Original Article

 Associations of Plasma Endothelin Concentration with Carotid Atherosclerosis and Asymptomatic Cerebrovascular Lesions in Patients with Essential Hypertension

Shigetoshi MINAMI, Shigeru YAMANO, Yuta YAMAMOTO, Rie SASAKI, Takao NAKASHIMA, Minoru TAKAOKA, and Toshibo HASHIMOTO

We studied the association of endothelin (ET)-1 with carotid atherosclerosis and asymptomatic cerebrovascular lesions in patients with essential hypertension. Neurologically normal patients with essential hypertension (n=293; 138 male, 155 female; mean age, 65 years) and age-matched control subjects (n=242) were studied with B-mode ultrasonography of the common and internal carotid arteries and magnetic resonance imaging of the brain. Plasma ET-1 was measured by enzyme immunoassay. Hypertensive patients were divided into groups with carotid plaques and low ET-1 concentrations (<0.75 pg/ml; PL group); carotid plaques and mid-range ET-1 (0.75 to 1.55 pg/ml; PM group); carotid plaques and high ET-1 (≥1.55 pg/ml; PH group); no plaques and low ET-1 (NPL); no plaques and mid-range ET-1 (NPM); and no plaques and high ET-1 (NPH). Overall, ET-1 concentrations were significantly higher in patients than in control subjects. Carotid plaque prevalence was significantly related to ET-1 in hypertensive patients. ET-1 showed a significant positive relationship with the number of asymptomatic lacunar infarcts of the brain in hypertensive patients with carotid plaques (r=0.48, p<0.001). No significant relationship was seen between ET-1 and periventricular hyperintensity scores in patients with plaques. ET-1 did not show a relationship to either brain lesion type in patients without carotid plaques. Thus, ET-1 may foster asymptomatic lacunar cerebral infarcts by promoting carotid atherosclerosis in patients with essential hypertension. (Hypertens Res 2001; 24: 663–670)

Key Words: asymptomatic lacune, carotid plaque, endothelin-1, essential hypertension, periventricular hyperintensity

Introduction

Endothelin (ET)-1, a 21-amino acid peptide initially purified from the medium of cultured endothelial cells, is a potent vasoconstrictor that exerts its effects mainly in a paracrine or autocrine manner (1). Beginning in 1991, attention has focused on ET-1 as an indicator of atherosclerosis (2). ET-1 possesses mitogenic properties, and therefore may play a role in regulating the proliferation of intimal smooth muscle cells (3). Plasma ET-1 concentrations are increased in patients with advanced atherosclerosis or aortoarteritis, and correlate with the severity of the disease (2, 4). Direct introduction of ET-1 to the brains of experimental animals induces constriction in both the microcirculation and in large vessels (5), and this constriction can produce ischemic injury (5, 6). Recently, the cardiac hypertrophy induced by the paracrine mechanism through its attenuation of ET-1 production in the heart can be at least partially attenuated by benidipine hydrochloride (7). In addition to its vasoconstrictor

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Table 1. Clinical Background of Hypertensive Subject Groups Defined by Carotid Plaques and Plasma Endothelin (ET)-1 Concentrations

<table>
<thead>
<tr>
<th>Variables</th>
<th>PL group</th>
<th>PM group</th>
<th>PH group</th>
<th>NPL group</th>
<th>NPM group</th>
<th>NPH group</th>
<th>Significance of intergroup difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>55</td>
<td>56</td>
<td>79</td>
<td>42</td>
<td>42</td>
<td>19</td>
<td>NS</td>
</tr>
<tr>
<td>Age (mean)</td>
<td>40–79 (65)</td>
<td>42–79 (65)</td>
<td>41–79 (66)</td>
<td>40–79 (64)</td>
<td>41–79 (64)</td>
<td>42–79 (66)</td>
<td>NS</td>
</tr>
<tr>
<td>Male / Female</td>
<td>27/28</td>
<td>26/30</td>
<td>38/41</td>
<td>20/22</td>
<td>19/23</td>
<td>8/11</td>
<td>NS</td>
</tr>
<tr>
<td>Plaque</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(−)</td>
<td>(−)</td>
<td>(−)</td>
<td>NS</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>153±16</td>
<td>156±17</td>
<td>153±16</td>
<td>151±15</td>
<td>150±16</td>
<td>152±17</td>
<td>NS</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>84±12</td>
<td>88±14</td>
<td>86±10</td>
<td>89±12</td>
<td>85±15</td>
<td>87±9.7</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>69±15</td>
<td>65±15</td>
<td>70±14</td>
<td>69±12</td>
<td>69±14</td>
<td>67±13</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.8±1.8</td>
<td>23.5±1.9</td>
<td>23.3±1.9</td>
<td>23.3±2.0</td>
<td>23.4±2.0</td>
<td>23.4±1.8</td>
<td>NS</td>
</tr>
<tr>
<td>TC (mg/dl)</td>
<td>183±27</td>
<td>179±23</td>
<td>179±27</td>
<td>181±33</td>
<td>182±28</td>
<td>177±31</td>
<td>NS</td>
</tr>
<tr>
<td>TG (mg/dl)</td>
<td>121±48</td>
<td>111±35</td>
<td>108±32</td>
<td>109±26</td>
<td>101±22</td>
<td>121±27</td>
<td>NS</td>
</tr>
<tr>
<td>HDLC (mg/dl)</td>
<td>60±15</td>
<td>52±11</td>
<td>61±21</td>
<td>56±10</td>
<td>58±13</td>
<td>64±11</td>
<td>NS</td>
</tr>
<tr>
<td>Scr (mg/dl)</td>
<td>0.77±0.37</td>
<td>0.57±0.26</td>
<td>0.90±0.27</td>
<td>0.70±0.16</td>
<td>0.71±0.18</td>
<td>0.83±0.55</td>
<td>NS</td>
</tr>
</tbody>
</table>

PL group, plaques present and lowest ET-1 group (plasma ET-1 concentration <0.75 pg/ml); PM group, plaques present and mid-range ET-1 group (plasma ET-1 concentration ≥0.75, and <1.55 pg/ml); PH group, plaques present and highest ET-1 group (plasma ET-1 concentration ≥1.55 pg/ml); NPL group, plaques absent and lowest ET-1 group; NPM group, plaques absent and mid-range ET-1 group; NPH group, plaques absent and highest ET-1 group. SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; TC, total cholesterol; TG, triglycerides; HDLC, HDL cholesterol; Scr, serum creatinine; NS, not significant. When no range is given, mean values are followed by SD.

activity, ET-1 also promotes leukocyte adhesion (8) and thrombus formation (9). However, no reports have considered associations between ET-1 and atherosclerosis or cerebrovascular lesions.

This study was designed to evaluate associations of ET-1 with carotid atherosclerosis and asymptomatic cerebrovascular lesions in patients with essential hypertension.

**Methods**

**Study Population**

Neurologically normal outpatients with essential hypertension treated at the Oyodo Municipal Hospital between August 1994 and January 1998 were enrolled in this study. The 293 hypertensive patients (138 males and 155 females) ultimately admitted to the study ranged in age from 40 to 79 years (mean, 65). Hypertension was defined according to the criteria for arterial hypertension established in 1993 by the World Health Organization / International Society for Hypertension (WHO / ISH): a systolic pressure of at least 140 mmHg and/or a diastolic pressure of at least 90 mmHg (10). Patients with diabetes mellitus, hyperlipidemia, a history of clinical cerebrovascular disease, or a history of smoking were excluded.

The normal control group consisted of 242 normotensive subjects who were either outpatients treated for unrelated conditions or were undergoing routine clinical checkups at the same hospital during the same interval as specified for the hypertensive subjects. The controls exhibited no risk factors for stroke or coronary heart disease such as diabetes mellitus, hyperlipidemia, or arrhythmia. Matched by age and gender with the hypertensive subjects, the controls ranged in age from 40 to 79 years (mean, 63 years).

Hypertensive patients were divided according to plasma ET-1 concentration into the lowest third (L; ET-1, 0.50 to 0.73 pg/ml; 97 patients); the middle third (M; ET-1, 0.75 to 1.54 pg/ml; 98 patients); and the highest third (H; ET-1, 1.55 to 16.0 pg/ml; 98 patients). Further, each ET-1-defined group was divided into patients with one or more carotid plaques (P) and patients with no plaques (NP), thus producing six groups: PL, PM, PH, NPL, NPM, and NPH. The following data were collected from the medical records of each patient: age, gender, systolic and diastolic blood pressure, heart rate (HR), body mass index, fasting serum concentrations of total cholesterol and total triglycerides, and serum creatinine concentration (Table 1).

**Plasma ET-1 Measurements**

Blood samples (7 ml) were drawn into tubes from the antecubital vein in hypertensive and normal subjects who had been in the sitting position for 20 min. Samples were centrifuged at 1,000×g for 10 min and stored in polypropylene tubes containing a final concentration of 300 KIU/ml aprotinin and 2 mg/ml disodium EDTA. Plasma was stored at −40 °C until assay. Plasma ET-1 was measured by a sandwich enzyme immunoassay (EIA). In brief, 1 ml of plasma
was acidified with 4% acetic acid (3.0 ml) and applied to a Seppak C-18 cartridge (Water Associates, Milford, Massachusetts) that had been prewashed sequentially with 86% ethanol/ 4% acetic acid, methanol, distilled water, and 4% acetic acid. Materials adsorbed to the cartridge were eluted with 86% ethanol/ 4% acetic acid. Endothelin-1 was measured using an ELIA kit (Wako, Osaka, Japan) (11).

**Carotid Ultrasonography**

Carotid ultrasonography was performed with a high-resolution linear-array 7.5 MHz probe (SSA 270A; Toshiba, Tokyo, Japan). The subject was comfortably seated during bilateral imaging of the extracranial carotid arteries in the neck. To detect atherosclerotic plaques, B-mode scanning of the common and internal carotid artery was begun just above the clavicle, proceeding cephalad beyond the bifurcation and along the internal carotid as far distally as possible. A plaque was defined as a distinct area with an intimal-medial end-diastolic thickness (IMT) judged visually to be more than 50% thicker than in neighboring sites (12). This IMT was calculated using two-dimensional longitudinal sections of the carotid artery as the distance from the leading edge of the first echogenic (bright) line to the leading edge of the second echogenic line according to methods validated by Pignoli et al. (13) and Salonen et al. (14). All subjects were examined for plaques in this manner.

**Magnetic Resonance Imaging of the Brain**

MRIs of the brain were performed using a 1.5 Tesla scanner (MRT-1.5; Toshiba, Tokyo, Japan). T1-weighted and T2-weighted images were acquired at a slice thickness of 7 mm. A repetition time of 600 ms and an echo time of 20 ms were used for T1 weighting. T2-weighted images were acquired using a repetition time of 2,500 ms and an echo time of 80 ms. Three neuroradiologists without knowledge of subjects, clinical or serologic findings interpreted the images.

Asymptomatic lacunes were defined as areas with a low signal intensity on T1-weighted images measuring between 5 and 15 mm. These were visible as increased signal intensity on T2-weighted images (15). The number of lacunar infarctions was evaluated. Areas of periventricular hyperintensity (PVH) observed on T2-weighted images were defined according to their anatomic relationship to the ventricles (16). The areas of PVH were classified into four groups according to the categories of Matsubayashi et al. (17). When PVH was absent, it was scored as 0 points; when PVH was observed in no white matter lesions except for small triangular foci surrounding the frontal horns, it was scored as 1 point; when PVH was observed in caps in both the anterior and posterior horns of the lateral ventricles, it was scored as 2 points; when PVH was observed to be more extensive and confluent, it was scored as 3 points.

**Fig. 1.** Plasma endothelin (ET)-1 concentrations in the control group (C) and essential hypertension group (HT). *****p<0.001.**

**Statistical Analyses**

Statistical analysis was performed using an unpaired Student’s t test, one-way analysis of variance followed by the Scheffe post hoc test for multiple comparisons, a closeness-of-fit test for chi-squared, or using Spearman’s rank correlation coefficient. Multivariate logistic regression analysis was employed to determine the risk factors for asymptomatic lacunes. Values are expressed as the mean±SD. Differences were considered statistically significant when p was <0.05.

**Results**

**Plasma ET-1 Concentration in Hypertensive Patients and Normal Subjects**

Plasma ET-1 concentrations were 1.62±1.84 pg/ml in hypertensive patients, which is significantly higher than in normotensive control subjects (0.98±0.38 pg/ml, p<0.001; Fig. 1).

**Relationship between Plasma ET-1 and Carotid Plaques**

Carotid plaques were detected in 55 of the 97 hypertensive patients with the lowest ET-1 concentrations (57%), in 56 of the 98 hypertensive patients with mid-range ET-1 concentrations (57%), and in 79 of the 98 hypertensive patients with the highest ET-1 concentrations (81%). The prevalence of plaques differed significantly between our ET-1-defined groups of hypertensive patients (p<0.001; Fig. 2). Conversely, ET-1 concentrations were significantly higher in patients with one plaque or multiple plaques than in those without plaques (p<0.05 and p<0.01, respectively; Fig. 3).
Relationship between Plasma ET-1 and Asymptomatic Cerebral Lesions in Hypertensive Patients

Plasma ET-1 concentrations showed a significant positive relationship with the number of asymptomatic lacunar infarcts of the brain ($\rho=0.44, \ p<0.001$). On the other hand, no significant relationship was seen between plasma endothelin-1 concentrations and PVH scores (Table 2).

Relationship between Plasma ET-1 and Asymptomatic Cerebral Lesions in Hypertensive Patients with Carotid Plaques

In patients with plaques, plasma ET-1 concentrations showed a significant positive relationship with the number of asymptomatic lacunes ($\rho=0.48, \ p<0.001$). On the other hand, no significant relationship was seen between plasma endothelin-1 concentration and PVH score (Table 3).

Relationship between Plasma ET-1 and Asymptomatic Cerebral Lesions in Hypertensive Patients without Carotid Plaques

In patients without plaques, plasma ET-1 concentrations did not show a significant relationship with either the number of asymptomatic lacunes or with PVH scores (Table 4).

Multivariated Logistic Regression Analysis

To determine the risk factors for asymptomatic lacunes, age, systolic blood pressure, diastolic blood pressure, plasma ET-1 concentrations, and the existence of carotid plaque were employed in a multivariated regression analysis. Age, plasma ET-1 concentrations, and the existence of carotid plaque were associated with a significant risk of asymptomatic lacunes (Table 5).

Discussion

Recent data indicate that endothelin is synthesized not only by endothelial cells but also by cultured vascular smooth muscle cells; further, endothelin is an effective stimulator of smooth muscle cell proliferation (1). The proliferation of vascular smooth muscle cells is a key event in the development of atherosclerotic lesions (18). Previous immunohistochemical investigations have localized endothelin-like immunoreactivity to smooth muscle cells in coronary arterial plaques (19), while only weak labeling was found in medial smooth muscle cells from a normal human aorta (20). These findings suggest that atherosclerosis is associated with enhanced endothelin production in smooth muscle cells, and that endothelin may be involved in the pathogenesis or progression of atherosclerosis.

Asymptomatic cerebrovascular lesions are considered to be a preliminary event in ischemic stroke (21). While several studies have examined the relationship between endothelin and clinical stroke, no reports have addressed the possible relationship between endothelin and asymptomatic cerebrovascular lesions. In the present study we evaluated the association of ET-1 with carotid lesions and with asymptomatic cerebrovascular lesions in patients with essential hypertension.

Hypertension and ET-1

The discovery of endothelins in porcine endothelial cell cultures was followed by the demonstration that these peptides are potent vasoconstrictors. Intense investigation was then undertaken with the aim of determining whether endothelins participate in the vasoconstriction of arterial hypertension.
Table 2. Effect of Endothelin (ET)-1 Concentration on Asymptomatic Cerebral Lesions in Hypertensive Patients

<table>
<thead>
<tr>
<th>Item</th>
<th>ET-1</th>
<th>ρ</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lowest</td>
<td>Mid-range</td>
<td>Highest</td>
</tr>
<tr>
<td>No. of ASL</td>
<td>0.39±0.80</td>
<td>0.59±1.08</td>
<td>1.21±1.26</td>
</tr>
<tr>
<td>Score of PVH</td>
<td>0.96±1.08</td>
<td>0.73±0.94</td>
<td>0.89±1.04</td>
</tr>
</tbody>
</table>

Mean values are followed by SD. NS, not significant; ASL, asymptomatic lacunar; PVH, hypertensive patients with periventricular hyperintensity; lowest, hypertensive patients with plasma ET-1 concentration <0.75 pg/ml; mid-range, plasma ET-1 concentration ≥0.75 and <1.55 pg/ml; highest, plasma ET-1 concentration ≥1.55 pg/ml.

Table 3. Effect of Endothelin (ET)-1 Concentration on Asymptomatic Cerebral Lesions in Hypertensive Patients with Carotid Plaques

<table>
<thead>
<tr>
<th>Item</th>
<th>ET-1</th>
<th>ρ</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lowest</td>
<td>Mid-range</td>
<td>Highest</td>
</tr>
<tr>
<td>No. of ASL</td>
<td>0.36±0.08</td>
<td>0.79±0.15</td>
<td>1.42±0.14</td>
</tr>
<tr>
<td>Score of PVH</td>
<td>1.13±0.15</td>
<td>0.90±0.13</td>
<td>0.96±0.12</td>
</tr>
</tbody>
</table>

Mean values are followed by SD. NS, not significant; ASL, asymptomatic lacunar; PVH, hypertensive patients with periventricular hyperintensity; lowest, plasma ET-1 concentration <0.75 pg/ml; mid-range, plasma ET-1 concentration ≥0.75, and <1.55 pg/ml; highest, plasma ET-1 concentration ≥1.55 pg/ml.

Table 4. Effect of Endothelin (ET)-1 Concentration on Asymptomatic Cerebral Lesions in Hypertensive Patients without Carotid Plaques

<table>
<thead>
<tr>
<th>Item</th>
<th>ET-1</th>
<th>ρ</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lowest</td>
<td>Mid-range</td>
<td>Highest</td>
</tr>
<tr>
<td>No. of ASL</td>
<td>0.42±0.82</td>
<td>0.31±0.64</td>
<td>0.41±0.82</td>
</tr>
<tr>
<td>Score of PVH</td>
<td>0.73±0.16</td>
<td>0.50±0.13</td>
<td>0.58±0.22</td>
</tr>
</tbody>
</table>

Mean values are followed by SD. NS, not significant; ASL, asymptomatic lacunar; PVH, hypertensive patients with periventricular hyperintensity; lowest, plasma ET-1 concentration <0.75 pg/ml; mid-range, plasma ET-1 concentration ≥0.75, and <1.55 pg/ml; highest, plasma ET-1 concentration ≥1.55 pg/ml.

Table 5. Odds Ratio for Asymptomatic Lacunes

<table>
<thead>
<tr>
<th>Variables</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.042</td>
<td>1.012–1.074</td>
<td>0.0062</td>
</tr>
<tr>
<td>SBP</td>
<td>0.995</td>
<td>0.978–1.012</td>
<td>0.5307</td>
</tr>
<tr>
<td>DBP</td>
<td>1.010</td>
<td>0.987–1.032</td>
<td>0.3964</td>
</tr>
<tr>
<td>ET-1</td>
<td>1.316</td>
<td>1.093–1.586</td>
<td>0.0038</td>
</tr>
<tr>
<td>Carotid plaque</td>
<td>2.190</td>
<td>1.234–3.885</td>
<td>0.0074</td>
</tr>
</tbody>
</table>

SBP, systolic blood pressure; DBP, diastolic blood pressure; ET-1, plasma endothelin-1 concentration; CI, confidence interval.

(22). While some reports concluded that plasma ET-1 concentrations are not elevated in patients with mild to moderate essential hypertension (23, 24), other studies (25, 26), including the present study have found patients with essential hypertension to have higher ET-1 in plasma than do normal subjects. The considerable elevation of plasma ET-1 in hypertensive patients reported by Saith et al. (25, 26) may have been affected by patient selection, particularly the inclusion of patients with target organ damage. In another study, mildly hypertensive patients showed no increase in the expression of endothelial preproET-1 mRNA in the endothelium of small arteries, while in moderately to severely hypertensive patients this expression was significantly enhanced (27). Increased production of ET-1 could contribute to the hypertrophic remodeling of the size of small arteries in subcutaneous gluteal fat in moderately to severely hypertensive patients, in addition to playing a role in blood pressure elevation (27). Saith et al. (26) mentioned that hypertensive patients in stages II and III according to the World Health Organization classification showed higher plasma ET-1 concentrations than patients in stage 1. These researchers also found that the elevation of plasma ET-1 was related to organ complications associated with hypertension, including atherosclerosis. As mentioned, plasma ET-1 concentrations in our hypertensive patients were significantly higher than in normal subjects. Among these 293 hypertensive patients, 190 (64%) had carotid plaques, representing one of the organ complications of hypertension likely to contribute to elevation of ET-1.
Carotid Plaques and ET-1

In patients with symptomatic atherosclerotic vascular disease (aortic or peripheral vascular disease, renovascular disease, coronary artery disease, or clinically evident carotid artery disease), plasma ET-1 concentrations are higher than in normal subjects, and a significant correlation is demonstrable between plasma ET-1 and the number of vascular sites exhibiting atherosclerosis (2). Immunostaining has shown reactivity for ET-1 in foam cells and in the intimal and medial smooth muscle cells of human carotid atherosclerotic lesions (28).

Animal experiments have provided compelling evidence that endothelin promotes vascular disease. Smooth muscle cells and macrophages are present within the intimal layer in atherosclerotic lesions (29). The injection of exogenous ET-1 accelerated the incidence of balloon-injured rat carotid arteries in smooth muscle cells in the neointima (30). Conversely, a selective ETα receptor antagonist reduced the size of smooth muscle cell-rich neointima in a rat model of intima hyperplasia (31). In addition to smooth muscle proliferation, plaque growth includes an expansion of the extracellular matrix (32). ET-1 increases fibronectin transcription and synthesis by the vascular smooth muscle cells in rats (33). In our present study, the prevalence of plaques was significantly correlated with the ET-1 concentrations in hypertensive patients. Like the experiments in animal models, our study suggests that endothelin participates in human atherosclerosis.

Asymptomatic Lacunes and ET-1

In the present study, plasma ET-1 concentrations showed a significant positive association with the number of asymptomatic lacunar infarcts of the brain in hypertensive patients with plaques, but showed no association with lacunes in patients without plaques. In multivariated logistic regression analysis, age, plasma ET-1 concentration, and carotid plaque were independently associated with asymptomatic lacunes. Lacunar infarcts are small infarcts located deep in the brain or brainstem (34), and usually are caused by a local obstruction of a small perforating artery (35). At autopsy, Fisher distinguished two causes of local small-vessel obstruction: lipohyalinosis and microatheromatous disease (35). Another mechanism of lacunar infarction, embolism (36), has been demonstrated both in an experimental study (37) and in clinical studies (38–42). Ay et al. (38) demonstrated that lacunar infarcts were associated with an embolic source in a clinical investigation using diffusion-weighted imaging. Millikan et al. (36) emphasized that emboli from the carotid artery occasionally cause the occlusion of small cerebral arteries such as penetrating arteries. Hougaku et al. (39) reported that the severity and characteristics of asymptomatic carotid lesions estimated by B-mode ultrasonography were closely related to the occurrence of silent infarcts. Recently, other investigators (40–42) reported that lacunar infarcts were associated with embolic sources in the carotid artery as demonstrated by transcranial Doppler ultrasonography.

Whether ET-1 vasoconstricts blood vessels in the brain in hypertensive patients is unclear, although the selective ETα receptor antagonist PD156707 increases cerebral perfusion surrounding ischemic areas after experimental focal cerebral ischemia (43). Our data suggest that ET-1 may promote carotid atherosclerosis, thus indicating that asymptomatic lacunar infarcts may be caused in large part by microemboli from the carotid artery.

Periventricular Hyperintensity and ET-1

No reports have considered the relationship between PVH and ET-1 concentration. We found no link between PVH and this endothelin. Many reports have suggested that PVH is an ischemic change in white matter resulting from arteriosclerosis of the penetrating arteries (44, 45). Adachi et al. found PVH to correlate with age, the presence of hypertension, and past history of cerebrovascular disease, but not with carotid artery stenosis (46). Based on our data, ET-1 may not contribute to PVH.

In conclusion, ET-1 appears to promote carotid atherosclerosis in hypertensive patients, and may be related to the occurrence of asymptomatic lacunar infarcts after carotid lesions have appeared. To evaluate whether ET-1 is useful in predicting the occurrence of asymptomatic lacunar infarcts will require further prospective study.

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