Inhibition of Angiotensin-Converting Enzyme Modulates the Autoregulation of Regional Cerebral Blood Flow in Hypertensive Rats

Seizo Sadoshima, Tetsuhiko Nagao, Setsuro Ibayashi, Masatoshi Fujishima

Abstract

The inhibition of angiotensin-converting enzyme activities is considered to favorably modulate the hemodynamics of the brain. We designed the present study to examine the effects of angiotensin-converting enzyme inhibitors on regional differences in the lower limits of cerebral blood flow autoregulation in spontaneously hypertensive rats. Angiotensin-converting enzyme inhibitors (either 10 mg/kg captopril or SQ 29,852 in saline) were intravenously injected 15 minutes before hemorrhagic hypotension was induced. Cerebral blood flows to the parietal cortex and thalamus were simultaneously measured by hydrogen clearance. Both captopril and SQ 29,852 significantly decreased mean arterial pressure by 14 to 18 mm Hg and also reduced calculated cerebral vascular resistance by 11% to 15% of resting values, which resulted in a well-maintained cerebral blood flow. The lower limits of autoregulation were 76±2% (mean±SEM) and 77±2% of resting values in the cortex and thalamus, respectively, in control rats. Administration of either captopril or SQ 29,852 significantly reduced the lower limits to 65±3% (P<.01 versus control) and 67±2% (P<.05), respectively, in the cortex, which were slightly but always larger than the 71±3% and 71±2% reduction, respectively, in the thalamus. The inhibition of angiotensin-converting enzyme activities thus may be more protective against acute hypotension for cerebral microcirculation in the cortex than in the thalamus. (Hypertension. 1994;23[part 1]:781-785.)

Key Words • angiotensin-converting enzyme inhibitors • captopril • homeostasis • rats, inbred SHR

In the present study we examined the blood pressure-flow relation of the cerebral vessels during hemorrhagic hypotension after the administration of either captopril or SQ 29,852 in spontaneously hypertensive rats (SHR). We also studied whether there are any characteristic differences in the changes in the lower limits of CBF autoregulation between those observed in the parietal cortex and in the thalamus during treatment with these two ACE inhibitors.

Methods

Thirty-three 6-month-old male SHR (255 to 260 g) were separated into three groups: rats (n=12) receiving a bolus injection of captopril (10 mg/kg IV), rats (n=12) treated with a bolus injection of SQ 29,852 (10 mg/kg IV), and rats (n=9) used as controls. The animals, which were bred in the Kyushu University animal center, were housed in air-conditioned quarters (25°C) with light control (12-hour light/dark cycle) and were fed a stock chow diet (Oriental Co Japan). Drugs were stored as a dry powder at 5°C and carefully protected from light. Just before the study the drugs were dissolved in 0.9% saline, and a 1 mL/kg solution was made to inject into the rats. Control rats received an injection of vehicle (1 mL/kg saline IV).

CBF to the parietal cortex and thalamus was measured with the hydrogen (H2) clearance method. With rats under amobarbital anesthesia (100 mg/kg IP), one femoral artery was cannulated for continuous measurement of arterial pressure and blood sampling for measurement of arterial PaCO2, PaO2, and pH with an IL meter. A femoral vein was cannulated for injection of drugs. The animal's head was fixed in a head holder, and two small burr holes were made on the skull 2 mm lateral to the bregma on each side. Two polytetrafluoroethylene-coated platinum electrodes, 200 μm in diameter with a 1-mm portion at their tops uncoated and plated with platinum black, were stereotaxically placed in the right parietal cortex and left thalamus. The depths of the electrode tips were 1 and...
were maintained at constant levels in each rat, and no significant differences were observed among the groups. Blood flow to the thalamus tended to be larger than that to the cortex (p > 0.05) in each rat. Resting mean arterial pressure was approximately 190 mm Hg in all rats. At 15 minutes after the administration of either captopril or SQ 29,852, mean arterial pressure reached stable levels and showed a slight but significant reduction of 14 to 18 mm Hg or 8% to 10% from resting values.

Systemic arterial pressure was lowered by the administration of ACE inhibitors. CBF to the cortex and thalamus remained unchanged or slightly increased; thus, cerebral vascular resistance, calculated as mean arterial pressure/CBF, at 15 minutes was decreased by 12% to 15% in rats treated with captopril and by 11% to 13% in rats treated with SQ 29,852. Thereafter, despite a stepwise decrease in mean arterial pressure over a wide range, CBF to the cortex and thalamus was maintained at relatively constant levels, and CBF autoregulatory function was well preserved in all groups. Mean arterial pressure was reduced further and reached a certain level below which CBF began to decrease steeply, depending on each fall in blood pressure thereafter. This blood pressure level was defined as the lower limit of autoregulation at which regional CBF decreased by approximately 10% of the resting value. These lower limits of autoregulation were 144 ± 5 mm Hg (76 ± 2% of the resting values) in the cortex and 147 ± 4 mm Hg (77 ± 2%) in the thalamus in control rats receiving saline, whereas no regional differences were observed. Compared with the vehicle-treated group, administration of ACE inhibitors more significantly shifted these values to lower limits: to 125 ± 4 mm Hg (65 ± 3% of the resting, p < 0.01 versus control) in the cortex and 134 ± 2 mm Hg (71 ± 3%, p < 0.05) in the thalamus in SHR treated with captopril and to 129 ± 3 mm Hg (67 ± 2%, p < 0.05) in the cortex and 136 ± 4 mm Hg (71 ± 2%, p < 0.05) in the thalamus in rats treated with SQ 29,852 (Table 2 and Figs 1, 2, and 3). In SHR treated with captopril (Fig 3) or SQ 29,852, the downward shift of the lower limits was slightly but always larger in the cortex than the thalamus, even though the differences failed to reach statistical significance. Moreover, blood flow to the thalamus decreased more steeply than that to the cortex beyond the blood pressure levels of these lower limits.

Table 1 summarizes mean values for blood gases and pH during the autoregulation study. PACO2 (32 to 36 mm Hg), PaO2 (94 to 104 mm Hg), and pH (7.25 to 7.38) were maintained at constant levels in each rat, and no significant differences were observed among the groups. The pressure-flow relations in the animals treated with either saline (control), captopril, or SQ 29,852 are shown in Table 2 and Figs 1, 2, and 3. Resting CBF values were 51 to 53 mL/100 g per minute to the cortex and 56 to 59 to the thalamus and were almost the same among the groups. Blood flow to the thalamus tended to be larger than that to the cortex (p > 0.05) in each rat. Resting mean arterial pressure was approximately 190 mm Hg in all rats. At 15 minutes after the administration of either captopril or SQ 29,852, mean arterial pressure reached stable levels and showed a slight but significant reduction of 14 to 18 mm Hg or 8% to 10% from resting values.

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Results

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TABLE 2. Changes in Mean Arterial Pressure, Cerebral Blood Flow, and Lower Limits of Autoregulation After ACE Inhibitor Administration

<table>
<thead>
<tr>
<th></th>
<th>Control (n=9)</th>
<th>Captopril (n=12)</th>
<th>SQ 29,852 (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MAP, mm Hg</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At rest</td>
<td>192±4</td>
<td>190±6</td>
<td>192±5</td>
</tr>
<tr>
<td>15 Minutes</td>
<td>192±3</td>
<td>172±2†</td>
<td>178±4*</td>
</tr>
<tr>
<td><strong>Vascular resistance, (mm Hg/ml)/100 g per minute</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At rest</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortex</td>
<td>3.694±0.125</td>
<td>3.723±0.081</td>
<td>3.623±0.138</td>
</tr>
<tr>
<td>Thalamus</td>
<td>3.438±0.116</td>
<td>3.230±0.101</td>
<td>3.430±0.162</td>
</tr>
<tr>
<td>15 Minutes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortex</td>
<td>3.767±0.130</td>
<td>3.195±0.112*</td>
<td>3.189±0.120*</td>
</tr>
<tr>
<td>Thalamus</td>
<td>3.452±0.128</td>
<td>2.833±0.108*</td>
<td>3.018±0.116*</td>
</tr>
<tr>
<td><strong>CBF, (mL/100 g)/min</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At rest</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortex</td>
<td>52±3</td>
<td>51±3</td>
<td>53±4</td>
</tr>
<tr>
<td>Thalamus</td>
<td>56±2</td>
<td>59±2</td>
<td>56±2</td>
</tr>
<tr>
<td>15 Minutes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortex</td>
<td>51±3</td>
<td>54±2</td>
<td>56±3</td>
</tr>
<tr>
<td>Thalamus</td>
<td>56±3</td>
<td>61±2</td>
<td>59±2</td>
</tr>
<tr>
<td><strong>Lower limits of autoregulation, mm Hg</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortex</td>
<td>144±5 (76±2)</td>
<td>125±4 (65±3)†</td>
<td>129±3 (67±2)§</td>
</tr>
<tr>
<td>Thalamus</td>
<td>147±4 (77±2)</td>
<td>134±2 (71±3)§</td>
<td>136±4 (71±2)§</td>
</tr>
</tbody>
</table>

ACE indicates angiotensin-converting enzyme; MAP, mean arterial pressure; and CBF, cerebral blood flow. Values are mean±SEM. Number in parentheses signifies percentage of baseline value.

*P<.05, †P<.02 vs at rest.

+P<.01, §P<.05 vs control.

demonstrated that either a bolus or continuous infusion of captopril in SHR significantly decreased arterial pressure while preserving CBF. Recently, we reported that in addition to the reductions of cerebral vascular resistance, calculated by mean arterial pressure/CBF, both captopril and SQ 29,852 may have a protective effect against ischemic insult in SHR.16 In the present study we examined the effects of acute administration of these two ACE inhibitors on regional differences in the lower limits of CBF autoregulation in hypertensive rats, because the major aim of these drugs is to decrease high blood pressure to lower levels without causing any significant changes in CBF.

Figure 1. Line graph shows mean arterial pressure (MAP)-cerebral blood flow (CBF) relation in cortex of spontaneously hypertensive rats treated with either captopril, SQ 29,852, or vehicle (control). Lower-limit blood pressure levels were 125±4 (65±3% of resting MAP), 129±3 (67±2%), and 144±5 (76±2%) mm Hg, respectively. Arrows indicate lower limits of autoregulation in each group. Values are mean±SEM. *P<.05 vs blood flow to thalamus at corresponding MAP; †P<.01; §P<.05 vs vehicle.

Figure 2. Line graph shows mean arterial pressure (MAP)-cerebral blood flow (CBF) relation in thalamus of spontaneously hypertensive rats treated with either captopril, SQ 29,852, or vehicle (control). Lower-limit blood pressure levels were 134±2 (71±3% of resting MAP), 136±4 (71±2%), and 147±4 (77±2%) mm Hg, respectively. Arrows indicate lower limits of autoregulation in each group. Values are mean±SEM. §P<.05 vs vehicle.
As shown in this study acute administration of both captopril and SQ 29,852 decreased systemic arterial pressure by 14 to 18 mm Hg, and regional CBF either remained unchanged or actually increased; also, calculated cerebral vascular resistance was reduced by 11% to 15%. A downward shift of the lower limits of CBF autoregulation in the cortex as well as the thalamus was observed in SHR treated with both ACE inhibitors. Blood pressure levels of the lower limits in rats treated with either captopril or SQ 29,852 were reduced to approximately 65% and 71% of resting values in the cortex and thalamus, respectively, and were significantly lower, by 11 to 19 mm Hg, than the level of approximately 76% observed in control rats. Compared with the findings of Barry et al., PACO2 in the present study was approximately 5 mm Hg lower, which may tend to improve CBF autoregulation and shift the lower limits toward a lower blood pressure. Contrary to this, basal mean arterial pressure in our SHR is approximately 190 mm Hg, which is much higher than 120 mm Hg, and thus, the levels of the lower limits are higher than those noted in the report of Barry et al.

We previously reported that in addition to ACE inhibitors, phenoxybenzamine shifts the lower limits of CBF autoregulation to the left, and thus, the shift may be nonspecific and not related to the renin-angiotensin system. In the present study our data are in close accord with previous studies on the effects of ACE inhibitors on the cerebral microcirculation.6—11 ACE inhibitors first dilate large vessels; this is then accompanied by a compensatory constriction of the downstream resistant arteries/arterioles, and CBF is restored to levels compatible with normal values. During a further decrease in systemic blood pressure, the downstream smaller arteries would exhibit a greater dilatory capacity, explaining the well-maintained CBF. Thus, the lower limits and also the upper limits of CBF autoregulation shift to the lower levels of arterial pressure after treatment with ACE inhibitors. We therefore suggest that ACE inhibition beneficially redistributes CBF during either a short- or long-term reduction in arterial pressure; thus, ACE inhibitors may be useful for the treatment of chronic hypertension with cerebral vascular complications.

Most previous studies on the lower or upper limits of global CBF autoregulation have been performed with the use of the 133Xe clearance method in rats,9,10,11 and it is still not fully known whether there are any regional differences in autoregulatory capacity after inhibition of ACE activities. We speculate that the incidence of the development of ischemic lesions in each area of the brain depends at least in part on the capacity to regulate CBF during changes in perfusion pressure. Because ischemic stroke is more frequently observed in the deep gray matter including the thalamus than in other structures,26 the pressure-flow relation in these areas might be more easily disturbed, especially in the acute reduction of systemic arterial pressure. After treatment with ACE inhibitors the lower limits of autoregulation in the thalamus are 7 to 9 mm Hg higher, and the regional blood flow beyond the lower limits decreases more steeply than in the cortex. It is suggested that the function for regulation of blood flow in the thalamus may be more insufficiently activated during hypotension, thus resulting in a more severe state of hypoperfusion and a higher prevalence of ischemic damage in this area than in the cortex.

Several possibilities may be proposed to explain the regional differences in the lower limits of CBF autoregulation in the present study. First, the small arteries in the deep gray matter branch off directly from the proximal portion of the middle cerebral arteries. The vessels in this area are exposed to a relatively high blood pressure that is almost systemic, and therefore, the hypertensive structural or constrictive changes with luminal encroachment may be more advanced than those found in the cortex, leading to a further inhibition of the maximum vasodilatation during systemic hypotension. Second, the compensatory vasoconstriction of the downstream vessels after the administration of ACE inhibitors may be insufficiently released during a further decrease in systemic blood pressure, again as a consequence of the marked hypertensive changes. Thus, the perfusion pressure in the downstream vessels may remain decreased during hypotension and thus fail to maintain a sufficient CBF. Third, the small arteries in the thalamus are innervated by bilateral sympathetic nerves, which may be important in the inhibition of forced dilation of the arteries and the regulation of blood flow during an acute rise in arterial pressure.27 Although ACE inhibitors decrease cerebral vascular sympathetic tone, their effect may be different in each area or vessel in the brain.14,28 During hemorrhagic hypotension, as noted in this study, systemic sympathetic tone increases and thus the neurogenic effects on vasoconstriction may be greater in the thalamus than the cortex. Fourth, we are not aware of any previous studies that have compared the metabolism of the thalamus with that of the cortex,9 but the changes in metabolism in each brain area during hypotension may reflect different responses for maintaining blood flow rather than autoregulatory responses to changes in arterial pressure. All these factors may thus contribute to the protection of the microcirculation in the deeper structures of the brain against an acute rise in perfusion pressure and, in contrast, could also enhance a further reduction in blood flow during a decrease in systemic arterial pressure, which may therefore also partially

![Graph showing CBF (%) vs MAP (mmHg) with data points and lines for cortex and thalamus.](image-url)
explain the high incidence of ischemic stroke in the thalamus.

In conclusion, the acute administration of ACE inhibitors successfully maintains CBF, presumably partially because of the effects of the drugs and partially because of the autoregulatory capacity, reduces cerebral vascular resistance, and shifts the lower limits of cortical and thalamic CBF autoregulation to lower blood pressure levels. ACE inhibitors therefore seem to have a beneficial effect on the cerebral circulation, although the lower limits of the autoregulatory plateau and thus the responsiveness of the vessels to changes in arterial pressure may be substantially different in various regions of the brain after the inhibition of ACE activities.

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References

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