearts ACE inhibitors as well as bradykinin produce a pattern of changes in cardiodynamics and cardiac metabolism similar to that observed in normoxic hearts in the present study, in which SHRSP were treated chronically with an ACE inhibitor.

It is important to emphasize that cardiac performance in adult SHRSP was found to be impaired when compared with normotensive Wistar rats. Our data show that chronic ACE inhibitor treatment in SHRSP can return this impaired cardiac performance to normal. This finding, together with the observation that in normotensive Wistar rats cardiac function and metabolism were not altered by treatment with high-dose ramipril for 8 weeks, suggests that chronic ACE inhibition does not induce a supernormal cardiac performance but rather improves heart function in the hypertrophied heart.

Low-dose ACE inhibitor treatment improved cardiac functional and metabolic parameters without affecting the development of left ventricular hypertrophy. Thus, although an increase in muscle mass can be instrumental in the development of left ventricular dysfunction, other factors that can be influenced by ACE inhibition, for instance, an impairment of myocardial perfusion, appear to be more important in this respect.

Left ventricular hypertrophy is considered an independent cardiovascular risk factor giving rise to cardiac failure, ischemia, and arrhythmias. Hypertension development is accompanied by an adaptive development of left ventricular hypertrophy to overcome the chronically increased afterload imposed on the heart. However, in hypertension-induced left ventricular hypertrophy the rate of capillary growth does not keep pace with the increase in muscle mass. Thus, a reduced capillary supply may eventually lead to cardiac ischemia. Several studies demonstrated that chronic antihypertensive treatment with different ACE inhibitors can prevent the reduction in coronary flow and coronary reserve in SHR by preventing the development of left ventricular hypertrophy and increasing capillary density.

In a more recent study in SHR using the same treatment protocol and drug regimen as in the present study we demonstrated that low-dose ACE inhibitor treatment can induce myocardial capillary growth without affecting the development of hypertension or left ventricular hypertrophy. Thus, long-term ACE inhibition can counteract the reduction in capillary density normally observed in hypertension-induced left ventricular hypertrophy. In the present study we hypothesized that an ACE inhibitor–induced potentiation of bradykinin in myocardial tissue could stimulate myocardial capillary proliferation by augmenting myocardial perfusion, a well-known trigger mechanism of angiogenesis in the heart. The results of the present study lend support to this hypothesis by demonstrating marked increases in coronary flow after chronic ACE inhibitor treatment even at doses too low to reduce blood pressure or left ventricular hypertrophy.

The degree of blood pressure reduction observed after treatment with high-dose ramipril alone or ramipril plus Hoe 140 was similar, suggesting that chronic bradykinin B2-receptor blockade did not attenuate the antihypertensive action of the ACE inhibitor in SHRSP. These results confirm previous studies from our group demonstrating that chronic bradykinin B2-receptor blockade by Hoe 140 did not attenuate the depressor effects of ramipril in SHR.

Similar findings were obtained after acute ACE inhibitor treatment in SHR, although a study by Cacho-
feiro et al. suggested an attenuation of the acute antihypertensive effect of an ACE inhibitor. In contrast, blockade of bradykinin B2 receptors has frequently been shown to attenuate the hypotensive effect after an acute bolus injection of an ACE inhibitor in two-kidney, one clip hypertensive Wistar rats and in rats with hypertension induced by aortic ligation between the renal arteries. In addition, in a chronic study in two-kidney, one clip hypertensive Wistar rats, we could demonstrate that coadministration of Hoe 140 attenuated the antihypertensive effect of ramipril throughout the treatment period of 6 weeks or partially reversed the antihypertensive effect in ramipril-pretreated animals. Therefore, bradykinin potentiation seems to play a more important role in the antihypertensive actions of ACE inhibitors in renovascular models of hypertension associated with a stimulated renin-angiotensin system but appears to be less important in genetic hypertension with normal to low plasma renin, such as in SHR or SHRSP. This assumption is also supported by findings demonstrating that, in contrast to results in SHR, the ACE inhibitor ramipril in subantihypertensive doses prevented the development of left ventricular hypertrophy in a renin-dependent model of hypertension after aortic banding. Paradoxically, this antihypertrophic effect of the ACE inhibitor could be abolished by bradykinin receptor blockade, indicating that bradykinin plays an important role in the development of left ventricular hypertrophy in this renin-dependent model of hypertension.

In conclusion, our study in SHRSP demonstrates that early-onset chronic treatment with the ACE inhibitor ramipril improved cardiac function and metabolism even at a low dose that did not affect the development of hypertension and left ventricular hypertrophy. The observed cardiac effects of the ACE inhibitor were due to bradykinin potentiation because they could be prevented by the bradykinin receptor antagonist Hoe 140. However, bradykinin potentiation does not seem to contribute to the antihypertensive and antihypertrophic action of the ACE inhibitor in this model of hypertension.

References


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