Bradykinin Mediates the Acute Effect of an Angiotensin-Converting Enzyme Inhibitor on Cerebral Autoregulation in Rats

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Background and Purpose—In patients with stroke and long-standing hypertension, the autoregulation curve of cerebral blood flow (CBF) shifts toward higher blood pressure levels. Angiotensin-converting enzyme (ACE) inhibitors reduce blood pressure and shift the autoregulation curve back to normal in hypertensive patients. ACE inhibitors have 2 major pharmacological properties: they inhibit both the production of angiotensin II and the breakdown of kinins. Hence, we investigated whether the effect of an ACE inhibitor on the lower limit of CBF autoregulation is mediated by the potentiation of bradykinin-mediated vasodilatation.

Methods—In 28 male Sprague-Dawley rats, CBF was measured by laser-Doppler flowmetry during stepwise controlled hypotension. The lower limit of CBF autoregulation was defined as the mean arterial pressure at which CBF decreased by 20% of the baseline value. The rats were treated with an ACE inhibitor, captopril, in the captopril group; a bradykinin BK2-receptor antagonist, Hoe140, in the Hoe140 group; and both agents in the captopril + Hoe140 group. Other rats served as a control group. The lower limits of CBF autoregulation were compared among the 4 groups.

Results—In the captopril group, the lower limit of CBF autoregulation was 43 ± 8 mm Hg (mean ± SD), which was significantly lower than that in the control group (57 ± 14 mm Hg). Inhibition of bradykinin abolished the effect of captopril on the lower limit of CBF autoregulation. Hoe140 alone had no significant effect on the lower limit of CBF autoregulation.

Conclusions—These results suggest that the shift of the lower limit of CBF autoregulation by captopril is mediated, at least in part, by bradykinin. (Stroke. 2001;32:1216-1219.)

Key Words: angiotensin converting enzyme inhibitors ■ autoregulation ■ bradykinin ■ cerebral blood flow
dent Ventilator model 683, Harvard Apparatus) with room air and supplemental oxygen. We used a heating pad to keep the rectal temperature constant at 37°C. CBF in the parietal cortex was continuously monitored by laser-Doppler flowmetry (ALF21, Advance Co Ltd) through the burr hole in the skull.8,9 A laser-Doppler probe was placed above the dura mater approximately 4 mm posterior and 2 mm lateral to the bregma.

### Experimental Protocol

The animals were divided into 4 groups (n=7 in each group). In the captopril group, we administered the ACE inhibitor captopril (46 μmol/kg [10 mg/kg] IV) 15 minutes before the reduction of systemic arterial pressure. In the Hoe140 group, the rats were given the Bradykinin BK2-receptor antagonist Hoe140 (4 nmol/kg IV) 15 minutes before the reduction of systemic arterial pressure. In the captopril group, we administered the ACE inhibitor captopril (46 μmol/kg [10 mg/kg] IV) 15 minutes before the reduction of systemic arterial pressure. In the Hoe140 group, the rats were given the Bradykinin BK2-receptor antagonist Hoe140 (4 nmol/kg IV) 15 minutes before the reduction of systemic arterial pressure. In the captopril group, we administered the ACE inhibitor captopril (46 μmol/kg [10 mg/kg] IV) 15 minutes before the reduction of systemic arterial pressure. In the Hoe140 group, the rats were given the Bradykinin BK2-receptor antagonist Hoe140 (4 nmol/kg IV) 15 minutes before the reduction of systemic arterial pressure. In the captopril group, we administered the ACE inhibitor captopril (46 μmol/kg [10 mg/kg] IV) 15 minutes before the reduction of systemic arterial pressure. In the Hoe140 group, the rats were given the Bradykinin BK2-receptor antagonist Hoe140 (4 nmol/kg IV) 15 minutes before the reduction of systemic arterial pressure.

#### Results

The results were expressed as mean±SD. Statistical analyses were performed with ANOVA, followed by post hoc Fisher’s protected least significant difference test. P<0.05 was regarded as significant.

### Discussion

The major new finding of the present study is that Hoe140, a Bradykinin BK2-receptor antagonist, inhibited the captopril-induced change in CBF auto regulation. The result suggests that the modulation of CBF auto regulation by captopril is mediated, at least in part, by Bradykinin.

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### Table 1. Physiological Variables in 4 Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control (n=7)</th>
<th>Captopril (n=7)</th>
<th>Hoe140 (n=7)</th>
<th>Captopril+Hoe140 (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight, g</td>
<td>436±33</td>
<td>363±71</td>
<td>357±91</td>
<td>403±80</td>
</tr>
<tr>
<td>Body temperature, °C</td>
<td>37.0±0.1</td>
<td>37.0±0.1</td>
<td>37.0±0.1</td>
<td>37.0±0.1</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>0.43±0.04</td>
<td>0.45±0.03</td>
<td>0.45±0.02</td>
<td>0.44±0.03</td>
</tr>
<tr>
<td>At rest</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>109±7</td>
<td>113±11</td>
<td>107±13</td>
<td>114±10</td>
</tr>
<tr>
<td>pH</td>
<td>7.428±0.016</td>
<td>7.409±0.021</td>
<td>7.406±0.033</td>
<td>7.420±0.028</td>
</tr>
<tr>
<td>PaO2, mm Hg</td>
<td>36.9±2.8</td>
<td>37.6±2.8</td>
<td>38.1±3.0</td>
<td>39.3±1.9</td>
</tr>
<tr>
<td>PaCO2, mm Hg</td>
<td>106±11</td>
<td>116±15</td>
<td>114±18</td>
<td>105±11</td>
</tr>
<tr>
<td>After administration of drugs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>105±10</td>
<td>105±14†</td>
<td>107±14</td>
<td>101±11†</td>
</tr>
<tr>
<td>pH</td>
<td>7.418±0.011</td>
<td>7.404±0.016</td>
<td>7.405±0.015</td>
<td>7.416±0.015</td>
</tr>
<tr>
<td>PaO2, mm Hg</td>
<td>36.6±1.0</td>
<td>39.0±4.1</td>
<td>37.7±1.3</td>
<td>38.0±3.2</td>
</tr>
<tr>
<td>PaCO2, mm Hg</td>
<td>109±12</td>
<td>122±16</td>
<td>122±20</td>
<td>111±12</td>
</tr>
<tr>
<td>∆CBF, %*</td>
<td>1±8</td>
<td>−2±3</td>
<td>0±7</td>
<td>3±3</td>
</tr>
</tbody>
</table>

Values are mean±SD.

* ∆CBF = |CBF (baseline after administration of drugs) − CBF(at rest)|/CBF(at rest)×100 (%).

† P<0.002 vs MAP(at rest) in captopril group.

‡ P<0.005 vs MAP(at rest) in captopril+Hoe140 group.
Captopril inhibits not only ACE but also kininase II, which catalyzes the breakdown of bradykinin. Hence, captopril would cause autoregulatory vasodilation by either the inhibition of angiotensin II or the preservation of bradykinin. In the present study the bradykinin receptor blocker inhibited captopril-induced CBF autoregulation. This observation implies that the effect of captopril on the lower limit of CBF autoregulation is mediated by potentiated bradykinin-induced vasodilatation. In support of this idea, a previous study demonstrated that acute administration of an ACE inhibitor augmented cerebral vasodilatation to exogenous bradykinin, suggesting that the local kinin-kininase system is operating in cerebral vascular beds. Taken together, it is probable that captopril inhibited the breakdown of endogenous bradykinin, potentiated cerebral vasodilation, and thereby maintained CBF at lower perfusion pressures.

In a previous report, in which Hoe140 (0.75 nmol) was infused into the aorta in Sprague-Dawley rats, bradykinin-induced hypotension was still impaired by 71% 1 hour after infusion. In the present intravenous study, the dose of Hoe140 was similar to or even greater than that in the previous study, and it completely prevented the hypotensive effect of bradykinin. In a steady state, Hoe140 concentration in the circulating blood should be constant in the whole body, including cerebral vessels. This means that a sufficient concentration of Hoe140 to block BK2 receptors should have reached cerebral arteries during the experiment. Furthermore, there is no report that the distribution of BK2 receptor is different between endothelial cells (main target of BK2 stimulation) in cerebral and systemic arteries. Therefore, we can reasonably expect that the dose of Hoe140 used in the present study was sufficiently high to inhibit the effect of bradykinin in cerebral arteries.

In the present study, the lower limit of CBF autoregulation in the Hoe140 group was not significantly higher than that in the control group. This implies that the role of endogenous bradykinin is minor, if any, in the determination of the lower limit of CBF autoregulation under physiological conditions. The result also argues against the possibility that Hoe140 shifts the lower limit of cerebral autoregulation rightward in a nonspecific manner.

The result also argues against the possibility that Hoe140 abolished the shift in the captopril group. The lower limit of autoregulation in the captopril + Hoe140 group was 64±10 mm Hg (double open squares).
of angiotensin II production) on the luminal side of the endothelium. The blood-brain barrier permeability for angiotensin II would be low as well since angiotensin II is octapeptide. Thus, it appears unlikely that angiotensin II produced by ACE on the luminal surface of the endothelium reaches and contracts smooth muscle cells (Figure 3). The observation that intraluminal injection of captopril shifted the lower limit of CBF autoregulation also supports the view that the site of action of captopril is the intima rather than the vascular smooth muscle.26 However, it is doubtful that angiotensin II produced on the luminal side of endothelial cells reaches to the adventitial side of the cell across the blood-brain barrier and contracts cerebrovascular smooth muscle.

In conclusion, the present results suggest that the effect of acute administration of the ACE inhibitor captopril on the lower limit of CBF autoregulation is mediated, at least in part, by bradykinin.

References
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