Behaviour of adrenomedullin during acute and chronic salt loading in normotensive and hypertensive subjects

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(Received 4 December 1995/13 May 1996; accepted 29 May 1996)

1. Responses of adrenomedullin to acute and chronic salt loading were examined in normotensive and hypertensive subjects.

2. In the acute salt load study, isotonic saline (50 ml/kg for 1 h) was intravenously infused into nine normotensive subjects and 11 patients with essential hypertension. Plasma adrenomedullin was higher in hypertensive than in normotensive subjects but was unchanged by saline infusion in either the normotensive (before infusion, 2.4 ± 0.2 fmol/ml; after infusion, 2.4 ± 0.1 fmol/ml) or hypertensive (before infusion, 3.0 ± 0.1 fmol/ml; after infusion, 2.9 ± 0.2 fmol/ml) group, while renin was suppressed and atrial natriuretic peptide was markedly increased. Plasma endothelin was not affected either.

3. In the chronic salt load study, seven normotensive subjects and 23 patients with essential hypertension underwent two 7-day periods of 30 and 260 mmol/day sodium intake. Depending on the blood pressure change, 13 hypertensive subjects were classified as salt-resistant and 10 as salt-sensitive. Salt-sensitive hypertensive subjects had suppressed plasma renin activity even during low salt intake. Plasma adrenomedullin or endothelin were not affected by the salt intake changes in any group; however, the high salt intake increased atrial natriuretic peptide in all groups.

4. These data indicate that the circulating level of adrenomedullin is not changed by either acute or chronic salt loading in normotensive subjects and patients with essential hypertension.

INTRODUCTION

Adrenomedullin (AM) is a potent vasodilator peptide discovered in human phaeochromocytoma by Kitamura et al. [1]. As expected from the origin of tissue in which this peptide was discovered, the adrenal gland prominently expresses AM mRNA. However, besides the adrenal, considerable mRNA expression has been seen in the cardiovascular system including the heart, kidney, lung and vascular wall [2, 3]. A significant level of AM has been also identified in human plasma by means of specific RIA coupled with liquid chromatography [1, 4]. Moreover, we have recently reported that plasma AM is increased in various cardiovascular disorders such as hypertension, renal dysfunction, and heart failure [5, 6]. In particular, plasma AM is markedly increased in patients with heart or renal failure. In these patients, body fluid volume is increased due to dysfunctions of the heart and kidneys. Therefore, it is possible that plasma AM increases in response to the body fluid volume expansion as in the case of atrial natriuretic peptide (ANP) [7, 8].

The purpose of this study was to investigate the responses of AM during body fluid volume changes. Specifically, the effects of acute and chronic salt loading on circulating levels of AM were examined in normotensive subjects and hypertensive patients. This is expected to provide information about the pathophysiological implications of AM in the cardiovascular system.

SUBJECTS AND METHODS

Intravenous saline infusion

The saline infusion study was performed in nine normotensive healthy subjects (five men and four women, 35–66 years of age) and 11 patients with essential hypertension (five men and six women, 34–63 years of age) after obtaining informed consent. The study protocol was in accordance with the Declaration of Helsinki (1989) of the World Medical Association and was approved by the institutional...
review committee. Hypertension was defined as elevated blood pressure exceeding 160 mmHg in systole or 95 mmHg in diastole for three consecutive measurements over a period of 4 weeks at the outpatient clinic. Secondary causes of hypertension were ruled out through a comprehensive check-up. According to the World Health Organization (WHO) classification for organ damage, six hypertensive patients were classified as stage I, and five as stage II. Three patients had been treated with calcium channel blockers for 2 weeks to 4 months. This treatment was stopped for at least 2 weeks before entering the study. The subjects were given a sodium intake of 120-140 mmol/day for 2 weeks or more.

At 08.30 hours, after an overnight fast and 30 min of supine rest, 50 ml/kg body weight of sterile 154 mmol/l NaCl solution was infused over 1 h through a catheter inserted in an antecubital vein. The subjects adopted a supine and recumbent position throughout the study. Just before and after the infusion, venous blood was collected from the non-infused arm into two chilled tubes, one containing EDTA (1 mg/ml) and the other supplemented with aprotinin (500 units/ml) in addition. Plasma was separated by centrifugation at 4°C and stored at -80°C until assayed.

**Dietary salt loading**

The study subjects were seven normal subjects (three men and four women, 38–69 years of age) and 23 patients with essential hypertension (11 men and 12 women, 34–73 years of age). Hypertensive patients met the criteria described in the saline infusion study. Twelve were classified as stage I of the WHO classification for organ damage, and 11 were classified as stage II. Ten patients had been treated with calcium channel blockers and two with β-blockers for 1 week to 7 months. These treatments had been stopped at least for 2 weeks before entering the study. All subjects gave their informed consent and were hospitalized during the study period. The study protocol was approved by the institutional review committee. After a 1-week acclimation period on a diet containing 120 mmol/day sodium, low- and high-salt diets containing sodium, 30 mmol/day and 260 mmol/day respectively, were given for 7 days each in a randomized crossover fashion. Each diet contained 50 mmol of potassium per day.

At 08.00 hours on the last day of each regimen, antecubital venous blood was taken after an overnight fast and 30 min of supine rest. The blood sample was handled in the manner described in the saline infusion study. On the same day, 24 h urine was collected, and blood pressure was measured at 07.00, 11.00, 15.00 and 20.00 hours by a physician or a trained nurse using a mercury manometer after 15 min of supine rest. Hypertensive patients were divided into two groups according to their changes in mean blood pressure between low- and high-salt periods. A hypertensive individual was arbitrarily classified as salt-sensitive (SS) when the mean blood pressure rose by 10% or more during high salt intake compared with low salt intake, and as salt-resistant (SR) when the blood pressure change was less than 10% [9, 10].

**Analysis of plasma and urine samples**

Aprotinin-supplemented plasma was used for the assays of AM, ANP, and endothelin-1 (ET-1). Plasma AM concentration was measured by specific RIA after extraction and purification as described previously [4]. Briefly, 2 ml of plasma was applied to a conditioned Sep-Pak C18 cartridge (Waters of Millford, Milford, MA, U.S.A.), and the column was sequentially washed with 5 ml of isotonic saline, 5 ml of 0.1% (vol/vol) trifluoroacetic acid and 5 ml of 20% (vol/vol) acetonitrile in 0.1% trifluoroacetic acid. The absorbed material was then eluted with 4 ml of 50% (vol/vol) acetonitrile, and the eluate was lyophilized. The residue was dissolved in 0.3 ml of 50 mmol/l phosphate buffer (pH 7.4), and was subjected to RIA using the radioiodinated AM and antiserum raised against synthetic AM in rabbits. The mature AM peptide consists of 52 amino acid residues [1]. Crossreactivities of the anti-AM serum with AM1–12, AM13–31, AM40–52 and AM13–52 were <0.01%, <0.01%, 0.5% and 2%, respectively. The 50% inhibition of radioiodinated AM was observed at 4 fmol/tube of AM, and 0.5 to 32 fmol/tube AM, namely 0.75 to 48 fmol/ml in plasma, was measurable by this RIA. The intra- and interassay coefficients of variance were 5% and 8%, respectively.

Plasma concentration of ET-1 was measured, after extraction and purification with a Sep-Pak C18 cartridge, using a sandwich enzyme immunoassay kit (Wako Pure Chemical Industries, Osaka, Japan) which specifically detects intact and active ET-1 [11]. Plasma ANP was measured using a ShionoRIA ANP assay kit (Shionogi & Co. Ltd, Osaka, Japan) [12]. Plasma renin activity (PRA) and aldosterone concentration (PAC) were determined by RIA. Plasma and urinary electrolytes were measured by flame photometry.

**Statistical analysis**

Data were given as mean ± SEM. Data were analysed using two-way analysis of variance with repeated measures and Bonferroni test for comparison between groups (Tables 2 and 4). Changes in variables were compared using Kruskal–Wallis H-test followed by Bonferroni/Dunn procedure for multiple comparisons. Background characteristics of the two groups in the saline infusion study were compared by unpaired Student’s t-test (Table 1),
and those of the three groups in the dietary salt study were compared using one-way analysis of variance followed by the Scheffé test (Table 3). A P value less than 0.05 was considered statistically significant.

RESULTS

Saline infusion study

Table 1 shows the basic characteristics of the subjects. Except for blood pressure values, both normotensive and hypertensive groups had similar background profiles. Table 2 presents the measured variables before and after acute intravenous saline infusion. Although blood pressure was greater than 160/95 mmHg in all subjects of the hypertensive group at the outpatient clinic, their mean blood pressure was lower than this when measured before saline infusion after an overnight fast and 30 min of supine rest. However, the value was still in the hypertensive range and was much higher than that of the normotensive group. Heart rate and blood pressure were not affected by the saline infusion either in the normotensive or the hypertensive group. Plasma Na⁺ did not change after the saline infusion; however, plasma K⁺ was significantly decreased in either group.

With regard to changes in hormones of the cardiovascular system, PRA and PAC were significantly reduced by the saline infusion, as expected, in both normotensive subjects (PRA: \(-50 \pm 7\%\), P < 0.05; PAC: \(-55 \pm 7\%\), P < 0.01) and hypertensive patients (PRA: \(-36 \pm 6\%\), P < 0.05; PAC: \(-48 \pm 6\%\), P < 0.05) to similar degrees. ANP in plasma did not significantly differ between the two groups before infusion when the subjects were maintained on a normal salt intake. After the infusion, plasma ANP increased in both groups (normotensive: +99 \pm 22\%, P < 0.05; hypertensive: +75 \pm 21\%, P < 0.01). As shown in Fig. 1, plasma ET-1 levels before infusion were not different between the two groups, while two-way analysis of variance showed plasma AM was higher in hypertensive subjects than in normotensive patients (F = 4.16, P < 0.05). Plasma levels of these two hormones were not affected by the acute saline infusion in either the normotensive or hypertensive group.

Effects of dietary salt intake

Of 23 hypertensive patients, 10 were classified as SS on the basis of mean blood pressure response to the change in dietary sodium intake, and the remaining 13 were classified as SR. With regard to the WHO classification for organ damage, six SR and six SS patients were classified as stage I, and seven SR and four SS subjects were classified as stage II. Table 3 shows the basic characteristics of these SR and SS patients, and those of the normotensive group. Age, gender ratio, body weight, heart rate and blood pressure were not significantly different between SR and SS patients. The normotensive group also had comparable background characteristics, except for blood pressure.

Table 4 presents measured variables at the end of low- and high-salt regimens in the normotensive, SR and SS groups. Although the blood pressure levels of SR and SS patients were not different in the outpatient clinic, SS patients had lower blood pressure during low salt intake and higher blood pressure during high salt intake than SR patients. Mean blood pressure of normotensive subjects or SR patients was not significantly changed by the low- or high-salt diet (normotensive patients: +2 \pm 2 mmHg, not significant; SR: +3 \pm 1 mmHg, not significant), while SS patients showed a significant rise in blood pressure during the high-salt period compared with the low-salt period (+15 \pm 1 mmHg, P < 0.001). Body weight significantly increased during high salt intake compared with low salt intake in each group to a comparable extent (normotensive: +1.1 \pm 0.2 kg, P < 0.05; SR: +1.4 \pm 0.2 kg, P < 0.01; SS: +1.1 \pm 0.2 kg, P < 0.01). Heart rate did not vary in any group during the low- and high-salt periods.

Plasma electrolytes, Na⁺ and K⁺, did not change between low and high salt intake in any group. Urinary excretion of sodium was comparable among the three groups during both low and high salt intake, and urinary potassium excretion did not differ between groups or between the low- and high-salt periods.

During low salt intake, PRA was lower in SS patients than in SR patients or normotensive subjects. However, high salt intake suppressed PRA to similar levels in the three groups. PAC was also reduced during the high-salt regimen compared with low-salt in each group in a similar manner. Plasma levels of ANP did not differ among the three groups during low salt intake. Plasma ANP increased during high salt intake in each group (normotensive: +111 \pm 22\%, P < 0.05; SR: +204 \pm 27\%, P < 0.01; SS: +190 \pm 20\%, P < 0.005). The increase in ANP was more prominent in hypertensive groups than in normotensive subjects (H = 6.26, P < 0.05; either SR or SS compared with normotensive subjects,

<table>
<thead>
<tr>
<th>Table</th>
<th>General characteristics of the subjects in the saline infusion study. Data are means (\pm) SEM. Statistical significance: (\ast P&lt;0.001) compared with normotensive group.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
<td>Normotensives ((n=9))</td>
</tr>
<tr>
<td>Age (years)</td>
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</tr>
<tr>
<td>Sex (M/F)</td>
<td>5/4</td>
</tr>
<tr>
<td>Body weight (kg)</td>
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</tr>
<tr>
<td>Body mass index (kg/m²)</td>
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</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
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<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>76 (\pm) 3</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>67 (\pm) 3</td>
</tr>
</tbody>
</table>


DISCUSSION

The present study investigated, for the first time, the effects of acute and chronic salt loading on plasma levels of AM in normotensive subjects and hypertensive patients. Plasma AM was higher in hypertensive patients than in normotensive subjects [14-16]. Both AM and ET are endothelium-derived peptides, but they have contrasting characteristics; AM is a potent vasodilator, while ET is a strong vasoconstrictor. In the present study, either AM or ET failed to show a response to acute and chronic salt loading in normotensive subjects and hypertensive patients. However, this does not negate the significance of these peptides in the cardiovascular system, considering that selective ET receptor antagonists lack placebo experiments, the influence of factors other than salt loading cannot be excluded. However, considering that plasma AM does not show diurnal variations or changes during exercise either in normotensive or hypertensive subjects [13], and that PRA, PAC and ANP were markedly changed after the saline infusion, it can be said that plasma AM does not change even when other cardiovascular hormones are modified by acute saline infusion.

It still seems unclear as to whether circulating ET is increased in hypertension [14-16]. The present study adds a negative view in this respect. Probably, plasma ET may not rise distinctly except in cases of severe hypertension [17]. Little is known about the effect of salt loading on plasma ET. Predel et al. [18] have shown that plasma ET is unchanged by an acute saline infusion in patients with essential hypertension. Hoffman et al. [19] have reported that changing dietary sodium content does not affect urinary ET-1 excretion in either salt-resistant or salt-sensitive hypertensive patients, although they did not mention changes in plasma ET. Our data not only agree with these studies in hypertensive patients, but also demonstrate the lack of ET response to salt loading in normal subjects.

The vascular endothelium produces various vasoactive substances such as prostacyclin, nitric oxide and endothelin. Recently, AM has been added to the list of endothelium-derived hormones, because the cultured endothelial cells have been shown to synthesize AM and the vascular wall has been found to express the mRNA of AM [3]. Both AM and ET are endothelium-derived peptides, but they have contrasting characteristics; AM is a potent vasodilator, while ET is a strong vasoconstrictor. In the present study, either AM or ET failed to show a response to acute and chronic salt loading in normotensive subjects and hypertensive patients. However, this does not negate the significance of these peptides in the cardiovascular system, considering that selective ET receptor antagonists

\[P < 0.05]\). As shown in Fig. 2, plasma ET-1 did not differ among the three groups or between the low- and high-salt periods. Again, two-way analysis of variance showed significant group differences in plasma AM \((F = 3.42, P < 0.05)\), and when the normotensive group was compared with the two hypertensive groups using the contrast method, plasma AM was significantly higher in hypertensive groups than in normotensive subjects \((F = 5.93, P < 0.025)\). However, the levels did not change between low and high salt intake in any group.

\[\text{DISCUSSION}\]

\[\text{The present study investigated, for the first time, the effects of acute and chronic salt loading on plasma levels of AM in normotensive subjects and hypertensive patients. Plasma AM was higher in hypertensive patients than in normotensive subjects as reported previously [5]. However, the level was not affected by acute or chronic salt loading either in normotensive subjects or hypertensive patients. Although blood pressure rose in SS patients during high salt intake, plasma AM was unchanged between low and high salt intake. Therefore, the increased plasma AM level is not likely to be explained by a simple response to high blood pressure. Indeed, there is no correlation between blood pressure and plasma AM in this study or the previous study [5]. Because the saline infusion study lacks placebo experiments, the influence of factors other than salt loading cannot be excluded. However, considering that plasma AM does not show diurnal variations or changes during exercise either in normotensive or hypertensive subjects [13], and that PRA, PAC and ANP were markedly changed after the saline infusion, it can be said that plasma AM does not change even when other cardiovascular hormones are modified by acute saline infusion.}\]

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\[\begin{array}{cccc}
\text{Table 2. Response to saline infusion in normotensive and hypertensive subjects. Data are means±SEM. Statistical significance: } & \text{Normotensives} & \text{Hypertensives} \\
\text{Variable} & \text{(n=9)} & \text{(n=11)} & \\
\hline
\text{Heart rate (beats/min)} & 65±3 & 66±2 & 60±3 & 61±2 \\
\text{Systolic blood pressure (mmHg)} & 114±3 & 113±3 & 153±4 & 151±4 \\
\text{Diastolic blood pressure (mmHg)} & 72±3 & 74±2 & 94±3 & 93±3 \\
\text{Plasma Na⁺ (mmol/l)} & 146±1 & 147±1 & 145±1 & 147±1 \\
\text{Plasma K⁺ (mmol/l)} & 4.2±0.1 & 3.6±0.1 & 4.2±0.1 & 3.7±0.1 \\
\text{PRA (ng/h·ml⁻¹)} & 1.8±0.3 & 0.7±0.1 & 1.4±0.3 & 0.8±0.1 \\
\text{PAC (pg/ml)} & 92±14 & 35±6 & 102±20 & 45±6 \\
\text{Plasma ANP (pg/ml)} & 19±3 & 29±4 & 28±5 & 46±7 \\
\text{Plasma ET-1 (pg/ml)} & 2.1±0.1 & 2.2±0.2 & 2.4±0.2 & 2.1±0.1 \\
\text{Plasma AM (fmol/ml)} & 2.4±0.2 & 2.4±0.1 & 3.0±0.1 & 2.9±0.2 \\
\end{array}\]
Table 3. General characteristics of the subjects in the dietary salt load study. Data are means ± SEM. Statistical significance:

*P < 0.001 compared with the normotensive group.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normotensives (n = 7)</th>
<th>Salt-resistant hypertensives (n = 13)</th>
<th>Salt-sensitive hypertensives (n = 10)</th>
</tr>
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<tr>
<td>Age (years)</td>
<td>53 ± 4</td>
<td>55 ± 3</td>
<td>54 ± 3</td>
</tr>
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<td>4/6</td>
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<tr>
<td>Body weight (kg)</td>
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<td>59 ± 2</td>
<td>58 ± 3</td>
</tr>
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<td>Body mass index (kg/m²)</td>
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<td>23.2 ± 0.6</td>
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<td>Systolic blood pressure (mmHg)</td>
<td>136 ± 3</td>
<td>166 ± 3*</td>
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<td>Diastolic blood pressure (mmHg)</td>
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<td>100 ± 2*</td>
<td>99 ± 2*</td>
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<td>Heart rate (beats/min)</td>
<td>68 ± 2</td>
<td>67 ± 2</td>
<td>67 ± 2</td>
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Table 4. Response to low- and high-salt diet in normotensive subjects and salt-resistant and salt-sensitive hypertensive patients. Data are means ± SEM. Statistical significance: **P < 0.01, ***P < 0.001 compared with the normotensive group; *P < 0.05 compared with the salt-resistant hypertensive group; **P < 0.01, ***P < 0.001 compared with the low-salt period.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normotensives (n = 7)</th>
<th>Salt-resistant hypertensives (n = 13)</th>
<th>Salt-sensitive hypertensives (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (kg)</td>
<td>56.8 ± 2.8</td>
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<td>Heart rate (beats/min)</td>
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<td>62 ± 3</td>
<td>60 ± 2</td>
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<td>Systolic blood pressure (mmHg)</td>
<td>114 ± 3</td>
<td>146 ± 2††</td>
<td>137 ± 2††</td>
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<tr>
<td>Diastolic blood pressure (mmHg)</td>
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<td>92 ± 2††</td>
<td>86 ± 2††</td>
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<td>Plasma Na⁺ (mmol/l)</td>
<td>147 ± 1</td>
<td>144 ± 1</td>
<td>145 ± 1</td>
</tr>
<tr>
<td>Plasma K⁺ (mmol/l)</td>
<td>4.5 ± 0.1</td>
<td>4.3 ± 0.1</td>
<td>4.1 ± 0.1</td>
</tr>
<tr>
<td>PRA (ng h⁻¹ ml⁻¹)</td>
<td>3.0 ± 0.8</td>
<td>3.5 ± 0.6</td>
<td>1.1 ± 0.2†</td>
</tr>
<tr>
<td>PAC (pg/ml)</td>
<td>230 ± 39</td>
<td>227 ± 30</td>
<td>177 ± 35</td>
</tr>
<tr>
<td>Plasma ANP (pg/ml)</td>
<td>10 ± 1</td>
<td>11 ± 2†</td>
<td>13 ± 1†</td>
</tr>
<tr>
<td>Plasma ET-I (pg/ml)</td>
<td>2.2 ± 0.2</td>
<td>2.4 ± 0.2†</td>
<td>2.5 ± 0.2†</td>
</tr>
<tr>
<td>Plasma AM (fmol/ml)</td>
<td>2.3 ± 0.2</td>
<td>3.1 ± 0.2†</td>
<td>2.8 ± 0.1†</td>
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<tr>
<td>Urinary Na⁺ excretion (mmol/day)</td>
<td>22 ± 2</td>
<td>24 ± 1†</td>
<td>23 ± 2†</td>
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<tr>
<td>Urinary K⁺ excretion (mmol/day)</td>
<td>42 ± 3</td>
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</tbody>
</table>

Fig. 2. Plasma levels of ET-I and AM in normotensive subjects and salt-resistant and salt-sensitive patients with essential hypertension on a low- or a high-salt diet. LS, low-salt period; HS, high-salt period; NT, normotensive subjects; SR, salt-resistant hypertensive patients; SS, salt-sensitive hypertensive patients.

Salt load and adrenomedullin

have been shown to lower blood pressure in hypertensive rats [20-22] and ET is also assumed to be involved in the pathogenesis of vascular hypertrophy [23]. With regard to AM as well, recent studies have demonstrated that this peptide inhibits migration and proliferation of vascular smooth muscle cells [24, 25]. Future development of specific antagonists or gene targeting studies may reveal the significance of AM in the cardiovascular system.

Although a consensus has not yet been reached regarding the plasma ET in hypertensive patients, it has been reported that the level is increased in malignant hypertension in rats [17]. In addition, plasma ET has been shown to be increased in heart failure, renal failure and other cardiovascular disorders in which the vascular endothelium is considerably injured [26]. Plasma AM is also markedly increased in heart or renal failure [5, 6]. Thus, it is speculated that production of AM and ET is increased when the endothelium is injured and these endothelium-derived peptides play a role in the process of vascular lesion formation.

In conclusion, the present study indicates that the circulating level of AM is not changed by either acute or chronic salt loading in normotensive subjects and patients with essential hypertension.

ACKNOWLEDGMENTS

This work was supported by the Fugaku Trust for Medicinal Research and grants from the Science...
and Technology Agency (Encourage System of C.O.E.), the Ministry of Health and Welfare, and the Human Science Foundation of Japan. We thank Kazuhiro Iwasaki and Yoko Saito for technical assistance.

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