Effects of an Angiotensin-Converting Enzyme Inhibitor and a β-Blocker on Cerebral Arteriolar Dilatation in Hypertensive Rats

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Abstract—We examined the effects of the angiotensin-converting enzyme inhibitor perindopril and the β-blocker propranolol on dilator responses of cerebral arterioles in chronic hypertension. Dilator responses to acute hypotension were in untreated Wistar-Kyoto rats (WKY) and stroke-prone spontaneously hypertensive rats (SHRSP) that were untreated or treated for 3 months with a low (0.3 mg · kg⁻¹ · day⁻¹) or a high (2 mg · kg⁻¹ · day⁻¹) dose of perindopril or a dose of propranolol (250 mg · kg⁻¹ · day⁻¹) alone or in combination with the low dose of perindopril. Pressure (servo-null) and diameter were measured in cerebral arterioles during acute reductions in arterial pressure both before and during maximal dilatation (EDTA). The high dose of perindopril or the combination of propranolol and perindopril normalized cerebral arteriolar pressure (52 ± 2 mm Hg versus 50 ± 2 mm Hg in WKY and 96 ± 3 mm Hg in untreated SHRSP; P < 0.05). In contrast, the low dose of perindopril or propranolol alone did not normalize arteriolar pressure (74 ± 2 mm Hg and 58 ± 3 mm Hg). Both the low and high doses of perindopril improved autoregulatory dilatation, maximal dilatation, and dilator reserve of cerebral arterioles in SHRSP, with the low dose of perindopril being almost as effective as the high dose of perindopril. Propranolol alone did not significantly improve dilator function of cerebral arterioles. Furthermore, dilator function of cerebral arterioles was not further improved by the addition of propranolol to the low dose of perindopril. These findings suggest that angiotensin-converting enzyme inhibitors, such as perindopril, may be more effective than propranolol in attenuating the impairment of cerebral autoregulatory vasodilatation, maximal dilatation, and dilator reserve during treatment of chronic hypertension.

Key Words: hypertension, chronic ■ angiotensin ■ autoregulation ■ dilatation ■ remodeling ■ hypertrophy

Chronic hypertension impairs dilator responses of cerebral blood vessels to both submaximal1,2 and maximal stimuli.3 One of the explanations for altered vascular responsiveness is that hypertrophy of the vessel wall encroaches on the vascular lumen and reduces internal diameter.4–6 Another explanation that has been proposed for encroachment and reduced internal diameter is that “remodeling” occurs in cerebral blood vessels during chronic hypertension. In the context of chronic hypertension, we define remodeling as a reduction in external diameter of the vessels that is not produced by reduction in vascular compliance.3

We have speculated that impaired responses of cerebral blood vessels to submaximal dilator stimuli may be linked to impairment of maximal dilator capacity.7 It is far from clear, however, whether such a link exists. A first step toward examining this question would be to prevent or attenuate reductions in maximal dilator capacity of cerebral blood vessels during chronic hypertension and then determine whether dilator responses to submaximal dilator stimuli are improved. In a recent study,8 we found that treatment of stroke-prone spontaneously hypertensive rats (SHRSP) with the ACE inhibitor perindopril attenuated reductions in maximal dilatation of cerebral arterioles. In contrast, treatment of SHRSP with the β-blocker propranolol did not significantly attenuate reductions in maximal dilatation of cerebral arterioles.

We therefore undertook the present study to examine the possibility that treatment of SHRSP with perindopril, but not propranolol, may improve responses of cerebral arterioles to a submaximal dilator stimuli. We chose acute hypertension as the submaximal dilator stimulus because cerebral arteriolar dilatation in response to acute hypotension is a critical parameter of cerebral vascular autoregulation. A possible risk concerning vascular autoregulation during the treatment of hypertension is that a treatment that effectively lowers pressure without restoring dilator capacity may increase the potential susceptibility to cerebral ischemia, particularly if the treatment increases the likelihood of acute hypotension episodes.
Chillon and Baumbach

Five groups of SHRSP were examined: (1) an untreated group, (2) a group treated with a high dose of perindopril, (3) a group treated with a low dose of perindopril, (4) a group treated with the β-blocker propranolol, and (5) a group treated with a combination of propranolol and a low dose of perindopril. On the basis of the results obtained in the previous experiment, we anticipated that if maximal dilator capacity influences the responses of cerebral arterioles to submaximal dilator stimuli, treatment of SHRSP with both the low and high doses of perindopril, but not propranolol, would attenuate impaired responses of cerebral arterioles to acute hypotension.

Methods

Experiments were conducted on male Wistar-Kyoto rats (WKY) and male SHRSP. SHRSP and WKY were obtained from a well-established inbred colony that is maintained in the University of Iowa Animal Care Facility. At 3 months of age, the SHRSP were divided into 5 groups: (1) an untreated group (n=11) that drank tap water, (2) a group (n=7) that received a low dose of perindopril (0.3 mg/kg), (3) a group (n=8) that received a high dose of perindopril (2 mg/kg), (4) a group (n=9) that received propranolol alone (250 mg/kg), and (5) a group (n=7) that received a combination of the low dose of perindopril (0.3 mg/kg) plus propranolol (250 mg/kg). The doses of perindopril and propranolol were chosen according to the previous study. In the first study, the high dose of perindopril was chosen to normalize blood pressure in hypertensive rats in accordance to information from Servier Laboratories and an earlier study. The low dose of perindopril was chosen to have minimal impact on blood pressure. The dose of propranolol was chosen to decrease systemic pressure in SHRSP as effectively as the high dose of perindopril. Systolic blood pressure was measured weekly in all rats during the first month of the experiment and every 2 weeks thereafter by the tail-cuff method (results not shown). Perindopril and propranolol were administered in the drinking water. WKY that drank tap water were used as normotensive controls (n=10). Animals were allowed free access to food and water, housed at 25°C, and exposed to 12 hours of light each day. Procedures followed in this study were in accordance with the institutional guidelines set forth by the University of Iowa.

After 3 months of treatment, we examined the active and passive responses of cerebral arterioles using a surgery similar to the one used in our previous experiment.

Measurement of Cerebral Arteriolar Pressure and Diameter

Pressure and internal diameter were measured in first-order arterioles on the surface of the cerebrum through an open-skull preparation as previously described. After making a craniotomy over the left parietal cortex, the exposed brain was continuously suﬀused with artificial cerebral spinal fluid (CSF), warmed to 37°C to 38°C and equilibrated with a gas mixture of 5% CO2/95% N2. Pressure was measured continuously in cerebral arterioles with a micropipette connected to a servo-null pressure-measuring device (model 5, Instrumentation for Physiology and Medicine, Inc). Arterioles were monitored through a Leitz microscope (NPI ×10 objective) connected to a closed-circuit video system with a final magnification of ×356. Images of arterioles were digitized using a Macintosh computer (Quadra 900, Apple Computer). Arteriolar diameter was measured from the digitized images by the use of image analysis software (NIH Image, National Institutes of Health, Research Services Branch, National Institute of Mental Health).

Experimental Protocol

Approximately 20 to 30 minutes after completion of surgery, measurements of cerebral arterioles were obtained under baseline conditions. To examine active responses, pressure-internal diameter relationships were obtained in cerebral arterioles between cerebral arteriolar pressures of 60 and 10 mm Hg. Hemorrhage was used to reduce cerebral arteriolar pressure in decrements of 10 mm Hg at pressures down to 20 mm Hg of cerebral arteriolar pressure and decrements of 5 mm Hg at pressures between 20 and 10 mm Hg. Arterial blood gases in all groups of animals remained within normal limits during all manipulations before deactivation of cerebral arterioles (Table).

To examine passive responses, pressure-internal diameter measurements were repeated in cerebral arterioles during maximal dilatation. Maximal dilatation was obtained by suffusing cerebral vessels with artificial CSF that contained EDTA (67 mmol/L), which produces complete deactivation of smooth muscle in cerebral arterioles. At the end of each experiment, the animal was killed by an injection of anesthetic.

Statistical Analysis

ANOVA was used to compare systemic pressure, arteriolar pressure, and diameters. The probability values were calculated with a Student’s t test. Statistics were determined using the JMP statistics software (SAS Institute Inc) on a Macintosh computer.

Results

Baseline Values

Systemic arterial pressure and cerebral arteriolar pressure were significantly greater in untreated 6-month-old SHRSP than in age-matched WKY (Table). The low dose of perindopril reduced systemic arterial pressure and cerebral arteriolar pressure in SHRSP to a level approximately halfway between untreated SHRSP and WKY, whereas the high dose of perindopril nearly normalized systemic arterial pressure and completely normalized cerebral arteriolar pressure (Table). Although propranolol alone did not reduce systemic arterial pressure and cerebral arteriolar pressure in SHRSP as effectively as the high dose of perindopril, it was significantly more effective than the low dose of perindopril (Table). Combining the low dose of perindopril with propranolol fully normalized systemic arterial pressure and cerebral arteriolar pressure in SHRSP (Table).

Before the deactivation of cerebral arterioles with EDTA, the diameter of the cerebral arterioles was significantly less in untreated SHRSP than in WKY (Table). Treatment of SHRSP with the low and high doses of perindopril, as well as propranolol alone and combined with the low dose of perindopril, significantly increased cerebral arteriolar diameter (Table). Diameters were significantly less, however, in all of the treatment groups than in WKY.

After deactivation, the diameter of the cerebral arterioles was significantly smaller in untreated SHRSP than in WKY (Table). Diameter was significantly greater in SHRSP treated with both the low and high doses of perindopril than in untreated SHRSP. In contrast, diameter was not significantly increased in SHRSP treated with propranolol alone. Propranolol combined with the low dose of perindopril, on the other hand, significantly increased the diameter in SHRSP.

Active and Passive Responses

The pressure-diameter relationship before deactivation of vascular smooth muscle with EDTA was shifted to a lower level in the cerebral arterioles of untreated SHRSP than WKY (Figure 1, left). Although the difference in diameters between
the 2 groups became less at lower levels of arteriolar pressure, the diameter remained significantly decreased in untreated SHRSP, even at arteriolar pressures of 10 to 20 mm Hg. Treatment of SHRSP with the low (Figure 1, right) and high (Figure 1, left) doses of perindopril resulted in a significant upward shift of the pressure-diameter relationship at all levels of arteriolar pressure. The relationship in both groups of treated SHRSP, however, remained reduced relative to WKY. Treatment of SHRSP with propranolol alone significantly shifted the pressure-diameter relationship upward at arteriolar pressures of 30 mm Hg and higher (Figure 1, left). At arteriolar pressures of 20 mm Hg and lower, diameters were similar in SHRSP treated with propranolol alone and untreated SHRSP. The addition of propranolol to the low dose of perindopril resulted in no further shift in the pressure-diameter relationship in the cerebral arterioles of SHRSP (Figure 1, right).

During maximal dilatation of cerebral arterioles with EDTA, the diameter was significantly less in SHRSP than in WKY at all levels of cerebral arteriolar pressure between 60 mm Hg and 10 mm Hg (Figure 2, left). Both the low (Figure 2, right) and high (Figure 2, left) doses of perindopril...
Values are mean ± SEM. *P < 0.05 vs WKY; †P < 0.05 vs SHRSP.

Figure 2. Pressure–internal diameter relationship of cerebral arterioles without active tone (passive) in untreated WKY (●, n=10, left) and SHRSP that were untreated (●, n=11, left) or treated with the high dose of perindopril (Per-H, ○, n=8, left) or propranolol alone (Prop, ●, n=9, left) and in SHRSP that were treated with the low dose of perindopril (Per-L, ○, n=7, right) or the combination of propranolol and the low dose of perindopril (○, n=7, right). Measurements were obtained during maximal dilatation with EDTA. Values are mean ± SEM. *P < 0.05 vs WKY; †P < 0.05 vs SHRSP.

Dilator reserve, which was defined as the difference in the diameter of the cerebral arterioles before and after maximal dilatation, was significantly less in untreated SHRSP than WKY at arteriolar pressures of 15 mm Hg and higher. Treatment of SHRSP with either the low (Figure 3, right) or high (Figure 3, left) doses of perindopril completely normalized dilator reserve of cerebral arterioles. In contrast, treatment with propranolol alone had little effect on dilator reserve at arteriolar pressures < 40 mm Hg (Figure 3, left). In addition, combining propranolol with the low dose of perindopril did not result in further improvement of dilator reserve (Figure 3, right).

Discussion

There were 2 major findings in this study. First, treatment with both the high and low dose of perindopril improved submaximal dilator responses to acute reductions in pressure in cerebral arterioles of SHRSP. Propranolol, on the other hand, improved autoregulatory dilatation of cerebral arterioles less effectively than perindopril. Second, both the low and high doses of perindopril improved maximal dilator responses of cerebral arterioles in SHRSP. In contrast, propranolol was less effective than perindopril in improving maximal dilator responses of cerebral arterioles.

We undertook the present study to examine the possibility that the treatment of SHRSP with perindopril, but not propranolol, may improve responses of cerebral arterioles to a submaximal dilator stimuli as it did for responses to a maximal dilator stimuli. It is indeed tempting to speculate that the impairment of maximal dilatation may be a major contributor to reduced responses of cerebral vessels to submaximal dilator stimuli during chronic hypertension. The explanation for alterations in vascular responsiveness that has been most widely recognized is that hypertrophy of the vessel wall encroaches on the vascular lumen. Another explanation that has been proposed for encroachment on the lumen, and hence altered vascular responsiveness, is that “remodeling” occurs in cerebral blood vessels during chronic hypertension. We define remodeling in the context of chronic hypertension as a reduction in the external diameter of the vessels that is not produced by reduction in vascular compliance. Remember, however, that although structural changes in blood vessels interfere with maximal vasodilator responses during hypertension, it is not clear whether these changes contribute significantly to impaired responses to submaximal dilator stimuli. This unanswered question is quite important because submaximal dilator stimuli, such as acute hypotension, occur far more frequently than maximal dilator stimuli.

Results from the present study combined with our previous study suggest that the mechanism that underlies the effects of perindopril on autoregulatory dilatation and dilator reserve in cerebral arterioles of SHRSP may be related, at least in part, to its effects on remodeling. We found previously that perindopril in either a low or a high dose attenuated remodeling of cerebral arterioles in SHRSP, whereas propranolol did not. In the present study, both the low and high doses of perindopril, but not propranolol, improved submaximal and maximal dilator responses to acute reductions in pressure. Thus, the pattern of effects of treatment on remodeling of cerebral arterioles in SHRSP closely correlates with the pattern of effects of treatment on autoregulatory dilatation. If no correlation had been found between remodeling and autoregulatory dilatation of cerebral arterioles in SHRSP, we would be able to state with reasonable certainty that structural alterations in cerebral arterioles of SHRSP do not contribute to their impaired responses to submaximal dilator stimuli. The corollary, however, is not necessarily true. The correla-
tion we found between attenuation of remodeling and impaired autoregulatory dilatation in cerebral arterioles of SHRSP does not in and of itself confer a cause-and-effect relationship between remodeling and impaired autoregulatory dilatation. At least 2 other factors may have contributed to the improvement of submaximal dilator responses to acute reductions in pressure in cerebral arterioles of SHRSP treated with perindopril, independent of perindopril’s effect on remodeling.

One alternative is that ACE inhibitors dilate larger, but not smaller, cerebral arteries, which in turn leads to a compensatory autoregulatory constriction of smaller arteries downstream to counteract increases in cerebral blood flow that would otherwise occur. This autoregulatory constriction would in effect result in an apparent increase in the dilator reserve. This possibility is supported by the proposal that the constriction of cerebral blood vessels by the renin-angiotensin system is confined primarily to larger cerebral arteries and, thus, only larger cerebral arteries dilate during inhibition of ACE. This hypothesis, however, is not supported by our finding in this study that the diameter of cerebral arterioles under baseline conditions was larger, rather than smaller, in SHRSP treated with perindopril than in untreated SHRSP.

Another alternative to remodeling is that ACE inhibitors improve endothelium-dependent dilatation in hypertensive rats and humans. In contrast, β-blockers do not improve endothelium-dependent relaxation in hypertensive subjects except for new generation β-blockers, such as carvedilol, that scavenge free radicals. Several studies suggest that endothelial factors may play a role in cerebral autoregulation. Thus, by improving endothelium-dependent dilatation, ACE inhibitors may improve autoregulatory dilatation. However, we suggest caution with respect to this interpretation because others have reported that endothelial factors do not influence cerebral autoregulation.

The findings in this study and our previous study also may be relevant to the question of whether remodeling or hypertrophy is more important to impaired dilatation of cerebral arterioles in SHRSP. On the basis of calculations from measurements made in maximally dilated cerebral arterioles in WKY and SHRSP, we have speculated that remodeling contributes substantially more to impaired maximal dilatation than hypertrophy. In this study, we found that the low dose of perindopril improved autoregulatory dilatation, maximal dilatation, and dilator reserve of cerebral arterioles in SHRSP almost as effectively as the high dose. In a previous study, we have shown that both the low and high doses of perindopril significantly attenuate remodeling whereas only the high dose prevents arteriolar wall hypertrophy. The combination of these findings support the hypothesis that remodeling may play a greater role than hypertrophy in the impairment of cerebral arteriolar dilatation.

Conclusion
We conclude that antihypertensive treatment with perindopril attenuates reductions in autoregulatory dilatation, maximal dilator capacity, and dilator reserve in cerebral arterioles. In addition to its effects on cerebral arteriolar dilatation, perindopril also attenuates remodeling of cerebral arterioles. It is of particular interest that perindopril improves dilator function and attenuates remodeling, even in a dose that only partially normalizes arteriolar pressure and fails to prevent hypertrophy. Antihypertensive treatment with propranolol, on the other hand, does not attenuate reductions in cerebral arteriolar dilatation or remodeling, even in a dose that lowers arteriolar pressure more effectively than the low dose of perindopril. We cannot rule out the possibility that a higher dose of propranolol than was used in this study might have had greater effects on remodeling, hypertrophy, and autoregulatory dilatation. We think this outcome is unlikely, however, because a relatively high dose of propranolol was required in this study to decrease blood pressure in SHRSP as effectively as the high dose of perindopril. Furthermore, any additional effects that might have been observed with doses of propranolol significantly higher than the dose used in this study may have been difficult to interpret because of potential nonspecific effects of propranolol unrelated to its β-blocker activity.

The finding in this study that the ACE inhibitor perindopril was more effective than propranolol in restoring cerebral arteriolar dilatation may have important implications with respect to cerebral ischemia. Impairment of vasodilator responses by chronic hypertension can presumably cause cerebral ischemia during acute episodes of hypotension, because cerebral vessels may not be able to dilate sufficiently to meet tissue needs. Thus, the restoration of cerebral vasodilator capacity to prehypertensive levels with an ACE inhibitor may help to prevent cerebral ischemia during the treatment of chronic hypertension by enabling the cerebral circulation to respond more effectively to vasodilator stimuli.

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