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Effects of long-acting angiotensin-converting enzyme inhibitor, imidapril, on the lower limit of cerebral blood flow autoregulation in hypertensive rats

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Abstract

The objective of the present study was to examine the effects of a long-acting angiotensin converting enzyme inhibitor, imidapril ((4*S*)-1-methyl-3-{(2*S*)-2-[*N*-(1*S*)-1-ethoxycarbonyl-3-phenylpropyl) amino] propionyl}-2-oxoimidazolidine-4-carboxylic acid hydrochloride), for 7 days on the cerebral blood flow autoregulatory response to hypotension in hypertensive rats. We measured the cerebral blood flow at rest and during hemorrhagic hypotension, using laser-Doppler flowmetry. At the same time, the absolute baseline cerebral blood flow values in the parietal cortex were quantified with the hydrogen clearance method. After administration of imidapril at a dose of 5 mg/kg/day for 7 days, the resting value of mean arterial blood pressure was significantly decreased by 25 mm Hg ($P < 0.001$), cerebral vascular resistance was lowered by 14.4% ($P < 0.05$) and the lower limit of cerebral blood flow autoregulation was shifted to a lower level, 106 ± 11 mm Hg (mean ± S.D.), from 137 ± 8 mm Hg in the control group ($P < 0.001$), while resting cerebral blood flow remained unchanged. The present results demonstrated that imidapril preserves cerebral blood flow and significantly shifts the lower limit of cerebral autoregulation towards lower blood pressure levels. © 1998 Elsevier Science B.V.

Keywords: Angiotensin converting enzyme inhibitor; Imidapril; Cerebral blood flow autoregulation; Hemorrhagic hypotension; Spontaneously hypertensive rat (SHR)

1. Introduction

During the past decade, angiotensin converting enzyme inhibitors have become established as effective antihypertensive drugs that cause few side-effects (Gravas and Gravas, 1988; Unger et al., 1988; Banas, 1992). Angiotensin converting enzyme inhibitors are widely used for hypertensive patients with either heart disease or renal dysfunction (Rouleau et al., 1989; Jackson et al., 1991). Imidapril ((4*S*)-1-methyl-3-{(2*S*)-2-[*N*-(1*S*)-1-ethoxycarbonyl-3-phenylpropyl) amino] propionyl}-2-oxoimidazolidine-4-carboxylic acid hydrochloride), a relatively new angiotensin converting enzyme inhibitor, has a long-lasting antihypertensive effect (Kubo et al., 1990), which confers efficacy on once-daily dosing in humans. The antihypertensive effect of imidapril was approximately 5 times more potent than that of captopril, a short-acting agent (Kubo et al., 1990). This long-acting nature would be particularly important for the achievement of 24 h stable antihypertensive effectivity (Cesarone et al., 1994).

The lower limit of cerebral blood flow autoregulation is shifted to a higher level in chronic, long-standing hypertension (Strandgaard et al., 1973; Fujishima and Omae, 1976) and thereby an acute, excessive, reduction of systemic arterial pressure may occasionally lead to a marked reduction in cerebral blood flow or to brain ischemia (Graham, 1975; Strandgaard et al., 1984). Angiotensin converting enzyme inhibitors may be useful for the treatment of chronic hypertension with potential risk of cerebral vascular complications (Sadoshima et al., 1994), because of the beneficial effects of angiotensin converting enzyme inhibitors on compromised brain circulation or the lower limit of cerebral blood flow autoregulation (Paulson et al., 1985; Sadoshima et al., 1994). We have demonstrated that inhibition of angiotensin converting enzyme activity was protective against acute hypotension and brain

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ischemia (Sadoshima et al., 1993, 1994), using short-acting SQ 29852 and captopril. However, no study was so far tested a long-acting angiotensin converting enzyme inhibitor in this context. In the present study, therefore, our objective was to examine the effect of imidapril on cerebral blood flow autoregulation during hemorrhagic hypotension in spontaneously hypertensive rats (SHR).

2. Materials and methods

Male SHRs (6–7 months of age, 350–400 g), kept at Kyushu University Animal Center, were used in the present study.

14 SHR were divided into two groups. Seven rats were treated with imidapril (TA-6366) (5 mg/kg/day), and the other 7 rats were used as controls. Imidapril, which was dissolved in distilled water, was administered by gavage into the stomach once a day. The rats for control were treated with the same amount of distilled water alone (1 ml/kg/day). The animals had free access to food and water prior to the experiment.

The autoregulation study was carried out on the seventh day about 2.5 h after the final treatment with imidapril or distilled water. Under amobarbital anesthesia (100 mg/kg body weight, i.p.), both femoral arteries were cannulated, one for continuous recording of mean arterial blood pressure and for sampling blood, and the other for producing stepwise hypotension by controlled bleeding. The rats were mounted on a stereotaxic head-holder in a sphinx position. Rectal temperature was maintained at 37°C with a heating pad. One burr hole (5 mm in diameter) for cerebral blood flow measurement was made in the parietal bone with a high-speed drill under an operating microscope. Cerebral blood flow of the parietal cortex was continuously monitored by laser-Doppler flowmetry according to Dirnagl et al. (1989). Briefly, a laser-Doppler probe was placed on the dura mater approximately 4 mm posterior and 2 mm lateral to the bregma. This probe was connected to a perfusion monitor (PERIFLUX PF3, Perimed, Sweden). Baseline cerebral blood flow was also determined by the hydrogen clearance method (CBF_{H_2}) (Aukland et al., 1964) as described in detail elsewhere (Fujishima et al., 1981). A Teflon-coated platinum electrode with platinum black on its tip was placed 1.5 mm deep from the brain surface and 2 mm away from the laser-Doppler flowmetry probe. Twenty minutes after stabilization, baseline values of cerebral blood flow were measured at least three times by laser-Doppler flowmetry and the hydrogen clearance method at intervals of 10 min. Cerebral vascular resistance was calculated from the mean arterial blood pressure/cerebral blood flow ratio.

Arterial blood was withdrawn from the femoral arterial catheter to decrease systemic arterial pressure in a stepwise manner, by 10 mm Hg/step. Changes in cerebral blood flow determined by laser-Doppler flowmetry (CBF_{LDF}) were expressed as percentages of the baseline values. Arterial blood pressure was maintained at each pressure level for at least 5 min during which the arbitrary unit of cerebral blood flow (measured by laser-Doppler flowmetry) was recorded. Arterial gases and pH were determined three times, i.e., under resting conditions (before hypotension), during moderate hypotension and during severe hypotension.

At the end of the experiment, a plastic funnel was fitted onto the parietal skull and liquid nitrogen was poured into the funnel. The whole frozen brain was chiseled out carefully and separated grossly into the supratentorial and infratentorial portions. The supratentorial brain was weighed rapidly and ground after the addition of cold perchloric acid, 1 N. The tissue homogenates, kept at 0°C to 4°C, were centrifuged and neutralized with 3 N KOH at pH 5.6 ± 0.1. Lactate, pyruvate and adenosine triphosphate (ATP) concentrations in the homogenate were determined by a standard enzymatic method (Lowry and Passonneau, 1972).

The lower limit of cerebral blood flow autoregulation was defined as mean arterial blood pressure at which cerebral blood flow decreased by 10% of the baseline value. The results were expressed as means ± S.D. Statistical analysis was performed with the unpaired *t*-test.

3. Results

No significant differences were observed for the physiological variables listed in Table 1 between the control and the imidapril-treated groups. Resting values of mean arterial blood pressure were 190 ± 5 (mean ± S.D.) and 165 ±

Table 1
Physiological variables in control and imidapril-treated (5 mg/kg/day, 7 days) rats

	Control ($n = 7$)	Imidapril ($n = 7$)
$PaCO_2$ (mm Hg)		
Baseline	39 ± 2	38 ± 3
Moderate hypotension	39 ± 1	38 ± 2
Severe hypotension	32 ± 4	34 ± 4
PaO_2 (mm Hg)		
Baseline	91 ± 5	92 ± 7
Moderate hypotension	97 ± 5	96 ± 5
Severe hypotension	116 ± 16	111 ± 15
pH		
Baseline	7.41 ± 0.01	7.40 ± 0.02
Moderate hypotension	7.40 ± 0.01	7.39 ± 0.03
Severe hypotension	7.37 ± 0.08	7.37 ± 0.05
Hct (%)		
Baseline	42 ± 4	44 ± 2
Moderate hypotension	42 ± 4	42 ± 3
Severe hypotension	39 ± 4	40 ± 2

Values are means ± S.D., Hct: hematocrit.

Table 2
Mean arterial pressure, cerebral blood flow, cerebral vascular resistance at rest and lower limits of autoregulation in control and imidapril-treated (5 mg/kg/day, 7 days) rats

	Control ($n=7$)	Imidapril ($n=7$)
Baseline MAP (mm Hg)	190 ± 5	165 ± 6[a]
Baseline CBF_{H_2} (ml/100 g/min)	37 ± 3	38 ± 5
CVR (mm Hg/ml)/100 g/min	5.14 ± 0.49	4.40 ± 0.63[b]
Lower limits of autoregulation (mm Hg)		
CBF_{LDF} decreased by 10%	137 ± 8	106 ± 11[a]
CBF_{LDF} decreased by 20%	119 ± 6	91 ± 13[a]

MAP: mean arterial pressure, CVR: cerebral vascular resistance, CBF_{H_2}: cerebral blood flow measured by hydrogen clearance method, CBF_{LDF}: cerebral blood flow measured by laser-Doppler flowmetry.
Values are means ± S.D.
[a] $P < 0.001$, [b] $P < 0.05$ vs. control group.

6 mm Hg in the control and imidapril-treated groups, respectively. Although baseline mean arterial blood pressure was significantly lowered, by 25 mm Hg, in the imidapril-treated group ($P < 0.001$), the resting cerebral blood flow in the parietal cortex determined by the hydrogen clearance method showed no difference between the two groups (37 ± 3 ml/100 g/min in the control group and 38 ± 5 ml/100 g/min in the treated group) (Table 2). Cerebral vascular resistance, calculated as mean arterial blood pressure/cerebral blood flow, was 4.40 ± 0.63 (mm Hg/ml)/100 g per minute in the imidapril-treated group, thus was 14.4% lower than the 5.14 ± 0.49 (mm Hg/ml)/100 g per minute in the control group ($P < 0.05$).

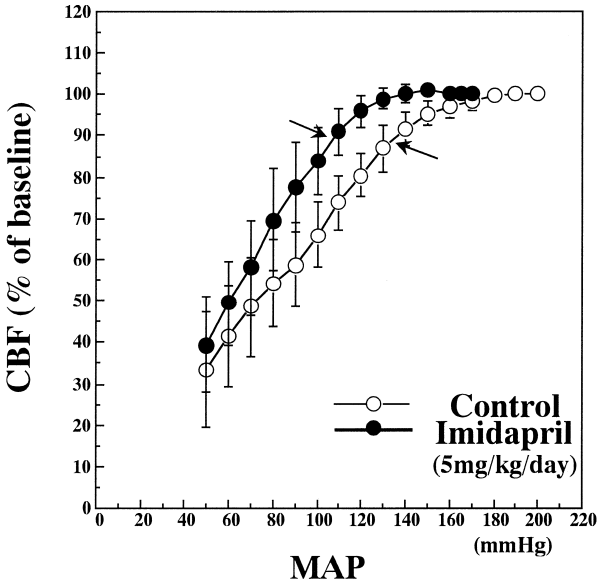

Fig. 1. Relation of mean arterial pressure (MAP) to cerebral blood flow (CBF) in the parietal cortex in spontaneously hypertensive rats after administration of imidapril (5 mg/kg/day) (closed circle) or distilled water as a control (open circle) for 7 days. Arrows indicate lower limits of autoregulation defined as the mean arterial pressure at which cerebral blood flow decreased by 10% of the baseline value.

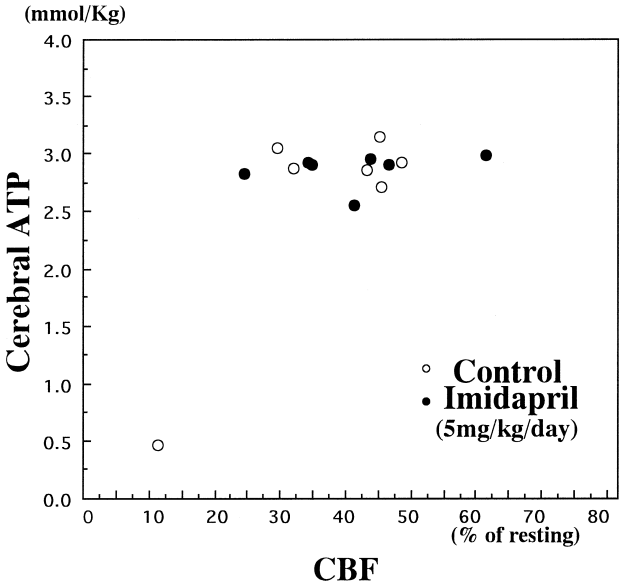

Fig. 2. Relationship between cerebral blood flow (CBF) and cerebral ATP in spontaneously hypertensive rats after administration of imidapil (5 mg/kg/day) (closed circle) or distilled water as a control (open circle) for 7 days. Cerebral ATP at the end of the severe hypotension showed no difference in the two groups.

The lower limit of cerebral blood flow autoregulation, defined as the mean arterial blood pressure at which cerebral blood flow decreased by 10% of the baseline value, was 106 ± 11 mm Hg in the treated group, which was significantly lower than the 137 ± 8 mm Hg in the control group ($P < 0.001$) (Fig. 1). The autoregulatory plateau, the range of mean arterial blood pressure between resting and the lower limit of cerebral blood flow, was approximately 50 to 60 mm Hg in each group.

Fig. 2 illustrates the relationship between cerebral blood flow and supratentorial ATP during severe hypotension (50 mm Hg for 15 min) in the two groups. While there was no marked decrease in ATP except for one case which showed a severe decrease in cerebral blood flow (10% of the resting), lactate and the lactate/pyruvate ratio were moderately increased in both the control and the imidapril-treated groups (lactate: 8.73 ± 9.59 mmol/kg, 7.24 ± 6.27 mmol/kg; and lactate/pyruvate ratio: 60.0 ± 100.9 and 28.1 ± 22.9, respectively), indicating that the ischemic level was moderate or so-called 'penumbral'. However, there were no significant differences in these parameters of brain energy metabolism between the two groups.

4. Discussion

The major findings in our study were (1) oral administration of imidapril (5 mg/kg/day) for 7 days lowered mean arterial blood pressure by 25 mm Hg, while main-

taining a baseline cerebral blood flow within normal limits; and (2) the lower limit of cerebral blood flow autoregulation was significantly attenuated, from 137 to 106 mm Hg, by the treatment with imidapril.

Baseline cerebral blood flow remained unchanged even though mean arterial blood pressure was reduced from 190 to 165 mm Hg. This result seems to be consistent with the hypothesis proposed by Paulson et al. (Sadoshima et al., 1994; Torup et al., 1993) that angiotensin converting enzyme inhibitors dilates the large arteries with compensatory constriction of the small arteries or arterioles. According to previous reports (Barry et al., 1983; Postiglione et al., 1991; Sadoshima et al., 1994), the vascular renin–angiotensin system appears to play a role in maintaining the resistance of large cerebral arteries in the cerebral circulation. Angiotensin I also constricts large cerebral arteries (Whalley et al., 1983). However, angiotensin II itself produces dilatation of the small cerebral arteries (Toda and Miyazaki, 1981; Haberl et al., 1990; Tamaki et al., 1992). Therefore, the hypothesis is still controversial.

Cerebral autoregulation is a regulatory mechanism that maintains cerebral blood flow at a constant level within a wide range of systemic arterial blood pressure or cerebral perfusion pressure. A number of hypotheses have been proposed to explain the autoregulatory mechanism (Paulson et al., 1990). First, the smooth muscle of arterioles and small arteries constricts or dilates in response to an increase or decrease in the transmural pressure gradient (i.e., myogenic mechanism). Second, changes in the metabolic microenvironment are thought to be responsible for the vasomotor response (i.e., metabolic theory). Third, perivascular nerves have been proposed to play a role in cerebral autoregulation. However, the effect of angiotensin converting enzyme inhibition on cerebral blood flow autoregulation is still evident after sympathetic denervation (Postiglione et al., 1991). In recent years, endothelial cell-related factors have been suggested to be of major significance.

Chronic hypertension is associated with attenuated endothelium-dependent relaxation in response to acetylcholine and to bradykinin (Lüscher et al., 1987; Vanhoutte, 1989; Yang et al., 1991). The impairment of endothelium-dependent relaxation in hypertension may be improved after chronic antihypertensive therapy (Lüscher et al., 1987). Previous studies (Levy et al., 1990; Clozel et al., 1990) have demonstrated that angiotensin converting enzyme inhibitors such as lisinopril and cilazapril improve endothelium-dependent vasorelaxation in SHRs. This improvement of endothelium-dependent vasorelaxation by cilazapril was apparent after only 4 days as well as 4 months of treatment. In contrast, angiotensin II antagonists do not lead to bradykinin accumulation (Rhaleb et al., 1991) and are therefore not expected to release nitric oxide (NO) from the endothelium; the effects of angiotensin II receptor antagonists on cerebral blood flow autoregulation thus remain controversial (Stromberg et al., 1993; Naveri et al., 1994; Vraamark et al., 1995). Several studies (Freslon and Giudicelli, 1983; Christensen et al., 1988; Frohlich and Horinaka, 1991) have shown that angiotensin converting enzyme inhibitors are effective to attenuate vascular structure changes associated with hypertension, but with variable efficacy. In our study, we treated SHRs with imidapril for 7 days, which may have been too short a duration to attenuate structural changes or remodeling in cerebral arteries (Ibayashi et al., 1986; Hajdu et al., 1991). Angiotensin converting enzyme plays an important role not only in the renin–angiotensin system but also in the kallikrein–kinin system by inactivating the vasodilator, bradykinin, a potent releaser of endothelium-derived relaxing factor (EDRF) (Vanhoutte et al., 1989). Therefore, one plausible explanation for the improved cerebral blood flow autoregulation would be that imidapril improved endothelial function through augmenting bradykinin.

We also examined the effects of angiotensin converting enzyme inhibition on metabolic changes in brain tissue after global ischemia. Administration of angiotensin converting enzyme inhibitors, either SQ 29852 or captopril, significantly reduced the concentration of lactate and maintained the ATP levels (Sadoshima et al., 1993). This result indicates that angiotensin converting enzyme inhibitors protect neuronal energy metabolism against ischemic insult, probably because of the opening of the blood–brain barrier, even transiently by cerebral ischemia and/or reperfusion (Kuroiwa et al., 1988). In the present study, brain energy metabolism was not influenced by administration of imidapril (5 mg/kg/day) for 7 days. After global incomplete ischemia induced by 15 min of severe hypotension in both groups, cerebral blood flow was preserved above 20% of the resting value in almost all cases, and the changes in lactate, lactate/pyruvate ratio and ATP were modest. Thus, it may be possible that the ischemic level was too mild to show any beneficial effects of imidapril on energy metabolism.

In conclusion, the present results indicated that the lower limit of cerebral blood flow autoregulation is shifted to a lower level after 7-day administration of the long-acting angiotensin converting enzyme inhibitor, imidapril. Such a long-acting angiotensin converting enzyme inhibitor may be quite useful for maintaining cerebral blood flow during antihypertensive therapy.

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