Angiotensin converting enzyme inhibition and cerebral circulation—a review

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1 The identification of a vascular wall renin angiotensin system and of angiotensin converting enzyme on the luminal surface of the endothelium in many tissues, including the brain, has stimulated research on the influence of the renin angiotensin system on regional blood flows.

2 In experimental studies inhibition of the angiotensin converting enzyme shifts the limits of cerebral blood flow autoregulation towards lower blood pressure values.

3 In patients with chronic arterial hypertension and in patients with chronic heart failure cerebral blood flow is not changed by acute or chronic angiotensin converting enzyme inhibition, despite in some cases pronounced reductions in the mean arterial blood pressure. Angiotensin converting enzyme inhibition does not change ischaemic regional cerebral blood flow in acute stroke.

4 It is concluded that following angiotensin converting inhibition cerebral blood flow is maintained at an unchanged level. The mechanism may include inhibition of locally produced angiotensin II leading to a selective dilation of larger cerebral arteries with a compensatory constriction of the smaller cerebral arteries.

Keywords angiotensin II angiotensin converting enzyme autoregulation cerebral blood flow

Introduction

The angiotensin converting enzyme (ACE) determines an important pathway in the renin angiotensin system (RAS) by converting the inactive decapeptide angiotensin I released by renin to the active octapeptide angiotensin II (Erdös & Skidgel, 1987). Angiotensin II is a potent vasoconstrictor and it stimulates aldosterone secretion. Inhibitors of the ACE have become established antihypertensive drugs causing few side effects (Brunner *et al.*, 1985), and they also induce sustained improvement in the clinical status and haemodynamics (Dzau *et al.*, 1980), and reduce mortality (The CONSENSUS Trial Study Group, 1987) in congestive heart failure. Recently their use in peripheral artery disease has been suggested, as captopril, a potent ACE inhibitor, preserves

lower limb circulation possibly by maintaining the collateral blood supply (Roberts *et al.*, 1987).

During the past decade the effects of ACE inhibitors have been extensively investigated, but their mechanisms of action are not yet fully understood. Increasing evidence has demonstrated the existence of local extra-circulatory RAS in many tissues, including the brain (Dzau *et al.*, 1986; Ganten *et al.*, 1983; Healey & Printz, 1984; Mendelsohn, 1985). The identification of renin, ACE and angiotensin II receptors in the endothelium of the vascular wall throughout the vasculature, including brain arteries (Dzau, 1984, 1988; Ganten *et al.*, 1983; Swales & Thurston, 1973), has stimulated research on the influence of the RAS on regional blood flows.

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Locally produced angiotensin II may exert a significant effect on the vascular tone directly by vascular smooth muscle contraction and indirectly by facilitation of catecholamine release from surrounding nerve endings (Dzau, 1984, 1988). Thus, the classic concept of the RAS as an endocrine system with a circulating hormone angiotensin II is only partially true.

We will discuss the concept of cerebral blood flow (CBF) autoregulation, and then review experimental and clinical evidence that ACE inhibitors induce a selective effect on cerebral blood flow.

Autoregulation of cerebral blood flow

Cerebral blood flow autoregulation is defined as the process which maintains CBF at a rather constant level despite changes in arterial perfusion pressure within certain limits (Strandgaard, 1978). Although the mechanism is still unclear, this effect is known to be mediated by dilation or constriction of the cerebral resistance vessels, the arterioles. As the arterial perfusion pressure decreases these vessels dilate. The lower limit of CBF autoregulation is reached when the dilation becomes insufficient to maintain CBF, which then falls with further decreases in the arterial perfusion pressure. During increases in the arterial perfusion pressure the resistance vessels constrict. The upper limit of CBF autoregulation is reached when the arterial perfusion pressure causes a forceful dilation (breakthrough) of the maximally constricted resistance vessels.

CBF autoregulation is affected by changes in the arterial carbon dioxide tension, and by the tonus of the sympathetic nervous system. The sympathetic nerves exert a protective effect against breakthrough of autoregulation of CBF during acute hypertension: during sympathetic activation the limits are shifted to higher blood pressure levels (Edvinsson *et al.*, 1976).

In chronic arterial hypertension, the autoregulatory curve is shifted to higher blood pressure levels, leaving the brain less tolerant to acute reductions of the arterial blood pressure. This shift is partly reversed by long term antihypertensive treatment (Barry *et al.*, 1982; Strandgaard, 1978; Vorstrup *et al.*, 1984).

Single doses of antihypertensive drugs may affect the autoregulation of CBF in several ways (Barry & Lassen, 1984). Vasodilators with a direct pharmacological action on cerebrovascular smooth muscle, e.g. dihydralazine, may cause CBF autoregulation to be lost, because of a cerebral vasodilation superimposed on the autoregulatory response. Vasodilators with no direct

pharmacological action on cerebrovascular smooth muscle, e.g. diazoxide, do not change the limits or plateau of autoregulation, but may sometimes lead to excessive falls in blood pressure to levels far below the lower limit of autoregulation. As discussed below inhibitors of the ACE affect CBF autoregulation in a unique way.

ACE inhibition changes the limits of CBF autoregulation in experimental studies

The results of experimental investigations of the effect of acute or prolonged ACE inhibition on systemic and CBF are controversial. In renal hypertensive rats captopril (3 mg kg⁻¹) and alacepril (3 and 10 mg kg⁻¹) did not change regional CBF in the frontal cortex or the dorsal hippocampus, as measured by the hydrogen clearance technique. A higher dose of captopril (10 mg kg⁻¹), which also caused a marked blood pressure reduction, did induce a significant fall in frontal cortex blood flow (Takeyama *et al.*, 1986). In normotensive sodium-depleted dogs teprotide caused an unexplained significant increase in cerebral blood flow (Gavras *et al.*, 1978). In spontaneously hypertensive rats, 8 days treatment with five different ACE inhibitors did not change CBF (Richer *et al.*, 1987). In those studies, which were aimed at studying blood flow with the radioactive microspheres technique to several organs, no repetitive CBF measurements were performed as the blood pressure was lowered.

Figure 1 Autoregulation of CBF after captopril 10 mg kg⁻¹ i.v. (solid line) and during a control study (dotted line) in spontaneously hypertensive rats. Captopril shifts the autoregulation curve towards lower blood pressure levels. Redrawn, with permission from Barry *et al.* (1984).

The mechanism by which ACE inhibitors, in contrast to direct vasodilators, could maintain cerebral perfusion has not been fully elucidated, but may be understood by analyzing the effect on CBF autoregulation. Following acute ACE inhibition with captopril in normotensive and in spontaneously hypertensive rats (Figure 1), the lower and upper limits of autoregulation are shifted to lower blood pressure levels, and the autoregulatory plateau shortened (Barry *et al.*, 1984; Jarden *et al.*, 1984). Under these conditions, the tolerance of the brain to acute blood pressure lowering is improved, but the tolerance to acute hypertension is reduced. Fosinopril, a new ACE inhibitor of the phosphinic acid class, appears to reduce primarily the lower limit of autoregulation (Paulson *et al.*, 1988; Waldemar *et al.*, 1987).

Inhibition of vascular wall ACE in cerebral arteries: a possible mechanism of action

After having excluded an effect via the brain RAS (Jarden *et al.*, 1984), it was hypothesized that ACE inhibition prevents angiotensin II formation on the luminal side of the large arteries, leading to a dilation of the large arteries and a compensatory constriction of the small arteries/arterioles. Therefore, at resting arterial blood pressure CBF would be unchanged, but during a blood pressure decrease these vessels would have a larger dilatory capacity—explaining the decreased lower limit of CBF autoregulation

(Barry *et al.*, 1984; Jarden *et al.*, 1984; Paulson *et al.*, 1988).

The effect of ACE inhibition on the limits of autoregulation could also be explained by a reduction of the tonus of the cerebral perivascular sympathetic nerves, since (as shown in Figure 2) concomitant stimulation of the cervical sympathetic nerves attenuates the effect of captopril on the upper limit of CBF autoregulation (Waldemar *et al.*, 1989 a, b). The latter mechanism seems unlikely, however, because the effect of captopril on CBF autoregulation is also present in rats subjected to sympathetic denervation (Waldemar *et al.*, 1988).

Finally as ACE also degrades the vasodilator bradykinin, the effect of captopril could also involve enhancement of bradykinin induced dilation of large brain arteries. This mechanism also seems unlikely, as captopril does not alter the response of pial arteries to topically administered bradykinin (Wahl *et al.*, 1983).

Although the existence of a vascular wall renin angiotensin system, and of ACE on the luminal surface of the endothelium, including brain arteries, is well-established, there is no direct evidence for the postulated dilatory effect of captopril on the larger cerebral arteries. However, captopril dilates larger cerebral arteries *in vitro* (Whalley & Wahl, 1983, 1988), and in a clinical study, using pulsed Doppler methods, captopril caused an increase in arterial diameter of the common carotid artery (Bouthier *et al.*, 1986).

Figure 2 The effect of stimulation of the cervical sympathetic nerves during ACE inhibition with captopril 10 mg kg^{-1} i.v. in spontaneously hypertensive rats. In control animals (dotted line) the upper limit of CBF autoregulation cannot be reached. As shown in Figure 1 captopril shifts the upper limit of CBF autoregulation, which is now reached in the MAP interval 120–139 mm Hg (broken line). However, during concomitant sympathetic stimulation the upper part of the autoregulation curve is restored (solid line). Redrawn with permission from Waldemar *et al.* (1989 a).

Clinical studies

Chronic arterial hypertension

The effect of a single oral dose of captopril (25–50 mg) on CBF autoregulation was recently investigated in patients with chronic arterial hypertension as well as in normotensive volunteers (Waldemar *et al.*, 1989c). Compared with the experimental studies the clinical effect on CBF autoregulation was less pronounced, probably as a consequence of a lower sympathetic tonus induced by the blood pressure lowering technique in the human studies. It is, however, important to note, that despite a reduction of the average mean arterial pressure (MAP) by 18%, captopril did not change the baseline CBF as measured by xenon-133 inhalation tomography and by the arterio-venous oxygen difference method.

Two separate studies have examined the effect of prolonged treatment schedules on CBF. Enalapril administered daily (10–80 mg)

for 8 weeks to patients with chronic hypertension did not change CBF as measured by the intravenous xenon-133 method (Frei & Müller-Brand, 1986). Treatment with captopril for 7 days did not change CBF as measured by xenon-133 inhalation technique (Minematsu *et al.*, 1987). In both studies the mean MAP was reduced by 10%–15%, but not below the expected lower limit of CBF autoregulation. The preservation of CBF indicates that autoregulation was intact, but cannot be taken into account for a shift of the limits of autoregulation.

Acute stroke

Based on the findings as reviewed above, ACE inhibition could be expected to increase ischaemic regional CBF in the early phase after an acute stroke. However, in a recent study including 12 patients with acute stroke a single oral dose of captopril (25 mg) did not improve ischaemic regional cerebral blood flow (Figure 3) as measured by xenon-133 inhalation tomography (Waldemar *et al.*, 1989d).

Chronic heart failure

Vasodilators have been used in the treatment of chronic heart failure (CHF) for many years. Because patients with severe congestive heart failure are often hypotensive, direct vasodilators should be used with caution, to avoid cerebral hypoperfusion. After the introduction of ACE inhibitors in the treatment of CHF, there have been two reports on the effect of captopril on CBF in patients with CHF. We measured CBF using xenon-133 inhalation tomography following acute and prolonged treatment with captopril in patients with severe CHF. CBF remained unchanged and no cerebral symptoms were noted, despite reductions of MAP by 5%–40%, and thus in some cases to values below the expected lower limit of CBF autoregulation (Paulson *et al.*, 1986). In a similar study pre-treatment CBF, as measured by the intravenous xenon-133 method was lower in patients with CHF compared to controls. After 4–15 days treatment with captopril MAP was reduced by 11%, but CBF was restored to levels comparable to the control values (Rajagopalan *et al.*, 1984).

Figure 3 Regional CBF before and 1 h after an oral dose of captopril (25 mg). The patient had suffered an acute stroke with right-sided hemiparesis and global aphasia a few hours before the CBF study. The tomograms were obtained 5 cm above the orbitomeatal line and the left hemisphere is shown to the left. The colour scale indicates CBF in ml (100 g⁻¹ min). The regional distribution of CBF was not changed by captopril.

Conclusion

Despite marked reductions of the arterial blood pressure, cerebral blood flow is preserved during treatment with ACE inhibitors in patients with chronic arterial hypertension or chronic heart failure. This effect may be caused by a direct effect of ACE inhibitors on CBF autoregulation, as shown in experimental studies. The mechanism could involve inhibition of locally

produced angiotensin II, leading to a selective dilation of the larger cerebral arteries. Direct experimental evidence for a direct dilatory effect on cerebral arteries is, however, still lacking.

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References

- Barry, D. I., Jarden, J. O., Paulson, O. B., Graham, D. I. & Strandgaard, S. (1984). Cerebrovascular aspects of converting-enzyme inhibition I: Effects of intravenous captopril in spontaneously hypertensive and normotensive rats. *J. Hypertension*, **2**, 589–597.
- Barry, D. I. & Lassen, N. A. (1984). Cerebral blood flow autoregulation in hypertension and effects of antihypertensive drugs. *J. Hypertension*, **2** (suppl 3), 519–526.
- Barry, D. I., Strandgaard, S., Graham, D. I., Braendstrup, O., Svendsen, U. G., Vorstrup, S., Hemmingsen, R. & Bolwig, T. G. (1982). Cerebral blood flow in rats with renal and spontaneous hypertension: Resetting of the lower limit of autoregulation. *J. Cereb. Blood Flow Metab.*, **2**, 347–353.
- Bouthier, J. D., Safar, M. E., Benetos, A., Simon, A. C., Levenson, J. A. & Hugues, C. M. (1986). Haemodynamic effects of vasodilating drugs on the common carotid and brachial circulations of patients with essential hypertension. *Br. J. clin. Pharmacol.*, **21**, 137–142.
- Brunner, H. R., Nussberger, J. & Waeber, B. (1985). Effects of angiotensin converting enzyme inhibition: A clinical point of view. *J. cardiovasc. Pharmacol.*, **7** (suppl 4), S73–S81.
- The CONSENSUS trial study group (1987). Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *New Engl. J. Med.*, **316**, 1429–1435.
- Dzau, V. J. (1984). Vascular wall renin-angiotensin pathway in control of the circulation: A hypothesis. *Am. J. Med.*, **77** (suppl 4A), 31–36.
- Dzau, V. J. (1988). Vascular renin-angiotensin system in hypertension. New insights into the mechanism of action of angiotensin converting enzyme inhibitors. *Am. J. Med.*, **84** (suppl 4A), 4–8.
- Dzau, V. J., Colucci, W. S., Williams, G. H., Curfman, G., Meggs, L. & Hollenberg, N. K. (1980). Sustained effectiveness of converting enzyme inhibition in patients with severe congestive heart failure. *New Engl. J. Med.*, **302**, 1373–1379.
- Dzau, V. J., Ingelfinger, J., Pratt, R. E. & Ellison, K. E. (1986). Identification of renin and angiotensinogen messenger RNA sequences in mouse and rat brains. *Hypertension*, **8**, 544–548.
- Edvinsson, L., Owman, C. & Siesjö, B. (1976). Physiological role of cerebrovascular sympathetic nerves in the autoregulation of cerebral blood flow. *Brain Res.*, **117**, 519–523.
- Erdős, E. & Skidgel, R. A. (1987). The angiotensin I-converting enzyme (Editorial). *Lab. Invest.*, **56**, 345–348.
- Frei, A. & Müller-Brand, J. (1986). Cerebral blood flow and antihypertensive treatment with enalapril. *J. Hypertension*, **4**, 365–367.
- Ganten, D., Hermann, K., Unger, T. & Lang, R. E. (1983). The tissue renin-angiotensin systems: Focus on brain angiotensin, adrenal gland and arterial wall. *Clin. exp. Hypertension*, **A5**, 1099–1118.
- Gavras, H., Liang, C. & Brunner, H. R. (1978). Redistribution of regional blood flow after inhibition of the angiotensin converting enzyme. *Circ. Res.*, **43** (suppl 1), I–59–63.
- Healey, D. P. & Printz, M. P. (1984). Autoradiographic localization of angiotensin II binding sites in the brain, pituitary, kidney and adrenal gland of the rat. *J. Hypertension*, **2** (suppl 3), 57–61.
- Jarden, J. O., Barry, D. I., Juhler, M., Graham, D. I., Strandgaard, S., Paulson, O. B. (1984). Cerebrovascular aspects of converting-enzyme inhibition II: Blood-brain barrier permeability and effect of intracerebroventricular administration of captopril. *J. Hypertension*, **2**, 599–604.
- Mendelsohn, F. A. O. (1985). Localization and properties of angiotensin receptors (Editorial review). *J. Hypertension*, **3**, 307–316.
- Minematsu, K., Yamaguchi, T., Tsuchiya, M., Ito, K., Ikeda, M. & Omae, T. (1987). Effect of angiotensin converting enzyme inhibitor (captopril) on cerebral blood flow in hypertensive patients without a history of stroke. *Clin. exp. Hypertension*, **A9**, 551–557.
- Paulson, O. B., Jarden, J. O., Vorstrup, S., Holm, S. & Godtfredsen, J. (1986). Effect of captopril on the cerebral circulation in chronic heart failure. *Eur. J. clin. Invest.*, **16**, 124–132.
- Paulson, O. B., Waldemar, G., Andersen, A. R., Barry, D. I., Pedersen, E. V., Schmidt, J. F. & Vorstrup, S. (1988). Role of angiotensin in autoregulation of cerebral blood flow. *Circulation*, **77** (suppl 1), I–55–I–58.
- Rajagopalan, B., Raine, A. E. G., Cooper, R. & Ledingham, J. G. G. (1984). Changes in cerebral blood flow in patients with severe congestive cardiac failure before and after captopril treatment. *J. Hypertension*, **2** (suppl 3), 555–558.

- Richer, C., Doussau, M. & Giudicelli, J. (1987). Systemic and regional hemodynamic profile of five angiotensin I converting enzyme inhibitors in the spontaneously hypertensive rat. *Am. J. Cardiol.*, **59**, 12D–17D.
- Roberts, D. H., Tsao, Y., McLoughlin, G. A. & Breckenridge, A. (1987). Placebo-controlled comparison of captopril, atenolol, labetalol, and pindolol in hypertension complicated by intermittent claudication. *Lancet*, **ii**, 650–653.
- Strandgaard, S. (1978). Autoregulation of cerebral circulation in hypertension. *Acta Neurol. Scand.*, **57** (suppl 66), 1–82.
- Swales, J. D. & Thurston, H. (1973). Generation of angiotensin II at peripheral vascular level: studies using angiotensin II antisera. *Clin. Sci.*, **45**, 691–700.
- Takeyama, K., Minato, H., Nakatsuji, K., Suzuki, H., Nose, I., Oka, M., Hosoki, K., Hatano, N. & Kadokawa, T. (1986). Effect of the novel orally active angiotensin converting enzyme inhibitor alacepril on cardiovascular system in experimental animals. *Arzneimittelforschung*, **36**, 69–73.
- Vorstrup, S., Barry, D. I., Jarden, J. O., Svendsen, U. G., Braendstrup, O., Graham, D. I. & Strandgaard, S. (1984). Chronic antihypertensive treatment in the rat reverses hypertension-induced changes in cerebral blood flow autoregulation. *Stroke*, **15**, 312–318.
- Wahl, M., Young, A. R., Edvinson, L. & Wagner, F. (1983). Effects of kinase II inhibitors on the vasomotor response to bradykinin of feline intracranial and extracranial arteries *in vitro* and *in situ*. *J. Cereb. Blood Flow*, **3**, 339–345.
- Waldemar, G., Barry, D. I. & Paulson, O. B. (1989 b). The upper limit of cerebral blood flow autoregulation: Influence of the sympathetic nervous system and the renin angiotensin system. In *New trends in cerebrovascular diseases*. London: John Libbey & Co Ltd. (in press).
- Waldemar, G., Paulson, O. B. & Barry, D. I. (1988). Angiotensin converting enzyme inhibition and cerebral blood flow autoregulation: Influence of the sympathetic nervous system. *Acta Neurol. Scand.*, **77** (suppl 116), 116.
- Waldemar, G., Paulson, O. B., Barry, D. I. & Knudsen, G. M. (1989a). Angiotensin converting enzyme inhibition and the upper limit of cerebral blood flow autoregulation: Effect of sympathetic stimulation. *Circ. Res.* (in press).
- Waldemar, G., Pedersen, E. V. & Barry, D. I. (1987). Cerebral blood flow autoregulation during angiotensin converting enzyme inhibition. *J. Cereb. Blood Flow Metab.*, **7** (suppl 1), S283.
- Waldemar, G., Schmidt, J. F., Andersen, A. R., Vorstrup, S., Ibsen, H. & Paulson, O. B. (1989c). Angiotensin converting enzyme inhibition and cerebral blood flow autoregulation in normotensive and hypertensive man. *J. Hypertension*, (in press).
- Waldemar, G., Vorstrup, S., Andersen, A. R., Pedersen, H. & Paulson, O. B. (1989d). Angiotensin converting enzyme inhibition and regional cerebral blood flow in acute stroke. *J. cardiovasc. Pharmac.* (in press).
- Whalley, E. T. & Wahl, M. (1983). The effect of kininase II inhibitors on the response of feline cerebral arteries to bradykinin and angiotensin. *Pflügers Arch.*, **398**, 175–177.
- Whalley, E. T. & Wahl, M. (1988). Cerebrovascular reactivity to angiotensin and angiotensin-converting enzyme activity in cerebrospinal fluid. *Brain Res.* **438**, 1–7.

Discussion

Peter S. Sever (London): Clearly it would be premature to draw definitive conclusions about the comparative effects of these different types of vasodilators on so few patients. In designing the clinical studies it must be very difficult because you would have to ensure that the blood flow studies were done for the different vasodilators at doses that produced comparable falls in arterial pressure. Having said that have you got any information on other classes of vasodilators such as the alpha-blockers, calcium channel blockers, potassium channel activators and so on, which might discriminate the ACE inhibitors from the others?

Olaf B. Paulson (Copenhagen): I wouldn't call captopril or the other ACE inhibitors true vasodilators. The probable mechanism of ACE

inhibitors in CBF autoregulation is a dilatation of the large resistance vessels. Only the limits of autoregulation are shifted so normal blood flow is maintained. This is different from the true vasodilators which dilate all vessels in the brain—both the smaller and the larger resistance vessels. Diamox acetazolamide is a commonly used vasodilator. In stroke patients Diamox frequently provokes an aggravation of the ischaemic area. Although calcium-channel blockers induce vasodilation in some patients, in others very little vasodilation is seen in the brain but aggravation of the ischaemia still occurs. In a larger series of patients we have shown this effect of the calcium-channel blocker to be dose-dependent. The decrease in blood flow seen following calcium-channel blockade could not be related to a drop in blood pressure.