Original Article

Hemodynamic Influences of Losartan on the Brain in Hypertensive Patients

Naohiko OKU, Kazuo KITAGAWA*, Masao IMAIZUMI*, Masashi TAKASAWA*,
Risyu PIAO*, Yasuyuki KIMURA, Katsufumi KAJIMOTO*,
Masayasu MATSUMOTO**, Masatsugu HORI*, and Jun HATAZAWA

The effects of angiotensin II receptor blockers on cerebral hemodynamics in humans have not been well elucidated. The present study evaluated the effects of losartan on cerebral hemodynamics in hypertensive patients using positron emission tomography. Ten patients with essential hypertension (mean age, 60.8 years) were examined. In each patient, regional cerebral blood flow was measured by [O-15] labeled water positron emission tomography before and after the oral administration of losartan for 8 to 23 weeks. In 8 patients, the baseline regional cerebral blood flow measurement was followed by 1,000 mg of acetazolamide challenge to measure the cerebral perfusion reserve. Systemic blood pressures before and after treatment were $153.8 \pm 10.8 / 96.0 \pm 6.5$ mmHg (systolic mean $\pm$ SD / diastolic mean $\pm$ SD) and $133.4 \pm 11.2 / 83.6 \pm 6.5$ mmHg, respectively; this difference was significant. The baseline global cerebral blood flow values before and after treatment were 38.4 ± 6.9 ml/min/100 g and 38.2 ± 8.2 ml/min/100 g, respectively; this difference was not significant. The results of the global cerebral blood flow response to the acetazolamide challenges were not statistically different before and after treatment. A regional analysis showed no statistical difference in regional cerebral blood flow or cerebral perfusion reserve throughout the brain before and after treatment. Losartan's effect on reducing the blood pressure did not affect either the baseline regional cerebral blood flow or the cerebral perfusion reserve in patients with mild to moderate hypertension. The inclusion of losartan in anti-hypertensive regimens could be advantageous for cerebral circulation in patients with essential hypertension. (*Hypertens Res* 2005; 28: 43–49)

Key Words: cerebral blood flow, hypertension, losartan, positron emission tomography, cerebrovascular reactivity

Introduction

Angiotensin II receptor blockers are the latest generation of anti-hypertensive drugs. Losartan, an angiotensin II receptor blocker, has been reported to have protective effects against hypertensive organ damage as well as on systemic blood pressure. The LIFE study (1) was a prospective, double-blinded and randomized clinical trial in which losartan was shown to

be more effective at preventing cardiovascular morbidity and death than atenolol. In the LIFE study, interest was focused on the preventive effects of losartan on primary fatal or non-fatal strokes. Losartan appeared to have beneficial effects on cerebral vessels beyond a reduction in blood pressure.

The effect of angiotensin II receptor blockers on cerebral hemodynamics is still controversial. Previous studies have suggested that angiotensin II receptor blockers do not influence cerebral blood flow under baseline conditions.

From the Department of Nuclear Medicine and Tracer Kinetics, and *Department of Internal Medicine and Therapeutics, Osaka University Graduate School of Medicine, Osaka, Japan; and **Department of Clinical Neuroscience and Therapeutics, Hiroshima University Graduate School of Biomedical Sciences, Hiroshima, Japan.

Address for Reprints: Naohiko Oku, M.D., Department of Nuclear Medicine and Tracer Kinetics, Osaka University Graduate School of Medicine, Yamadaoka 2-2, Suita 565-0871, Japan. E-mail: oku@medone.med.osaka-u.ac.jp

Received June 16, 2004; Accepted in revised form September 29, 2004.

Table 1. Characteristics of the Subjects

Patient No.	Age (years old)	Gender	Losartan dose (mg/day)	Duration (weeks)	Brain MRI	Coexisting disease
1	61	M	50	23	asym WMI	hyperchol
2*	60	F	100	20	ns	ns
3	60	M	50	19	ns	ns
4*	64	M	50	9	lacunar inf	ns
5	62	F	100	22	asym WMI	hyperchol
6	52	M	50	12	ns	ns
7	59	M	50	12	asym WMI	ns
8	62	M	100	11	asym WMI	ns
9	65	M	100	8	ns	ns
10	63	F	100	18	ns	hyperchol

M, male; F, female; MRI, magnetic resonance imaging; asym WMI, asymptomatic white matter ischemic lesion; lacunar inf, lacunar infarction; hyperchol, hypercholesterolemia; ns, not specific. *Patient refused to undergo acetazolamide challenge. Duration means the therapy period from the start of losartan administration to the second cerebral blood flow measurement.

Vraamark *et al.* (2) reported that candesartan shifted the autoregulation curve towards the left in hypertensive rats. Strömberg *et al.* (3) reported that losartan shifted the upper limit of the autoregulation curve towards the right in rats with experimental hypertension induced by angiotensin II. Finally, in an experiment by Näveri *et al.* (4), losartan increased cerebrovascular resistance in rats with acute hypotension induced by hemorrhage.

However, these previous results were based on animal models and some observed acute effects of angiotensin II receptor blockers on cerebral blood flow. Few reports have evaluated the chronic effects of losartan on cerebral hemodynamics in hypertensive patients. The purpose of this paper was to elucidate the hemodynamic status before and after losartan administration using positron emission tomography and an acetazolamide challenge.

Methods

Subjects

Subjects were selected from patients with essential hypertension, defined according to the criteria of the VIth Joint National Committee (5). We excluded patients who met any of the following conditions: age under 40 years; severe hypertension (systolic blood pressure >200 mmHg or diastolic blood pressure >120 mmHg) or uncontrolled diabetes (HbA1c >8%); a history of stroke within the previous 3 months; angina pectoris or myocardial infarction; heart failure; renal failure (serum creatinine >2 mg/dl); severe stenosis (>50%) of the carotid artery and/or middle cerebral artery (assessed by ultrasonography and magnetic resonance angiography); currently taking anti-hypertensive drugs; atherosclerosis obliterans; any type of dementia; or currently taking tranquilizers, histamine blockers, analgesics, or diuretics.

Eighteen patients were nominated for the study. Of these 18 patients, 10 patients agreed to participate in the study and provided their written informed consent after receiving a detailed explanation of the study, including the irradiation dosage used in the positron emission tomography procedure. The profiles of these patients are shown in Table 1. The mean age of the patients was 60.8 ± 3.4 (mean $\pm$ SD) years. Of the 10 patients, one had a non-disabling pure motor hemiparesis due to lacunar infarction and four had mild asymptomatic white matter ischemic lesions (Fazekas (6) grade 1, minimal patchy white matter foci), as revealed by brain magnetic resonance imaging. Three patients had hypercholesterolemia, and none had diabetes. All portions of the study were performed in agreement with the ethical guidelines of the hospital.

Drug Control

On enrollment in the study, the clinical history of the patients was thoroughly checked. The administration of drugs that might influence the baseline cerebral blood flow was prohibited during the study period. Prescriptions for chronic diseases such as hypercholesterolemia were continued unchanged throughout the study period. Patients underwent an initial cerebral blood flow measurement using positron emission tomography with [O-15] labeled water. Subsequently, the patients received a daily oral dose of losartan (NU-LOTAN™; Banyu Pharmaceutical Co., Ltd., Tokyo, Japan) titrated to 50 mg. Follow-up examinations were performed every 2 to 4 weeks, and the drug dosage was increased up to 100 mg a day unless the patient reached a target sitting blood pressure of less than 140/90 mmHg. When the sitting blood pressure reached the target range and stabilized with losartan administration, the patient underwent a second cerebral blood flow measurement.

Table 2. Systemic Blood Pressure, Pulse Rate, and Arterial Gas Tension during Cerebral Blood Flow Measurement

	Before losartan			After losartan		
	Baseline (n=10)	ACZ ₁₀ (n=8)	ACZ ₂₀ (n=8)	Baseline (n=10)	ACZ ₁₀ (n=8)	ACZ ₂₀ (n=8)
SBP (mmHg)	153.8±10.8	159.2±15.5	159.5±16.6	133.4±11.2*	138.0±15.8*	138.8±17.5*
DBP (mmHg)	96.0±6.5	95.9±6.3	97.6±7.2	83.6±6.5*	82.8±7.7*	84.5±6.5*
Pulse (bpm)	64.4±7.9	64.3±6.7	64.9±5.0	61.0±7.0	61.3±7.2	63.4±7.2
pH	7.409±0.021	7.426±0.023	7.423±0.033	7.406±0.014	7.416±0.010	7.412±0.019
PaCO ₂ (mmHg)	38.7±2.8	37.2±2.9	36.7±4.3	39.5±2.1	37.9±2.2	37.6±1.8
PaO ₂ (mmHg)	81.6±8.7	87.9±13.8	91.0±15.6	80.5±6.6	85.8±9.5	87.3±9.9

SBP and DBP, systolic and diastolic blood pressure, respectively; PaCO₂ and PaO₂, arterial gas tension for carbon dioxide and oxygen, respectively; ACZ₁₀ and ACZ₂₀, 10 and 20 min after acetazolamide injection, respectively; bpm, beats per minute. Data are listed in mean±SD. **p*<0.01 vs. baseline in before losartan.

Cerebral Blood Flow Measurement

All patients underwent two cerebral blood flow measurements. As described above, the first and second measurements were performed before and after the administration of losartan, respectively. We used a high-performance positron emission tomography scanner (SET-2400W; Shimadzu Co., Kyoto, Japan) that uses 63 slices (slice thickness of 3.1 mm) and a spatial resolution of 3.7 mm full width at half maximum. Regional cerebral blood flow was quantitatively measured using positron emission tomography, an [O-15] labeled water injection, and an autoradiographic method (7). During each session, the patient was asked to lie on the scanner bed in a supine position in a quiet, dimly lit room. One session consisted of four scans. First, two consecutive scans were performed for the baseline condition. Then, after the intravenous administration of acetazolamide titrated to 1,000 mg, two additional scans were performed at an interval of 10 min. At the end of every scan, the patient's blood pressure, pulse rate, and arterial blood gas tension were measured. The data obtained for the baseline condition were averaged using the two measurements.

Blood Pressure Measurements

Blood pressure was measured using a mercury sphygmomanometer and a 6-inch cuff, with the patient lying supine on the scanner bed. Systolic and diastolic blood pressure (Korotkoff phase I and phase V, respectively) were averaged using two readings obtained 3 min apart.

Cerebral Blood Flow Image Analysis

The regional cerebral blood flow image data set obtained by the positron emission tomography scanner was transformed stereotactically into an identical normal brain template using statistical parametric mapping-99 software (8) (SPM99; Wellcome Department of Cognitive Neurology, University College London, London, UK) running in a MATLAB™

(The MathWorks Inc., Natic, USA) environment. Identical regions of interest (the whole cerebrum, whole cerebellum, bilateral upper and lower frontal lobes, bilateral temporal lobes, bilateral occipital lobes, bilateral parietal lobes, bilateral basal ganglia areas, and bilateral thalami) were drawn on standardized cerebral blood flow images. Except for the whole cerebrum and whole cerebellum, the regions of interest were drawn on the gray matter of each region and consisted of multiple small circular regions of interest (20 mm in diameter) linked together.

Statistical Analysis

Blood pressure, pulse rate, arterial blood gas tensions, and baseline cerebral blood flow measurements obtained before and after treatment were compared using paired *t*-tests. The effects of acetazolamide on systemic conditions and an increased cerebral blood flow were analyzed using a one-way repeated-measure analysis of variance (ANOVA) followed by Bonferroni's multiple comparison. These analyses were performed using statistical analysis software (SPSS 11.5J; SPSS Japan Inc., Tokyo, Japan) on a personal computer running Windows™. Differences were considered to be significant when the statistical *p* value was less than 0.05.

Results

Losartan was well tolerated by all the patients and no complications or adverse effects occurred. The period of losartan therapy ranged from 8 to 23 weeks, and the final losartan dosages required to control the patients' blood pressures were 50 mg/day in 5 patients and 100 mg/day in 5 (Table 1). Of the 10 patients in the study, 8 patients safely underwent two acetazolamide challenges; the examination was well tolerated in these patients. Two patients (Nos. 2 and 4 in Table 1) refused to undergo the acetazolamide challenge. Thus, the physiological parameters and baseline regional cerebral blood flow were assessed in 10 patients, while the changes in these parameters after an acetazolamide challenge were assessed in

Table 3. Changes of Individual Cerebral Blood Flow, Response to Acetazolamide, and Systemic Parameters before and after Losartan Administration

PtNo	Baseline gCBF (ml/min/100 g)		INC%max (%)		Mean BP (mmHg)		PCO ₂ (mmHg)	
	Before	After	Before	After	Before	After	Before	After
1	31.7	32.3	29	42	114.3	111.7	41.2	41.4
2	39.0	41.1			111.1	98.2	37.8	36.2
3	34.7	35.4	42	39	116.5	94.2	37.1	38.5
4	48.0	50.3			130.7	105.3	35.0	42.0
5	48.6	39.9	65	58	113.5	109.8	44.6	40.5
6	31.6	38.8	29	41	112.8	104.3	38.8	37.4
7	28.1	28.2	23	28	109.7	87.5	39.0	38.4
8	40.4	29.6	34	50	110.3	93.2	37.7	40.3
9	40.4	33.7	68	47	107.2	94.3	39.8	38.1
10	41.1	52.6	49	39	126.3	103.5	35.9	42.6

gCBF, global cerebral blood flow; INC%max, maximum percent increase of gCBF from baseline after acetazolamide injection; BP, systemic blood pressure; PCO₂, arterial partial pressure of carbon dioxide; PtNo, patient number.

8 patients.

Table 2 shows the physiological data for the patients. The baseline systemic blood pressures before and after losartan administration were $153.8 \pm 10.8/96.0 \pm 6.5$ (systolic mean $\pm$ SD/diastolic mean $\pm$ SD) mmHg and $133.4 \pm 11.2/83.6 \pm 6.5$ mmHg, respectively. Both the systolic and diastolic blood pressures decreased significantly after losartan administration. Arterial blood gas tensions, arterial pH, and the pulse rate measured before and after losartan administration did not change significantly. Although a slight elevation in blood pressure was observed during the acetazolamide challenges, both before and after losartan administration, the effect of the acetazolamide challenge on the baseline blood pressure values was not significant.

None of the regional cerebral blood flow images obtained during the positron emission tomography examinations showed major abnormalities, and all of the images were successfully transformed into standardized normal brain images using the SPM99 software.

As the peak response time (*i.e.*, 10 or 20 min after acetazolamide injection) to acetazolamide differed by patient, we selected individual maximum cerebral blood flow value for the analysis. Table 3 shows the individual changes in global cerebral blood flow, the maximum percent increase in cerebral blood flow (INC%max) induced by acetazolamide, mean systemic blood pressure, and arterial partial pressure of carbon dioxide. In 3 patients (Nos. 5, 8, and 9), there was a considerable decrease in global cerebral blood flow after losartan administration. In contrast, the other 2 patients (Nos. 6 and 10), showed considerable increases in global cerebral blood flow after losartan administration. Table 4 shows the mean global and regional baseline cerebral blood flow values and the INC%max for the two conditions. The mean baseline global cerebral blood flow values obtained before and after losartan administration were 38.4 ± 6.9 ml/min/100 g and 38.2 ± 8.2 ml/min/100 g, respectively; these values were not

significantly different. The mean global INC%max before and after losartan administration were $42.4 \pm 17.0\%$ and $43.0 \pm 8.9\%$, respectively. No significant differences among the mean global INC%max values were observed. The same relationships were seen for every brain region examined, *i.e.*, there were no significant differences in the baseline cerebral blood flow and INC%max values obtained before and after losartan administration.

Discussion

In the present study, losartan was shown to reduce blood pressure without deteriorating baseline cerebral blood flow or the cerebral blood flow response to acetazolamide in patients with essential hypertension. No regional differences in this effect were observed in the brain. Only a few previous studies have evaluated the effect of losartan on the brain in hypertensive patients. Matulla *et al.* (9) indirectly suggested that losartan did not change the resting global cerebral blood flow in normal individuals, based on ultrasonography findings. This previous study measured blood flow velocities in the middle cerebral artery, not the cerebral blood flow, and only evaluated the acute effects of losartan. The present clinical study evaluated the chronic effects of losartan on regional cerebral blood flow. In this study, three patients (Nos. 5, 8, and 9) out of 10 showed considerable decrease in baseline cerebral blood flow after losartan administration. In one patient (No. 5), the decrease might be explained by the change in arterial carbon dioxide gas tension. In the rest 2, although it was possible that losartan affected the baseline cerebral blood flow, it was also possible that the drift in cerebral blood flow measurement by positron emission tomography partially influenced the result. The reproducibility of the method has been reported to have a SD of almost 10% (10).

Positron emission tomography, [O-15] labeled water, and SPM99 software were used in this study. These methods offer

Table 4. Regional Cerebral Blood Flow at Baseline and Cerebral Perfusion Reserve

Region	Before losartan		After losartan	
	Baseline CBF	INC%max	Baseline CBF	INC%max
	(ml/min/100 g) (n=10)	(%) (n=8)	(ml/min/100 g) (n=10)	(%) (n=8)
Cerebrum global	38.4±6.9	42.4±17.0	38.2±8.2	43.0±8.9
Cerebellum global	44.0±8.7	45.9±11.4	42.8±8.7	51.0±16.6
Frontal Base Rt	41.9±8.9	44.3±17.6	40.9±8.1	45.4±7.8
Top Rt	43.5±9.2	42.3±11.3	41.2±8.4	43.0±7.3
Base Lt	42.0±8.4	47.5±20.8	41.7±8.8	49.9±13.4
Top Lt	43.2±9.2	46.0±16.0	41.7±9.1	46.5±10.8
Temporal Rt	39.0±6.1	43.1±19.0	39.4±7.2	47.1±9.3
Lt	39.1±6.8	42.3±19.7	39.2±9.2	52.1±14.0
Parietal Rt	42.2±8.5	39.0±13.7	41.0±8.2	45.3±7.0
Lt	42.5±7.2	39.9±16.4	41.6±8.7	45.9±8.4
Occipital Rt	41.4±5.5	39.8±23.5	42.9±9.1	38.8±10.9
Lt	43.0±5.6	35.0±19.7	44.3±11.0	41.5±10.6
Basal ganglia Rt	50.8±9.9	51.4±18.6	50.8±11.5	52.9±11.7
Lt	49.4±9.9	53.5±26.1	49.7±13.1	62.3±19.4
Thalamus Rt	54.4±14.0	50.8±18.1	50.4±13.0	53.8±17.1
Lt	52.9±9.6	56.3±20.9	51.5±15.2	58.1±15.9

INC%max, maximum percent increase of regional cerebral blood flow from baseline after acetazolamide injection; Rt, right; Lt, left.

some advantages for this type of study. Regional cerebral blood flow measurement using positron emission tomography and [O-15] labeled water is a reliable and quantitative method. A single measurement requires only 2 min to perform, and measurements can be repeated every 10 min because the half-life of [O-15] is as short as 2 min. This characteristic enabled us to measure both the baseline cerebral blood flow and the cerebral blood flow after an acetazolamide challenge within about 1 h. To quantify the regional cerebral blood flow, we used a region of interest-based analysis. This type of analysis using native cerebral blood flow images is limited by positional changes of the head from session-to-session and by inter-subject differences in the shape of the brain. SPM99 have been developed as an analysis tool for detecting areas with statistically significant signal changes among images obtained under different scanning conditions and for different individuals. Using the SPM99 module enabled us to correct for inter-scan head motion and to minimize inter-individual structural differences in the head. Using these techniques, corresponding regions of interest were obtained in all of the patients.

Theoretically, organ blood flow is determined by blood pressure and vascular resistance. Our data indicated that losartan reduced the cerebral vascular resistance whereas the blood pressure reduced. Unlike in the present study, Näveri *et al.* (4) reported that the administration of losartan in a hemorrhagic hypotensive animal model increased cerebrovascular resistance. These conflicting results may be explained by the fact that Näveri *et al.* examined the acute effects of losartan in an experimental animal model, whereas our data were focused

on the chronic effects of losartan in humans in a clinical environment.

Under physiological conditions, global cerebral blood flow is controlled by autoregulation, irrespective of changes in systemic blood pressure. The vascular responses of large arteries and the resistance of small cerebral vessels play pivotal roles in this mechanism. Furthermore, the renin-angiotensin system is known to have a large effect on the regulation of vascular tonus (2–4, 11). It is thus of concern that losartan administration may have shifted the cerebral autoregulation curve to the left or right. However, elucidating the upper and lower limits of the cerebral autoregulation curve is difficult in real patients. In the present study, patients were categorized as having mild or moderate hypertension, and thus the average right shift of the autoregulation curve was likely to be small. It remains unclear whether or not losartan affects the cerebral hemodynamics in patients with severely impaired autoregulation.

Instead of elucidating the autoregulation range, we applied an acetazolamide challenge to test cerebral vasomotor reactivity. The intravenous administration of acetazolamide titrated to 1,000 mg causes a dramatic dilatation in the cerebral resistant vessels as a result of extracellular acidosis (12), which in turn causes the regional cerebral blood flow to increase to its maximum possible value. This effect has been used to evaluate cerebral vasomotor reactivity and the cerebral perfusion reserve (13). The cerebral perfusion reserve is considered a safety margin against a drift in cerebral perfusion pressure. This idea has been supported by several previous studies (14–16) which concluded that compromised

cerebral perfusion reserve was associated with an increased risk of cerebral ischemic events. Our data suggested that losartan did not affect the cerebral perfusion reserve. This property is thought to be beneficial to patients with cerebral ischemic lesions, such as those seen in the present study.

Stroke prevention is a major goal in the treatment of hypertension. Inada *et al.* (17) reported that candesartan treatment reduced the incidence of stroke in stroke-prone spontaneously hypertensive rats. In the LIFE (1) losartan was more effective at preventing fatal and non-fatal stroke events than atenolol (adjusted risk reduction, 24.9%) and resulted in fewer adverse events. The results raise the question of whether angiotensin II receptor blockers are superior to angiotensin-converting enzyme inhibitors. In patients with symptomatic heart failure (18) or acute myocardial infarction (19), losartan was equally beneficial but not superior to captopril. Which of these drugs is superior for stroke management remains uncertain, but both drugs owe their protective effects to the inhibition of the renin-angiotensin system. Many experimental studies have proved that the inhibition of the renin-angiotensin system modulates vascular tone (2–4, 10), prevents (20) or improves (21, 22) vascular wall remodeling or improves endothelial functions (23, 24). In a human study, candesartan reduced oxidative stress and inflammation (25), which were related to organ damage. Angiotensin II receptor blockers as well as angiotensin converting enzyme inhibitors seem to be promising for the prevention of stroke.

In conclusion, losartan has been accepted as an effective anti-hypertensive drug with good tolerability. Our results showed that losartan effectively lowered the blood pressure without affecting the baseline cerebral blood flow or cerebral perfusion reserve in patients with mild to moderate hypertension. This characteristic protects the brain from unexpected episodes of hypotension during treatment with losartan. The effect of this drug on the brain in patients with stroke or in those with severe hypertension awaits further study.

Acknowledgements

We are grateful to the cyclotron staffs of Osaka University Hospital for their technical support. We would also like to thank Ms. M. Ikuzawa, Ms. A. Kanzawa, Ms. K. Tsunoda, and Ms. M. Sudo for their secretarial assistance.

References

- Dahlöf B, Devereux RB, Kjeldsen SE, *et al*: LIFE Study Group: Cardiovascular morbidity and mortality in the losartan intervention for endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 2002; **359**: 995–1003.
- Vraamark T, Waldemar G, Strandgaard S, Paulson OB: Angiotensin II receptor antagonist CV-11974 and cerebral blood flow autoregulation. *J Hypertens* 1995; **13**: 755–761.
- Strömberg C, Näveri L, Saavedra JM: Nonpeptide angiotensin AT1 and AT2 receptor ligands modulate the upper limit of cerebral blood flow autoregulation in rats. *J Cereb Blood Flow Metab* 1993; **13**: 298–303.
- Näveri L, Strömberg C, Saavedra JM: Angiotensin II AT2 receptor stimulation increases cerebrovascular resistance during hemorrhagic hypotension in rats. *Regul Pep* 1994; **52**: 21–29.
- VIIth Joint National Committee: The sixth report of the Joint National Committee on prevention, detection, evaluation and treatment of high blood pressure. *Arch Intern Med* 1997; **157**: 2413–2447.
- Fazekas F, Chawluk JB, Alavi A, Hurtig HI, Zimmerman RA: MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. *Am J Roentgenol* 1987; **149**: 351–356.
- Kanno I, Iida H, Miura S, *et al*: A system for cerebral blood flow measurement using an H215O autoradiographic method and positron emission tomography. *J Cereb Blood Flow Metab* 1987; **2**: 143–153.
- Friston KJ, Frith CD, Liddle PF, Frackowiak RS: Comparing functional (PET) images: the assessment of significant change. *J Cereb Blood Flow Metab* 1991; **4**: 690–699.
- Matulla B, Streit G, Pieh S, *et al*: Effects of losartan on cerebral and ocular circulation in healthy subjects. *Br J Clin Pharmacol* 1997; **44**: 369–375.
- Weber B, Spath N, Wyss M, *et al*: Quantitative cerebral blood flow measurements in the rat using a beta-probe and H215O. *J Cereb Blood Flow Metab* 2003; **23**: 1455–1460.
- Saavedra JM, Nishimura Y: Angiotensin and cerebral blood flow. *Cell Mol Neurobiol* 1999; **15**: 553–573.
- Brickler PE, Litt L, Banville DL, Severinghaus JW: Effects of acetazolamide on cerebral acid-base balance. *J Appl Physiol* 1988; **65**: 422–427.
- Imaizumi M, Kitagawa K, Hashikawa K, *et al*: Detection of misery perfusion with split-dose 123I-iodoamphetamine single-photon emission computed tomography in patients with carotid occlusive diseases. *Stroke* 2002; **33**: 2217–2223.
- Silvestrini M, Vernieri F, Pasqualetti P, *et al*: Impaired cerebral vasoreactivity and risk of stroke in patients with asymptomatic carotid artery stenosis. *JAMA* 2000; **283**: 2122–2127.
- Kim JS, Moon DH, Kim GE, *et al*: Acetazolamide stress brain-perfusion SPECT predicts the need for carotid shunting during carotid endarterectomy. *J Nucl Med* 2000; **41**: 1836–1841.
- Ogasawara K, Ogawa A, Yoshimoto T: Cerebrovascular reactivity to acetazolamide and outcome in patients with symptomatic internal carotid or middle cerebral artery occlusion: a xenon-133 single-photon emission computed tomography study. *Stroke* 2002; **33**: 1857–1862.
- Inada Y, Wada T, Ojima M, *et al*: Protective effects of candesartan cilexetil (TCV-116) against stroke, kidney dysfunction and cardiac hypertrophy in stroke prone spontaneously hypertensive rats. *Clin Exp Hypertens* 1997; **19**: 1079–1099.
- Pitt B, Poole-Wilson PA, Segal R, *et al*: Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial—the losartan heart failure survival study ELITE II. *Lancet* 2000; **355**: 1582–1587.
- Dickstein K, Kjekshus J, and OPTIMAAL Steering Committee: Effects of losartan and captopril on mortality and mor-

- bility in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial. *Lancet* 2002; **360**: 752–60.
20. Hajdu MA, Heistad DD, Baumbach GL: Effects of antihypertensive therapy on mechanism of cerebral arteriols in rats. *Hypertension* 1991; **17**: 308–316.
 21. Chillon JM, Baumbach GL: Effects of an angiotensin-converting enzyme inhibitor and a beta-blocker on cerebral arteriolar dilatation in hypertensive rats. *Hypertension* 2001; **37**: 1388–1393.
 22. Ito T, Yamakawa H, Bregonzio C, Terrón JA, Falcón-Neri A, Saavedra JM: Protection against ischemia and improvement of cerebral blood flow in genetically hypertensive rats by chronic pretreatment with an angiotensin II AT₁ antagonist. *Stroke* 2002; **33**: 2297–2303.
 23. Yang ST, Faraci FM, Heistad DD: Effects of cilazapril on cerebral vasodilatation in hypertensive rats. *Hypertension* 1993; **22**: 150–155.
 24. Clozel M, Kuhn H, Hefti F: Effects of angiotensin-converting enzyme inhibitors and hydralazine on endothelial function in hypertensive rats. *Hypertension* 1990; **16**: 532–540.
 25. Dohi Y, Ohashi M, Sugiyama M, Takase H, Sato K, Ueda R: Candesartan reduces oxidative stress and inflammation in patients with essential hypertension. *Hypertens Res* 2003; **26**: 699–704.