Diabetic Brain Damage in Hypertension
Role of Renin-Angiotensin System

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Abstract—Diabetes and hypertension are potent risk factors for cerebrovascular disease. We studied the effects of an angiotensin II type 1 receptor blockade (ARB) on brain damage in hypertensives in relation to diabetes. We studied cerebral metabolism (by proton magnetic resonance spectroscopy) and hemodynamics (by phase-contrast magnetic resonance angiography) before and 3 to 4 months after candesartan therapy in 20 diabetic hypertensives (DHTs) and 20 matched nondiabetic hypertensives (HTs). Silent multiple cerebral infarcts detected by brain MRI were more common in DHTs than in HTs (50% versus 25%). Cerebral N-acetyl aspartate (NAA; an indicator of functional neuronal mass) was lower in DHTs than in HTs (8.35 versus 9.58 mmol/kg; \(P=0.007\)). Baseline quantitative volume flow in the internal carotid arteries (ICAs) and the middle cerebral arteries (MCAs) was comparable between the 2 groups, whereas cerebrovascular reserve (CVR) assessed using acetazolamide (a cerebral arteriolar dilator) in ICAs (25% versus 35%; \(P=0.03\)) and MCAs (20% versus 31%; \(P=0.01\)) was lower in DHTs than in HTs. These baseline CVR and NAA values of DHT group were lower than those of 12 matched normotensives (CVR: 44% for ICA; 41% for MCA; NAA: 10.5 mmol/kg; all \(P<0.005\)). After candesartan therapy, CVR in ICAs and MCAs was significantly increased (\(P=0.001\)) independently of the reduction of the 24-hour blood pressure level, whereas the cerebral NAA level did not change. In conclusion, brain damage is advanced in DHTs. ARB partly improved the impaired cerebral microvascular function in DHTs. (Hypertension. 2005;45:887-893.)

Key Words: metabolism ■ circulation ■ receptors, angiotensin ■ blood pressure

Diabetes is an independent major risk factor for cardiovascular events.\(^1\)\(^2\) In addition, cardiovascular mortality associated with mild systolic hypertension (140 to 159 mm Hg) compared with normal systolic blood pressure (BP; <140 mm Hg) is highly dependent on the glycemic status.\(^3\) Diabetes has been shown to be a strong independent risk factor for stroke and is associated with an \(\approx 1.8\)- to 6-fold increase of the risk of stroke.\(^1\) Diabetes is also associated with either an accelerated cognitive decline or an increased incidence of dementia.\(^4\) In our study on asymptomatic hypertensives, those having diabetes were found to be more likely to have advanced silent cerebral infarct (SCI) than those without diabetes.\(^5\) This silent cerebrovascular disease is a specific predictor not only for future stroke events but also for dementia.\(^6\)\(^7\)

Recent biochemical, physiological, and functional studies have suggested that the brain renin-angiotensin system (RAS) is regulated independently of the peripheral RAS.\(^8\) Angiotensin II type 1 (AT1) and type 2 (AT2) receptors have been identified in the brain. Selective nonpeptide AT1 receptor blockers (ARBs), applied systemically, have been shown to inhibit peripheral and brain AT1 receptors. Inhibition of brain AT1 receptors may contribute to the BP-lowering effects of ARBs. In animal models, blockade of brain and cerebrovascular AT1 receptors by ARBs prevents the reduction in blood flow during brain ischemia, reduces the volume of ischemic injury, and improves neurological outcome after brain ischemia.\(^9\)\(^10\) In addition, animal studies have shown that ARBs enable endogenous angiotensin II to stimulate neuronal regeneration via activation of AT2 receptors.\(^11\) Although the relationship between the tissue RAS and diabetic macrovascular and microvascular disease is well established,\(^12\) the effects of ARBs on cerebral metabolism and hemodynamics have not been fully investigated.

Recently developed magnetic resonance spectroscopy (MRS) methods can detect cerebral metabolites noninvasively.\(^13\)\(^14\) \(N\)-acetyl aspartate (NAA) is located only in neurons and their axons. Thus, cerebral NAA is considered to be an indicator of the functional neuronal mass and axons, and reduced NAA has been reported in patients with several cerebral diseases, such as atherosclerotic cerebral disease.\(^13\) Phase-contrast magnetic resonance angiography (PC-MRA) can noninvasively assess cerebral hemodynamics\(^16\)\(^17\) and cerebrovascular reserve (CVR) when combined with acetazolamide, a cerebral vasodilator.\(^18\)\(^19\)
In this study, we evaluated cerebral metabolism and hemodynamics in asymptomatic hypertensives with and without diabetes using MRS and PC-MRA, respectively, and examined the effects of the ARB candesartan on these cerebral parameters.

**Methods**

**Subjects**

The study subjects were 20 outpatients who were newly diagnosed hypertensive patients (clinic systolic BP [SBP] ≥140 mm Hg; or diastolic BP [DBP] ≥90 mm Hg) with type 2 diabetes (diabetic hypertensive [DHT] group) and 20 age- and sex-matched mild hypertensives without diabetes (nondiabetic hypertensive [HT] group). We also consecutively recruited 12 age- and sex-matched normotensive (NT) controls with clinic SBP <140 mm Hg and DBP <90 mm Hg, and with 24-hour SBP <120 mm Hg and 24-hour DBP <90 mm Hg (NT group). These subjects were recruited from the participants who underwent a health check examination. The period of the recruitment of this study was from October 2001 to January 2003.

Clinic BP was measured after patients had rested for at least 5 minutes in a sitting position, and the average of 3 consecutive measurements on 2 different days was used as clinic BP. Diabetes was newly diagnosed according to fasting glucose >7.73 mmol/L (139 mg/dL) or a 2-hour postload serum glucose >11.1 mmol/L (199 mg/dL) in all other cohorts, in accordance with the 1985 World Health Organization (WHO) criteria for diabetes. Fasting glucose of all the nondiabetic subjects (HT and NT groups) was <6.11 mmol/L (110 mg/dL), and the 2-hour postload glucose was <7.77 mmol/L (140 mg/dL). Exclusion criteria of all the DHT, HT, and NT groups included renal failure (serum creatinine level >7.77 mmol/L [140 mg/dL]), hepatic damage, obvious present illness, a past history of coronary artery disease, stroke (including transient ischemic attacks), or arrhythmia (including atrial fibrillation). Hypertension was defined as a total cholesterol level >6.21 mmol/L (240 mg/dL) or the use of an oral lipid-lowering agent. Smokers were defined as current smokers. Body mass index (BMI) was calculated as weight (in kilograms)/height (in meters).

**Study Protocol**

We studied the 24-hour ambulatory BP monitoring (ABPM), cerebral hemodynamics (by PC-MRA), and metabolism (by proton MRS) at the baseline in the DHT, HT, and NT groups. We also repeated the same procedure 3 to 4 months after candesartan therapy in the DHT and HT groups. Patients were started on 8 mg candesartan daily, taken in the morning. The dose was increased to 12 mg daily (the maximum dose permitted for use in Japan) after 2 weeks, regardless of the degree of BP reduction. This study was approved by the research ethics committee of the Department of Cardiology, Jichi Medical School, Japan, and all subjects studied gave informed consent.

**Twenty-Four-Hour ABPM**

Noninvasive ABPM was performed on a weekday with an automatic device (TM-2425; A&D Co., Inc.) that recorded BP and pulse rate every 30 minutes for 24 hours. The ambulatory BP data used in the present study were those obtained by the oscillometric method.

**Brain MRI**

Brain MRI was performed using a superconducting magnet with a main strength of 1.5T (SIGNA-Horizon version 5.8; General Electric). T1- and T2-weighted images were obtained in the transverse plane with 7.8-mm-thick sections. An SCI was defined as a low signal intensity area (3 to 15 mm) on T1-weighted images that was also visible as a hyperintense lesion on T2-weighted images, as described previously. SCI as defined above might include lesions other than true infarcts, such as unidentified bright objects and état criblé, dilated perivascular spaces, especially if they are <5 mm. The number of SCIs per patient was counted, and multiple SCIs were defined as ≥2 infarcts. All SCIs detected were lacunar infarcts with a size of <15 mm. The MRI images of the subjects were stored randomly and interpreted blind to the subjects’ names and characteristics. The k-statistics assessing inter-reader and intrareader agreement (non-SCI, 1 SCI, and multiple SCIs) were 0.70 and 0.80, respectively, in our laboratory.

Periventricular hyperintensities on T2-weighted images were classified into 4 grades, as described and illustrated previously. Briefly, grade I was defined as no abnormality or minimal periventricular signal hyperintensities in the form of caps confined exclusively to the anterior horns or rims lining the ventricle; grade II as caps in the anterior and posterior horns of the lateral ventricles or periventricular unifocal patches; grade III as multiple periventricular hyperintense punctate lesions and their early confluent stages; and grade IV as multiple areas of high signal intensity that reached confluence in the periventricular region. All of the magnetic resonance images were interpreted under blind conditions by 2 of the authors. Because only 2 patients showed grade IV, these patients and those with grade III were considered together as showing advanced white matter lesions.

**Proton MRS**

Proton MRS was performed in the left deep white matter area using a GE 1.5T Sigma system using a standard quadrature bird-cage head coil. A single voxel was located in the same area (defined by the horizontal and coronal sections of T2-weighted MRI) of the left periventricular deep white matter (voxel volume 8 mL) as described previously (Figure 1, left). Shimming of the magnetic field was performed, and then stimulated echo acquisition mode spectroscopy.
Phase-Contrast Magnetic Resonance Angiography

Quantitative MRA volume flow in the internal carotid arteries (ICAs) and the middle cerebral arteries (MCAs) was assessed by nontriggered PC-MRA, which is a fast, noninvasive, and widely available method to determine blood flow in the major cerebral arteries.17,18 The MRA measurements in the present study were made using a previously developed and optimized protocol.16 Measurement of flow in the ICAs (right and left) was performed at the level of the base of the skull (TR/TE 16/9 ms; 8 signals acquired; velocity-encoded cine [Venc] 100 cm/s; Figure 2A). On the basis of an axial 3D time-of-flight MRA scan of the circle of Willis, 2 flow measurement slices were positioned perpendicular to the left and right MCA (TR/TE 17/10 ms; 24 signals acquired; Venc 70 cm/s; Figure 2B). Volume flow values were obtained by integrating across a manually drawn region of interest enclosing the vessel lumen.

CVR was assessed as the percent increase in volume flow of ICAs and MCAs 10 minutes after administration of 500 mg of acetazolamide (an arteriolar dilator).18 There was no significant difference in BP before and after acetazolamide administration, as shown previously.19 Because there was no significant stenosis (>75%) in ICAs or MCAs detected by MRA, the values of volume flow and CVR taken were the averages of the values of the right and left sides.

Statistical Analysis

The 2-sided unpaired t test and χ² test were used to test differences between the 2 groups for the mean values of continuous measures and prevalence rates, respectively. One-way ANOVA was performed to evaluate differences among groups, and Tukey’s honestly significant difference test was used for comparison of the mean baseline values for pairs of groups (Tables 1 and 2). Repeated-measures ANOVA with Bonferroni’s test was used to detect statistically significant changes over time (before and after candesartan therapy) in cerebral parameters between the DHT and HT groups with 24-hour systolic BP as a covariate. Pearson’s correlation coefficient was used to assess the relationships between continuous measures. Multiple linear regression analysis was used to study the independent association between cerebral NAA and CVR with the presence of diabetes and 24-hour BP level. The statistical calculations were performed using SPSS version 8.0J (SPSS). Differences/associations with a 2-tailed P value <0.05 were considered statistically significant.

Results

Patient Characteristics

There were no significant differences in the clinical characteristics among the 3 groups (Table 1). The clinic and 24-hour BP levels were comparable between the DHT and HT groups.

Silent Cerebrovascular Disease

SCIs and advanced white matter lesions detected by brain MRI tended to be more common in the DHT than the HT and NT groups, but there was no significant difference among the groups (Table 2).

Cerebral Metabolism

Cerebral NAA was significantly lower in the DHT than in the HT and NT groups (Table 2), whereas there were no significant differences in the other metabolites examined. The cerebral NAA/creatine ratio was also significantly lower in the DHT group compared with the NT group (Table 2).

### TABLE 1. Clinical Characteristics of Diabetic and Nondiabetic Hypertension Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>DHT Group (n=20)</th>
<th>HT Group (n=20)</th>
<th>NT Group (n=12)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>69.9±9.2</td>
<td>69.9±9.2</td>
<td>69.4±9.4</td>
<td>0.989</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>7 (35)</td>
<td>7 (35)</td>
<td>4 (33)</td>
<td>0.995</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.5±3.4</td>
<td>23.5±3.1</td>
<td>24.1±3.5</td>
<td>0.601</td>
</tr>
<tr>
<td>Smoking, %</td>
<td>7 (35)</td>
<td>5 (25)</td>
<td>2 (17)</td>
<td>0.527</td>
</tr>
<tr>
<td>Hyperlipidemia, %</td>
<td>7 (35)</td>
<td>5 (25)</td>
<td>2 (17)</td>
<td>0.527</td>
</tr>
<tr>
<td>Statin use, %</td>
<td>5 (25)</td>
<td>4 (20)</td>
<td>2 (17)</td>
<td>0.852</td>
</tr>
<tr>
<td>ECG-LVH, %</td>
<td>3 (15)</td>
<td>2 (10)</td>
<td>0 (0)</td>
<td>0.393</td>
</tr>
<tr>
<td>Proteinuria, %</td>
<td>2 (10)</td>
<td>2 (10)</td>
<td>1 (5)</td>
<td>0.538</td>
</tr>
<tr>
<td>Clinic SBP, mm Hg</td>
<td>161±15†</td>
<td>158±11†</td>
<td>123±8.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Clinic DBP, mm Hg</td>
<td>85±10†</td>
<td>84±9.4†</td>
<td>70±7.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Clinic pulse rate, bpm</td>
<td>73±9.7</td>
<td>72±11</td>
<td>72±7.7</td>
<td>0.924</td>
</tr>
<tr>
<td>24-hour SBP, mm Hg</td>
<td>139±14†</td>
<td>136±15†</td>
<td>112±6.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>24-hour DBP, mm Hg</td>
<td>78±10†</td>
<td>78±7.5†</td>
<td>67±6.2</td>
<td>0.001</td>
</tr>
<tr>
<td>24-hour pulse rate, bpm</td>
<td>67±9.3</td>
<td>67±5.6</td>
<td>65±5.1</td>
<td>0.685</td>
</tr>
</tbody>
</table>

Data are shown as the mean±SD or the No. (percentage).

*Overall P values for 3 group comparisons of means (ANOVA F-test) or percentages (χ² test).

†P<0.001, ‡P<0.01 vs NT group.

ECG-LVH indicates left ventricular hypertrophy detected by ECG.
the DHT than in the NT group, and it tended to be lower in the DHT than in the HT group (P=0.06) (Table 2).

Cerebral Hemodynamics
Baseline quantitative volume flows in the ICAs and the MCAs were comparable among the 3 groups, except that there was lower MCA flow in the HT group than in the NT group (Table 2). The CVRs in ICAs (25% versus 35%; P=0.07) and MCAs (20% versus 31%; P=0.06) tended to be lower in the DHT than in the HT group, and CVR in the DHT group was significantly lower than that in the NT group (P<0.05). Neither baseline cerebral blood flow nor CVR in ICAs and MCAs was significantly correlated with a reduction in cerebral NAA (data not shown).

Diabetes and 24-Hour BP Level Effects on Cerebral NAA and CVR
We studied the effect of diabetes and 24-hour BP on the cerebral NAA and CVR in the total subjects (n=52) in the DHT, HT, and NT groups. After adjusting for other clinical characteristics (age, sex, BMI, and status of smoking and hyperlipidemia), cerebral NAA was independently associated with diabetes (standardized β=−0.466; partial R²=0.182; P<0.001), but it was not significantly associated with 24-hour SBP level (P=0.279). After adjusting for other clinical characteristics, CVR in ICAs (standardized β=−0.389; partial R²=0.127; P=0.011) and CVR in MCAs (standardized β=−0.380; partial R²=0.121; P=0.007) were independently associated with diabetes, and CVR in MCAs was marginally associated with 24-hour SBP level (standardized β=−0.261; partial R²=0.059; P=0.055).

Candesartan Therapy
Although candesartan therapy was well tolerated in 37 patients, 3 patients developed dizziness during candesartan therapy; however, because the BP reduction in these patients was mild, we did not discontinue medication. The data were successfully obtained from all 40 patients after candesartan therapy.

After candesartan therapy, CVRs in ICAs and MCAs were significantly increased in the DHT and HT groups, and these increases were significantly greater in the DHT group than in the HT group, even after controlling 24-hour systolic BP (ICAs P=0.03; MCAs P=0.015; Table 3). On the other hand, the cerebral NAA level did not change. The increases in CVRs in ICAs and MCAs were independent of the reduction of for the 24-hour BP level (Figure 3).

Discussion
This is the first study that assessed the cerebral metabolism and hemodynamics simultaneously in DHTs and HTs, and clarified that in DHT patients, brain damage is more advanced than that in HTs. The reduced levels of neuronal mass and CVR found in DHTs were predominantly determined by the presence of diabetes and independent of 24-hour BP level; however, they were independent of each other.

Reduced Neuronal Mass
Cerebral NAA, an indicator of functional neuronal mass and axons,13,14,22,23 was significantly lower in DHT patients than in HT patients and NT subjects. In previous studies on cerebral metabolism in congestive heart failure patients, occipital NAA was found to be decreased in patients with
severe heart failure with systolic dysfunction. This reduction of cerebral NAA was significantly associated with poor prognosis. The area we investigated in the brain was the deep white matter, which is an ischemia-prone watershed area between the cortical circulation and perforator circulation of the brain. The NAA in this area is predominantly located in axons, and hypertensive ischemic morphological change detected by brain MRI occurs most frequently in this area.6,14 Previous MRI studies showed that ischemic white matter lesions are associated with cognitive dysfunction, depression, gait disturbance, and future stroke.6,14 Thus, the reduced NAA in DHTs found in the present study seems to indicate a higher risk for psychocognitive dysfunction as well as cerebrovascular events in these patients. Actually, previous population studies showed that diabetes is associated with either an accelerated cognitive decline or an increased incidence of dementia.4 The prevalence of advanced white matter lesions tended to be higher in DHTs than in the HTs and NTs; however, there was no statistical significance. The reduction of NAA in deep white matter precedes this morphological change in DHTs.

The mechanism of the alteration of cerebral metabolism in DHTs remains unclear. Because the NAA concentration in white matter was reported to be significantly reduced in patients with symptomatic ICA,24 we speculated that an impaired cerebral circulation may contribute to neuronal damage. However, neither baseline cerebral blood flow nor CVR in ICAs and MCAs was significantly correlated with the reduction in cerebral NAA. In addition, reduced cerebral NAA was predominantly determined by the presence of diabetes and was independent of 24-hour BP level. The reduced NAA in DHTs may not be directly attributable to impaired cerebral microvessel function or elevated BP level, per se, but rather, may be predominantly attributable to direct adverse effects of diabetes-related activation of the apoptotic cell death pathway that exaggerate brain damage.25

Impaired CVR
CVR was significantly lower in the DHT group than in the NT group and marginally lower in the DHT group than in the HT group. The lower CVR in the MCA was determined not only by the presence of diabetes but also tended to be associated with higher 24-hour BP level. CVR is the capacity of cerebral microarteriolar dilation to occur in response to decreased cerebral perfusion pressure to maintain constant cerebral blood flow. Diminished CVR is considered to be a risk factor for stroke.26,27 Persistent high BP and other factors, such as the RAS and inflammatory reactions, all of which are activated in DHTs, may directly impair cerebral microvessel function.

| TABLE 3. Comparison of Changes in Cerebral Parameters After Angiotensin Receptor Blockade (candesartan) Therapy |
|----------------|----------------|----------------|
| Variables       | DHT Group (n=20) | HT Group (n=20) |
| BP, mm Hg       | CLINIC SBP       |      |
|                 | -13.0±19.7†      | -7.7±13.7‡ |
|                 | CLINIC DBP       |      |
|                 | -5.1±8.9†        | -0.4±6.7 |
|                 | 24-hour SBP      |      |
|                 | -7.4±11.9‡       | -2.6±13.3 |
|                 | 24-hour DBP      |      |
|                 | -3.5±5.7‡        | -3.0±6.5‡ |
| Cerebral metabolites, mmol/L per kg | NAA | 0.05±0.53 | 0.04±0.42 |
|                 | Creatine         | 0.13±0.91 | 0.04±0.51 |
|                 | Choline          | 0.01±0.19 | 0.09±0.21 |
| Cerebral volume flow, mL/min | ICAs | 5.5±57.4 | 6.5±46.4 |
|                 | MCAs             | -7.0±42.0 | 4.3±31.4 |
| Cerebrovascular reserve, % | ICAs | 14.8±13.6§ | 5.7±11.9‡ |
|                 | MCAs             | 20.2±19.0§ | 7.3±11.2† |

Changes were calculated as the values after candesartan therapy minus the baseline values, and data are shown as the mean±SD. *P<0.001, †P<0.01, ‡P<0.05 are the values after candesartan therapy minus the baseline values, analyzed by the paired t test within each group; §P<0.05 vs the HT group by repeated-measures ANOVA with Bonferroni test.

Figure 3. Association between changes of 24-hour systolic BP and CVR after candesartan therapy in DHT and HT groups.
In a recent report, despite effective antihypertensive treatment, resistance arteries from DHT patients showed marked remodeling that was greater than that of vessels from untreated HT subjects.28

**Effect of ARB on CVR**

Candesartan therapy for 3 to 4 months improved the reduced CVRs in ICAs and MCAs in the DHT and HT groups. This favorable effect was significantly greater in the DHT group than in the HT group. This result indicates that the RAS in cerebral microvessels might have some pathogenic role in the impaired CRV in hypertensives, particularly those with diabetes. The increases in CVR in ICAs and MCAs were independent of the reduction of the 24-hour BP level, indicating the BP-independent direct brain-protective effect of ARB. Clinically, this result appears to be in accord with the results of large clinical trials.29,30 In the Losartan Intervention For Endpoint reduction in hypertension study (LIFE) of high-risk hypertensives, the stroke reduction by ARB was more marked in DHTs than HTs, independent of the BP-lowering effect.29 The Study on Cognition and Prognosis in the Elderly (SCOPE) demonstrated that nonfatal stroke is impaired CRV in hypertensives, particularly those with diabetes. The increases in CVR in ICAs and MCAs were

**Perspectives**

The AT1 receptor is known to be involved in cognitive function. However, the potential role of ARB in neuroplasticity remains unclear. Oral candesartan treatment very effectively inhibits the centrally mediated effects of angiotensin II, indicating that candesartan is an effective ARB in terms of crossing the blood–brain barrier.31 In addition, because previous animal studies have shown that ARBs enable endogenous angiotensin II to stimulate neuronal regeneration via activation of AT2 receptors,11 we speculated that candesartan treatment might also restore the reduced cerebral NAA level, particularly in DHT patients. However, candesartan treatment for 3 to 4 months did not significantly alter the NAA level. Because NAA was measured in a small area of the brain, only changes in that small area would have been detected. This may have reduced the sensitivity of our ability to detect a change of NAA by candesartan therapy. A longer follow-up study of these patients may be required to demonstrate the potential beneficial effect of ARB on neuronal damage that has already occurred.

Because of the study limitation that the present study was an open one with ARB, a double-blind randomized controlled trial using renin-angiotensin-aldosterone system inhibitors and other antihypertensives of different classes will be necessary to confirm our results under similar levels of BP lowering. The results of this study provide a rationale for a long-term randomized controlled trial using RAS inhibitors for the prevention of stroke and cognitive dysfunction in preidentified DHT patients.

**Conclusion**

In hypertensive patients, the existence of diabetes is closely associated with advanced brain damage (reduced functional neuronal mass and CVR). ARB partly improved impaired cerebral microcirculation. This might provide an explanation if ARBs are found to have a benefit in improving clinical outcomes. This beneficial effect should be compared with the effect of a different class of antihypertensive with similar levels of BP lowering as a control in the future.

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