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

Junichi Takada, MD; Setsuro Ibayashi, MD; Tetsuhiko Nagao, MD; Hiroaki Ooboshi, MD; Takanari Kitazono, MD; Masatoshi Fujishima, MD

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
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>Paco2, 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>Paco2, 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>ΔCBF, %*</td>
<td>1±8</td>
<td>−2±3</td>
<td>0±7</td>
<td>3±3</td>
</tr>
</tbody>
</table>

Values are mean±SD.
*ΔCBF=(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.

Statistical Analysis
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.

Results
Under resting conditions, no significant differences were found in the physiological variables among the 4 groups (Table 1). Although captopril reduced MAP from 113±11 to 105±14 mm Hg, resting CBF remained unchanged (Table 1). MAP was comparable in each group when the bleeding was started (105±10, 105±14, 107±14, and 101±11 mm Hg in the control, captopril, Hoe140, and captopril+Hoe140 groups, respectively; P>0.05). Captopril shifted the cerebral autoregulation curve leftward (Figure 1). The lower limits in the control group and the captopril group were 57±14 and 43±8 mm Hg, respectively (Table 2). The shift was restored by Hoe140 (Figure 1). The lower limit in the captopril+Hoe140 group was 64±10 mm Hg (Table 2). Hoe140 slightly shifted the lower limit of cerebral autoregulation toward higher pressure levels, although the change in the lower limit of cerebral autoregulation did not reach statistical significance (Table 2 and Figure 2).

Discussion
The major new finding of the present study is that Hoe140, a bradykinin BK2-receptor antagonist, inhibited the captopril-induced change in CBF autoregulation. The result suggests that the modulation of CBF autoregulation by captopril is mediated, at least in part, by bradykinin.
The potent cerebral vasodilators. Hence, captopril would catalyze the breakdown of bradykinin. Bradykinin is one of the potent cerebral vasodilators. The lower limit of autoregulation in the captopril group (double closed circles; 43±8 mm Hg) shifted toward the left compared with the control group (double open circles; 57±14 mm Hg). However, 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).

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.

Captopril inhibits not only ACE but also kininase II, which catalyzes the breakdown of bradykinin. Bradykinin is one of the potent cerebral vasodilators. 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 vasodilation. 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.

We did not investigate the role of nitric oxide (NO) in bradykinin-induced changes in the lower limit of autoregulation. However, dilator responses of cerebral arteries to bradykinin appear to be mediated by NO in cerebral arteries. Previous studies demonstrated that NO modified the lower limit of cerebral autoregulation. Taken together, NO could be the mediator of the action of ACE inhibitors on CBF autoregulation. However, some investigators failed to demonstrate that the inhibition of NO synthesis changes the lower limit of CBF autoregulation, and others revealed that bradykinin-induced cerebral vasodilatation was mediated by oxygen radicals rather than NO. Therefore, the mediator of the action of ACE inhibitors on CBF autoregulation remains to be determined.

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 CBF autoregulation rightward in a nonspecific manner.

It has been proposed that ACE inhibitors, by inhibiting angiotensin II production, dilate larger cerebral arteries with compensatory constriction of smaller arteries or arterioles. Such vasoconstriction leads to the augmentation of vasodilatory reserve capacity and thereby shifts the lower limit of autoregulation leftward. However, the notion leaves some room for further discussion. First, the effects of angiotensin II on CBF vary depending on species and source of vessel. For instance, CBF increased in response to intravenously infused exogenous angiotensin II, while infusion of angiotensin II into the internal carotid artery decreased CBF even in the same species of animals (Sprague-Dawley rats). Second, since the blood-brain barrier permeability for captopril is negligible, captopril should exert its main effects (inhibition

**TABLE 2. MAP Lower Limit of Autoregulation in 4 Groups**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Captopril</th>
<th>Hoe140</th>
<th>Captopril + Hoe140</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBF (%)</td>
<td>62±10</td>
<td>57±14</td>
<td>43±8††</td>
<td>69±15</td>
</tr>
</tbody>
</table>

CBF decreased by 20%

<table>
<thead>
<tr>
<th>Values are mean±SD.</th>
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<tbody>
<tr>
<td>*P&lt;0.05 vs control group.</td>
</tr>
<tr>
<td>†P&lt;0.0005 vs Hoe140 group.</td>
</tr>
<tr>
<td>‡P&lt;0.005 vs captopril + Hoe140 group.</td>
</tr>
</tbody>
</table>
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. 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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