Plasma Endothelin Levels in Hypertension and Chronic Renal Failure

Masayoshi Shichiri, Yukio Hirata, Kenji Ando, Toshiaki Emori, Kazuki Ohta, Shigeaki Kimoto, Mitsuo Ogura, Atsushi Inoue, and Fumiaki Marumo

Endothelin (ET), a potent vasoconstrictor peptide with 21-amino acid residues, has recently been isolated from the supernatant of cultured porcine aortic endothelial cells. Complementary DNA (cDNA) cloning of human genomic DNA library revealed the presence of three ET-related isopeptides (ET-1, ET-2, and ET-3). ET-1 is identical to human/porcine ET. It induces a potent vasoconstrictive effect on a variety of blood vessels, including the renal artery, and a long-lasting elevation of systemic blood pressure in anesthetized dogs. We recently demonstrated the presence of ET-1-like immunoreactivity (ET-LI) in normal human plasma with a highly sensitive and specific radioimmunoassay (RIA), suggesting its potential role as a circulating vasoconstrictor. However, no information is yet available as to its pathophysiological role in hypertension. Therefore, the present study was designed to determine plasma ET-LI in normal subjects and in patients with essential hypertension as well as those with chronic renal failure with or without hypertension.

Methods

The study population consisted of 21 normal individuals (11 men and 10 women), 11 patients with essential hypertension (seven men and four women), 24 patients with nondialyzed chronic renal failure (18 men and six women), and 51 patients undergoing maintenance hemodialysis (34 men and 17 women). Informed consent was obtained from each subject. Essential hypertension was defined as elevated blood pressure while in a sitting position, exceeding 160/95 mm Hg, for three consecutive measurements over a period of at least 4 weeks. Clinical records regarding blood pressure and renal function for at least the previous several months were reviewed for all patients. Chronic renal failure patients were divided into hypertensive and normotensive groups. The hypertensive group included patients whose high blood pressure was controlled by antihypertensive drugs (calcium channel blockers, α-blockers and β-
Measurements of Immunoreactive Endothelin and Other Hormones

Blood samples (7 ml) from normal subjects, patients with essential hypertension, and those with nondialyzed renal failure were withdrawn, while the subject or patient was in a sitting position, from the antecubital vein into K₂-EDTA tubes placed on ice. For hemodialysis patients, blood sampling was done when they were in a recumbent position at the start of hemodialysis. Plasma was immediately separated and stored at -40°C until assayed. Plasma ET-LI levels among the following three groups: 32 subjects with normal renal function (21 normal subjects plus 11 patients with essential hypertension, 1.72±0.84 pg/ml), 24 patients with nondialyzed renal failure (2.46±1.12 pg/ml), and 51 patients undergoing chronic hemodialysis (1.81±1.41 pg/ml). Plasma ET-LI levels in the 21 normal subjects were 1.41±0.50 pg/ml. Eleven patients with essential hypertension showed higher plasma ET-LI levels (2.29±1.09 pg/ml) than the normal subjects (p<0.025). When both nondialyzed and hemodialyzed renal failure groups were further divided into hypertensive and normotensive subgroups, the hypertensive groups showed significantly higher plasma ET-LI levels than the comparable normotensive groups (nondialyzed 3.08±3.43 pg/ml [n=17], p=0.05; hemodialyzed 2.66±1.92 pg/ml [n=18] vs. 1.35±0.73 pg/ml [n=33], p<0.005) (Figure 1). There were no statistical differences in atrial natriuretic factor, arginine vasopressin, plasma renin activity, and plasma aldosterone concentration between normal subjects and patients with essential hypertension, between the hypertensive and the normotensive with nondialyzed renal failure groups, or between the two groups on hemodialysis (Table 1). Plasma ET-LI levels did not show any correlations with atrial natriuretic factor (r=-0.232), arginine vasopressin (r=-0.236), plasma renin activity (r=0.092), or plasma aldosterone concentration (r=-0.058) when all subjects were analyzed together.

Discussion

By using a sensitive RIA for ET-1 with a detectable plasma level as low as 0.5 pg/ml, we could measure

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Table 1. Summary of Control Subjects, Patients with Essential Hypertension and Chronic Renal Failure Studied, and Plasma Hormone Levels:

<table>
<thead>
<tr>
<th>Subject (n)</th>
<th>Mean blood pressure (mm Hg)</th>
<th>Age (yr)</th>
<th>Serum creatinine (mg/dl)</th>
<th>PRA (ng/ml/hr)</th>
<th>PAC (ng/dl)</th>
<th>ANF (pg/ml)</th>
<th>AVP (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal renal function</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normotensive (21)</td>
<td>88.5±7.7</td>
<td>31.8±11.8</td>
<td>0.90±0.25</td>
<td>2.10±0.25</td>
<td>9.60±0.97</td>
<td>56.1±11.5</td>
<td>5.85±1.21</td>
</tr>
<tr>
<td>Essential hypertension</td>
<td>127.5±4.1</td>
<td>58.5±10.5</td>
<td>0.97±0.15</td>
<td>2.60±2.90</td>
<td>8.29±2.05</td>
<td>72.3±37.4</td>
<td>3.56±2.27</td>
</tr>
<tr>
<td>Chronic renal failure (nondialyzed)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normotensive (7)</td>
<td>87.3±6.7</td>
<td>57.4±17.0</td>
<td>4.86±1.61</td>
<td>1.13±0.58</td>
<td>5.00±1.41</td>
<td>119.6±26.8</td>
<td>4.93±6.30</td>
</tr>
<tr>
<td>Hypertensive (17)</td>
<td>120.5±3.7</td>
<td>55.6±14.9</td>
<td>6.87±3.14</td>
<td>2.50±2.10</td>
<td>5.70±6.15</td>
<td>107.2±85.3</td>
<td>3.66±3.00</td>
</tr>
<tr>
<td>Chronic renal failure (hemodialyzed)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normotensive (33)</td>
<td>93.2±9.1</td>
<td>51.8±9.9</td>
<td>...</td>
<td>8.15±7.92</td>
<td>48.7±18.7</td>
<td>110.2±32.0</td>
<td>8.58±4.85</td>
</tr>
<tr>
<td>Hypertensive (18)</td>
<td>124.8±12.4</td>
<td>50.9±14.0</td>
<td>...</td>
<td>7.19±7.73</td>
<td>59.6±51.9</td>
<td>113.1±75.1</td>
<td>6.57±4.29</td>
</tr>
<tr>
<td>Normal range</td>
<td></td>
<td></td>
<td></td>
<td>0.3–4.0</td>
<td>4–18</td>
<td>10–60</td>
<td>0.8–6.3</td>
</tr>
</tbody>
</table>

Values are mean±SD. PRA, plasma renin activity; PAC, plasma aldosterone concentration; ANF, atrial natriuretic factor; AVP, arginine vasopressin.

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Statistical Analysis

Results were expressed as mean±SD. Analyses were performed using Wilcoxon's test for nonpaired data. Statistical significance was accepted for p<0.05.

Results

Clinical characteristics of each group are shown in Table 1. There was no statistical difference in plasma ET-LI levels among the following three groups: 32 subjects with normal renal function (21 normal subjects plus 11 patients with essential hypertension, 1.72±0.84 pg/ml), 24 patients with nondialyzed renal failure (2.46±1.12 pg/ml), and 51 patients undergoing chronic hemodialysis (1.81±1.41 pg/ml). Plasma ET-LI levels in the 21 normal subjects were 1.41±0.50 pg/ml. Eleven patients with essential hypertension showed higher plasma ET-LI levels (2.29±1.09 pg/ml) than the normal subjects (p<0.025).

When both nondialyzed and hemodialyzed renal failure groups were further divided into hypertensive and normotensive subgroups, the hypertensive groups showed significantly higher plasma ET-LI levels than the comparable normotensive groups (nondialyzed 3.08±3.43 pg/ml [n=17], p=0.05; hemodialyzed 2.66±1.92 pg/ml [n=18] vs. 1.35±0.73 pg/ml [n=33], p<0.005) (Figure 1). There were no statistical differences in atrial natriuretic factor, arginine vasopressin, plasma renin activity, and plasma aldosterone concentration between normal subjects and patients with essential hypertension, between the hypertensive and the normotensive with nondialyzed renal failure groups, or between the two groups on hemodialysis (Table 1). Plasma ET-LI levels did not show any correlations with atrial natriuretic factor (r=-0.232), arginine vasopressin (r=-0.236), plasma renin activity (r=0.092), or plasma aldosterone concentration (r=-0.058) when all subjects were analyzed together.

Discussion

By using a sensitive RIA for ET-1 with a detectable plasma level as low as 0.5 pg/ml, we could measure
circulating ET-LI levels in peripheral venous plasma in all normal subjects and patients with hypertension or chronic renal failure that were studied. The mean concentrations of plasma ET-LI in normal subjects in our present and previous studies are comparable with those by sandwich enzyme immunoassay and RIA recently reported. Because of a marked reduction in renal blood flow induced by ET-1 (4×10^{-11} to 2×10^{-10} M) in the isolated perfused rat kidney, the possible role of ET-1 in the development of acute renal failure has been suggested. However, plasma ET-LI levels in patients with chronic renal failure (1.2×10^{-13} to 2.4×10^{-12} M) are far lower than those required to induce pharmacological actions thus far reported, including renal blood flow reduction in experimental animals.

The present study clearly shows that plasma ET-LI levels were significantly higher in all three hypertensive groups than those in comparable normotensive subjects. These data suggest that circulating ET-1 may be causally related to the development or maintenance of hypertension. Recent preliminary studies have reported that plasma ET-LI levels were elevated in most of the hemodialyzed patients but undetectable in all normal subjects. Indeed, significantly elevated plasma ET-1 levels were observed in certain patients with chronic renal failure in the present study. However, plasma ET-1 levels do not correlate with residual renal function, which suggests that decreased glomerular filtration rate does not play an important role in the clearance of ET-1. Likewise, the difference in age of our normal group does not appear to contribute to the difference in plasma ET-1 levels. The apparent discrepancy between our results and those by other investigators may be accounted for by the heterogeneous populations of hypertensive or normotensive hemodialyzed patients studied or the different antibodies used in RIA. Full characterization of our antibody revealed that the principal antigenic determinant is directed toward C-terminal Trp21, which is the residue essential for the biological activity of ET-1 and is shared by all three isopeptides (ET-1, ET-2, and ET-3) as recently elucidated by cDNA cloning of human genome.

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**Key Words** • plasma endothelin levels • essential hypertension • chronic renal failure • hemodialysis • radioimmunoassay
Plasma endothelin levels in hypertension and chronic renal failure.
M Shichiri, Y Hirata, K Ando, T Emori, K Ohta, S Kimoto, M Ogura, A Inoue and F Marumo

Hypertension. 1990;15:493-496
doi: 10.1161/01.HYP.15.5.493

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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