Atrial Natriuretic Peptide in Non-modulating Essential Hypertension

Riccardo Leonetti Luparini, Claudio Ferri, Anna Santucci, and Francesco Balsano

To evaluate the atrial natriuretic peptide response to angiotensin II (Ang II) infusion in non-modulating hypertension, we studied 31 men with essential hypertension. These patients were subdivided into groups of low renin patients (n=8), non-modulators (n=11), and modulators (n=12) according to their renin profile and ability to modulate renin and aldosterone responses to a graded infusion of Ang II (1.0 and 3.0 ng/kg per minute) on a low Na+ intake (10 mmol Na+ per day). During basal conditions, plasma atrial natriuretic peptide was higher (p<0.05) in low renin patients (1634 ± 2.67 fmol/mL) than in both modulators (10.59 ± 4.29 fmol/mL) and non-modulators (9.85 ± 2.64 fmol/mL). During Ang II infusion, plasma atrial natriuretic peptide significantly increased in both low renin (27.67 ± 2.61 fmol/mL at 60 minutes, p<0.01) and modulating (20.67 ± 3.07 fmol/mL at 60 minutes, p<0.05) patients, whereas it did not change in non-modulators (13.94 ± 4.39 fmol/mL, NS). After 5 days on a high sodium intake (200 mmol Na+ per day), plasma atrial natriuretic peptide rose in modulating (20.61 ± 2.13 fmol/mL, p<0.01 versus low sodium intake), non-modulating (20.11 ± 6.48 fmol/mL, p<0.01 versus low sodium intake), and low renin (26.13 ± 3.81 fmol/mL, p<0.001 versus low sodium intake) hypertensive patients. When the Ang II infusion was repeated with a high sodium intake, plasma atrial natriuretic peptide increased again in low renin and modulating patients, whereas it did not change in non-modulators. Therefore, these data indicate that an impaired atrial natriuretic peptide responsiveness to Ang II that is not dependent on Na+ intake may represent another characteristic of the non-modulating phenotype. (Hypertension 1993;21:803-809)

Key words: hypertension, non-modulating • sodium • angiotensin II • atrial natriuretic peptide • renin • aldosterone

The term "non-modulators" was coined in the 1970s to identify a subgroup of essential hypertensive patients. At first, Hollenberg and Merrill1 indicated the lack of renal blood flow increase in response to dietary salt loading in some essential hypertensive patients. Then, an impaired aldosterone response to acute volume depletion was described by Williams et al2 in a similar subgroup of hypertensive patients. At present, other characteristics of non-modulating hypertension have been described (see References 3 and 4 for review), including an increased blood pressure sensitivity to dietary salt intake5 and decreased 1) renal blood flow response to both angiotensin II (Ang II) and sodium loading,5,6 2) aldosterone response to Ang II,6 3) renin suppression after both Ang II and saline infusions,8 and 4) sodium excretion after sodium loading.9 Because an impaired responsiveness to Ang II of the adrenal gland and kidney seems to determine the hormonal and hemodynamic characteristics of non-modulators, a tissue refractoriness to Ang II has been suggested as the \textit{primum movens} of non-modulating hypertension (see References 3 and 4 for review).

As is well known, atrial natriuretic peptide (ANP) is a natriuretic, diuretic, and vasorelaxant cardiac hormone (see Reference 10 for review) synthesized and secreted by atrial myocytes in response to an increase in atrial stretch or wall tension.10,11 Moreover, neurohormonal factors,12-20 the rate of atrial contraction,21 myocardial ischemia,22 and hypoxia23 can affect ANP release from the atria. An increase of plasma ANP levels has been described after Ang II infusion in both human and animal models,10,11,15,17 but neither ANP behavior nor the ANP response to Ang II in non-modulating essential hypertension has previously been investigated.

The aim of the present study was to verify the hypothesis that an alteration in ANP responsiveness to Ang II may represent another hormonal characteristic of non-modulating essential hypertension. Because sodium intake strongly influences the hormonal responses to Ang II infusion in non-modulators, Ang II-induced changes in ANP levels were evaluated during different Na+ intakes.

Methods

Patients

The study protocol was accepted by the Ethics Committee of the Andrea Cesalpino Foundation. Informed written consent to take part in this study was requested of all eligible hypertensive patients.

Forty-three mild to moderate male patients with essential hypertension participated in the study. The following criteria were used to select patients: age,
between 30 and 60 years; sex, male; body mass index, <26 and >18 kg/m²; supine diastolic blood pressure, between 95 and 114 mm Hg at the screening visit; serum creatinine, <100 µmol/L; and normality of both 99mTc-diethylenetriamine pentaacetic acid and [131I]-iodohippurate scintograms, absence of proteinuria, and normality of microalbuminuria. No patient had cardio-vascular alterations as evaluated by clinical and ultrasond studies. Patients with alcohol or smoking behavior were excluded from the study. Secondary forms of hypertension were excluded by clinical and laboratory assessments. Because ANP regulation can be influenced by a severe autonomic neuropathy, this latter was excluded by clinical tests according to Ewing's criteria.

A normal glucose tolerance was proved by the following criteria: fasting glucose levels <6.7 mmol/L, fructosamine levels <280 µmol/L, absence of glycosuria, and normal plasma glucose response to orally administered glucose (75 g). Patients who showed fasting insulin levels >110 pmol/L or abnormal insulin response to orally administered glucose (75 g) were excluded from the study. All patients had normal serum cholesterol and triglyceride levels.

During this part of the study, all patients were on a normocaloric diet with constant sodium intake (120 mmol sodium chloride daily) and took no medications for 1 month. Each patient was blind to his NaCl intake, which was achieved by a daily supplement of two capsules given twice a week. Two hypertensive patients had a diastolic blood pressure <95 mm Hg and were screened out. The remaining 37 patients were considered compliant when sodium and chloride excretions two times a week. Patients were advised to drink 1.5 L water per day. Compliance was assessed by measuring 24-hour urinary sodium and chloride excretions. All patients were compliant. However, at the end of this period, two hypertensive patients had a diastolic blood pressure <95 mm Hg and were screened out. The remaining 41 patients were hospitalized.

After hospitalization, all patients continued the normal sodium diet for another week. During this period, urinary NaCl excretion was controlled each day. All patients were considered compliant (i.e., had sodium and chloride excretions of >80 and <130 mmol/day, respectively). After 1 month of constant sodium intake, all patients were considered compliant. However, at the end of this period, two hypertensive patients had a diastolic blood pressure <95 mm Hg and were screened out. The remaining 41 patients were hospitalized.

After hospitalization, all patients continued the normal sodium diet for another week. During this period, urinary NaCl excretion was controlled each day. All patients were considered compliant (i.e., had sodium and chloride excretions of >80 and <130 mmol/day, respectively), but four patients who showed a supine diastolic blood pressure <95 mm Hg were screened out. A low sodium diet (10 mmol NaCl per day) was given to the remaining 37 patients for 10 days. The low sodium intake was achieved by continuing the previous diet but substituting the daily supplement of two capsules given twice a day with identical capsules containing placebo (meal). Compliance to the diet was verified by measuring each day both sodium and chloride excretions. Two patients with a 24-hour urinary sodium excretion >20 mmol/day and four patients with a diastolic blood pressure <95 mm Hg after the 10-day period of low sodium intake were screened out. Thus, 31 patients participated in the following part of the study.

A group of seven normotensive men without hypertensive heredity served as control subjects. Both inclusion criteria and study conditions were identical to those used for hypertensive patients.

In both hypertensive and normotensive individuals, hypertensive heredity was evaluated with a questionnaire and by consulting each family doctor. Hypertensive heredity was defined as the presence of at least one first-degree relative affected by essential hypertension.

p-Aminohippurate Infusion

On the morning of the study, blood samples for plasma renin activity (PRA) were taken with patients in a supine position and then again after 1 hour in an upright position. After blood collection, renal plasma flow was assessed in both hypertensive patients and control subjects according to the method described by Ryseth et al. Briefly, at 9 AM, after 1 hour in a supine position, patients had an intravenous catheter installed in the right arm. A control blood sample was obtained, and p-aminohippurate (PAH) (bolus injection of 8 mg/kg) was infused. A constant infusion of PAH (12 mg/min) was started immediately. Infusion rates were controlled by a peristaltic pump (Abbot/Shaw Life Care Pump, Chicago). PAH clearance was calculated from the plasma concentrations and infusion rate and was corrected for body surface area.

Angiotensin II Infusion

On the same morning of PRA evaluation, after 1 hour in the supine position (at 9 AM), both hypertensive patients and normotensive subjects received the loading doses of PAH. After basal PAH clearance was measured, Ang II amide (Hypertensin, CIBA-GEIGY Corp., Pharmaceutical Division, Summit, N.J.) was infused at successive doses of 1.0 and 3.0 ng/kg per minute for 30 minutes each using the above-mentioned peristaltic pump. The constant infusion of PAH continued throughout the Ang II infusion.

After Ang II had been infused on a low sodium diet, the peptide was infused again, according to the same protocol, after 5 days on a high sodium intake (200 mmol Na⁺ per day). The high sodium intake was achieved by continuing the previous diet but substituting the daily supplement of two capsules given twice a day with identical capsules containing a total amount of 190 mmol NaCl. Again, compliance to the diet was assessed by measuring each day 24-hour urinary sodium and chloride excretions. All patients were compliant with the diet (i.e., had urinary sodium and chloride excretions >190 mmol/day).

Blood and Urine Samples, Blood Pressure Measurements, and Laboratory Procedures

During both of the Ang II infusions, blood samples were drawn at 0, 30, and 60 minutes and analyzed for PRA, aldosterone, ANP, sodium, and potassium. Blood samples were collected by a heparin lock catheter system installed in a vein in the left forearm.

PRA and aldosterone were assayed by radioimmunoassay (Sorin Biomedica, Vercelli, Italy). Plasma ANP was evaluated by radioimmunoassay as described elsewhere. Before the two infusions of Ang II were started, patients were asked to void at 8 AM to complete the previous 24-hour collection and to make a 1-hour collection before each infusion was started. At the end of the infusion, another urine collection was made.
Sodium and potassium excretions were evaluated by the use of standard laboratory techniques.

During the entire study, blood pressure was taken by reseachers who did not know the diet followed by each patient, by using a standard Riva-Rocci sphygmonometer and a stethoscope. Blood pressure was taken after patients had been supine for 15 minutes; the first measurement was not considered, and the average of the following three measures, taken at 5-minute intervals, was taken as the measurement. Systolic blood pressure was taken at Korotkoff phase 1; diastolic blood pressure was taken at Korotkoff phase 5.

**Definition of Low Renin Hypertensive and Non-modulating Hypertensive Patients**

Low renin patients were identified on the basis of a PRA response to upright posture (1 hour of active orthostatism) after the 10-day period on a 10-mmol sodium intake that was <0.28 ng angiotensin I per liter per second.

According to Hollenberg’s criteria (see References 3 and 4), in the hypertensive patients having a normal to high renin activity, non-modulation was defined as the simultaneous presence of the following three characteristics: 1) an aldosterone increase <410 pmol/L in response to Ang II infusion during a low sodium diet (10 mmol Na+ per day),2) a PAH clearance decrement <120 mL/min per 1.73 m² in response to Ang II infusion during a high sodium diet (200 mmol Na+ per day),3.4.6.8 and 3) a PRA decrement <0.28 ng angiotensin I per liter per second in response to Ang II infusion during a low sodium diet (10 mmol Na+ per day).2.3.4

**Statistical Analysis**

All data were collected using the database SUPERCALC-3 (Computer Associates Inc., San Jose, Calif.). Statistical evaluations were made with software for biomedical statistics (Primer of Biostatistics, New York, McGraw-Hill Book Co.) and the use of a PC Olivetti M380 (Ivrea, Italy).

Data are presented as mean±SD. Statistical significance was considered at a value of p<0.05. Differences among the examined groups were tested for significance by one-way analysis of variance followed by Newman-Keuls test for pairwise comparisons. For multiple comparisons, we used analysis of variance with Bonferroni’s test.

**Results**

**Baseline Comparison**

All the normotensive subjects had a normal PRA. In the hypertensive group, eight patients had low renin activity, and in 23 it was normal to high (i.e., PRA >0.28 ng angiotensin I per liter per second after 1 hour of upright posture on a 10 mmol sodium intake). The group of 23 patients having normal to high renin activity was further divided into non-modulators (n=11) and modulators (n=12). As shown in Table 1, before the administration of Ang II, there were no differences in the evaluated clinical parameters, except for the prevalence of familial hypertension in the non-modulating subgroup and the presence of significantly higher (p<0.05) fasting insulin levels in the same group compared with the others. Although not significant, body mass index and serum triglyceride and cholesterol levels also were slightly higher in non-modulators than in the other hypertensive groups and in normotensive subjects.

**Renal and Hormonal Responses to Angiotensin II**

**Low sodium intake.** When patients were on a low sodium intake, PAH clearances were similar in all groups both before and during Ang II infusion (Table 2).

After Ang II infusion, PRA levels decreased in both nonmoderative subjects and modulating essential hypertensive patients (Figure 1). However, PRA levels remained unchanged in non-modulators (from 0.88±0.12 to 0.78±0.07 ng angiotensin per liter per second at 60 minutes). Also, plasma aldosterone levels failed to increase in response to Ang II infusion in the same patients (from 372.8±38.3 to 484.1±119 pmol/L, NS).
Before the Ang II infusion was started, plasma ANP levels were higher \( (p<0.05) \) in low renin patients \((16.34 \pm 2.67 \text{ fmol/mL})\) than in modulators \((10.59 \pm 4.29 \text{ fmol/mL})\), non-modulators \((9.85 \pm 2.64 \text{ fmol/mL})\), and normotensive subjects \((9.88 \pm 2.05 \text{ fmol/mL})\). Plasma ANP levels increased after Ang II infusion in both low renin \((27.67 \pm 2.61 \text{ fmol/mL at 60 minutes}, p<0.01)\) and modulating \((20.36 \pm 3.07 \text{ fmol/mL at 60 minutes, } p<0.05)\) patients (Figure 1). However, Ang II was not able to induce any change in ANP levels in non-modulators \((13.94 \pm 4.39 \text{ fmol/mL, NS})\) (Figure 1). Compared with non-modulators, significantly higher ANP levels were observed in low renin patients \((p<0.01 \text{ at 30 and 60 minutes})\), modulators \((p<0.05 \text{ at 60 minutes})\), and normotensive subjects \((p<0.05 \text{ at 60 minutes})\).

**High sodium intake.** Compared with the low Na\(^+\) intake, blood pressure increased at the end of the high Na\(^+\) intake period in low renin patients (systolic: from 165.1±3.5 to 175.4±4.0 mm Hg, \(p<0.05\); diastolic: from 98.2±1.5 to 105.5±3.1 mm Hg, \(p<0.05\)) and non-modulators (systolic: from 168.5±3.2 to 170.1±5.2 mm Hg, \(p<0.05\)).

**TABLE 2. \( p \)-Aminohippurate Clearance Responses to Angiotensin II**

<table>
<thead>
<tr>
<th>( p )-Aminohippurate clearance ( [(\text{mL/min})/1.73 \text{ m}^2] )</th>
<th>Hypertensive</th>
<th>Low renin ((n=8))</th>
<th>Non-modulators ((n=11))</th>
<th>Modulators ((n=12))</th>
<th>Normotensive ((n=7))</th>
</tr>
</thead>
<tbody>
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<td>Baseline</td>
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<td>563±42</td>
<td>541±91</td>
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<td>30 minutes</td>
<td>532±41</td>
<td>549±46</td>
<td>504±95</td>
<td>510±65</td>
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<td>60 minutes</td>
<td>512±36</td>
<td>536±55</td>
<td>533±76</td>
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<tr>
<td>High sodium intake ( (200 \text{ mmol Na}^+ \text{ per day}) )</td>
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<td>573±29</td>
<td>611±73</td>
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<tr>
<td>60 minutes</td>
<td>470±33( ^* )</td>
<td>505±51( ^{+} )</td>
<td>448±41( ^* )</td>
<td>411±43( ^{+} )</td>
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</tr>
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</table>

\( ^{+} p<0.01, ^{+} p<0.05, ^{+} p<0.001 \) vs. baseline.

**FIGURE 1.** Line graphs show effects of graded infusion of angiotensin II during low Na\(^+\) intake \( (10 \text{ mmol Na}^+ \text{ per day}) \) on plasma renin activity (top left panel), aldosterone (right panel), and atrial natriuretic peptide (bottom left panel). Hypertensive patients were divided into low renin \((n=8)\), non-modulating \((n=11)\), and modulating \((n=12)\) essential hypertension groups. Normotensive subjects, \( n=7 \). Statistical significance is shown for each group versus time 0 and (into the dotted lines) for differences among groups.
Atrial Peptide in Non-modulation

Leonetti Luparini et al

FIGURE 2. Line graphs show effects of graded infusion of angiotensin II during high Na⁺ intake (200 mmol Na⁺ per day) on plasma renin activity (top left panel), aldosterone (right panel), and atrial natriuretic peptide (bottom left panel). Hypertensive patients were divided into low renin (n=8), non-modulating (n=11), and modulating (n=12) essential hypertension groups. Normotensive subjects, n=7. Statistical significance is shown for each group versus time 0 and (into the dotted lines) for differences among groups.

NS; diastolic: from 100.2±3.0 to 106.2±2.4 mmHg, p<0.05), whereas it did not significantly change in modulators (systolic: from 170.4±4.6 to 170.5±4.8 mmHg, NS; diastolic: from 100.3±2.5 to 101.2±4.5 mmHg, NS) and in normotensive control subjects (systolic: from 125.0±5.1 to 129.5±3.5 mmHg, NS; diastolic: from 78.5±3.0 to 81.5±3.0 mm Hg, NS).

Analysis of the data obtained after a 5-day period of dietary Na⁺ load showed the expected defect in modulating renal plasma flow in non-modulating hypertensive patients (Table 2). In fact, PAH clearances were not increased by the high Na⁺ intake in these patients. Furthermore, on a high Na⁺ intake, non-modulators had a significantly (p<0.01) smaller decrease of PAH clearance with Ang II infusion than the modulating patients (p<0.001). At variance with non-modulators, low renin hypertensive patients and normotensive subjects showed a normal response to both dietary Na⁺ loading and Ang II infusion (Table 2).

With regard to hormonal behavior, PRA levels were suppressed after the 5-day period on a high Na⁺ intake in all patients, and slight further decrements were observed during angiotensin infusion in all groups (Figure 2).

Plasma aldosterone levels increased with angiotensin infusion in modulators (from 232.4±58.0 to 471.1±140.9 pmol/L at 60 minutes, p<0.001) and, to a lesser extent, in non-modulators (from 228.4±21.8 to 351.0±20.5 pmol/L, p<0.05). Baseline plasma aldosterone levels were similar in these two groups, whereas a significant difference was found at 60 minutes (p<0.05). A significant aldosterone increase was also observed in low renin patients (from 175.7±75.3 to 446.0±45.6 pmol/L, p<0.01) and normotensive subjects (from 229.7±33.7 to 405.8±81.0 pmol/L, p<0.05). During Ang II infusion, circulating aldosterone levels were higher in low renin patients and modulators than in non-modulators (p<0.05 at 60 minutes) (Figure 2).

The high Na⁺ intake increased plasma ANP levels in modulators (p<0.01), non-modulators (p<0.01), low renin patients (p<0.001), and normotensive subjects (p<0.01). Also, plasma ANP was higher (p<0.05) in low renin patients than in the other two hypertensive groups and in normotensive subjects. Despite the evident increase in plasma ANP after the dietary Na⁺ load, the cardiac hormone did not increase with Ang II infusion in non-modulators (from 20.11±6.48 to 24.59±11.08 fmol/mL at 60 minutes, NS). However, a significant Ang II–induced increase in plasma ANP was observed in both the remaining hypertensive groups and the control group (Figure 2).

Discussion

ANP promotes natriuresis through its effect on the kidney and on aldosterone secretion.10,28–32 Because non-modulating essential hypertensive patients have
both a reduced aldosterone response to Ang II and a decreased ability to eliminate a sodium load, it was conceivable to speculate that ANP might participate in determining those abnormalities. As also shown in previous studies,33,34 in this study plasma ANP levels were raised in low renin patients. However, no differences were found between non-modulating and modulating essential hypertensive patients. Nevertheless, plasma ANP increased after the Ang II infusion in modulators, low renin patients, and normotensive control subjects, whereas non-modulators showed a blunted ANP response to the infused angiotensin. Furthermore, although non-modulating hypertensive patients had a marked increment in plasma ANP levels after a 5-day period of dietary Na+ load, the Ang II–induced ANP increase was not significant in these patients during both the low and high Na+ diets. These findings suggest that in non-modulators the abnormality in ANP regulation mainly depends on the cardiac responsiveness to Ang II (the ANP response to short-term dietary Na+ load being conserved).

It is known a target tissue refractoriness to Ang II has been suggested as the primary cause of non-modulating essential hypertension. Ang II has been reported to promote ANP release in humans.16,17 This effect could be related to the rise of arterial pressure and to the consequent increase in atrial stretch. Nevertheless, pressor doses of Ang II also have been reported to raise plasma ANP levels in humans.16,17 A blood pressure–independent Ang II–mediated ANP release has been shown in isolated rat atria.15 In agreement with these findings, small blood pressure changes were observed in our patients during Ang II infusion, with no differences among the groups. Thus, it is possible that a primary abnormality in the Ang II–induced ANP secretion from the cardiac myocytes may have determined the reduced ANP response to Ang II infusion such as the one observed in non-modulators.

However, in contrast with the predominant role of a target tissue refractoriness to Ang II in the pathogenesis of non-modulating essential hypertension, other abnormalities have been recently described in non-modulators, such as elevated sodium–lithium countertransport15 and increased plasma norepinephrine and dopamine levels.36,37 The presence of these abnormalities suggests that the non-modulating phenotype is a multifaceted syndrome, involving different blood pressure–regulating mechanisms. Insulin levels were higher (p<0.05) in our non-modulating patients than in the other hypertensive groups. This finding is in agreement with some previous data suggesting a high prevalence of disturbances in glucose metabolism in non-modulators and supports the hypothesis that the non-modulating phenotype is due to different genetic traits predisposing individuals to hypertension. Similarly, the presence of disturbances in glucose metabolism suggests that hypertension itself represents only one of the multiple risk factors evoked by different genes involved in the non-modulating phenotype.

As is well known, renin suppression after infusion of Ang II1 and saline5,26 is reduced in non-modulators. A possible increase in intrarenal Ang II formation,1,26 as well as a suggested defect in both volume- and sodium-sensitive intrarenal receptors,8 has been indicated as the primary defect leading to the lack of renin suppression.

The restoration of the renin response to Ang II after 3 days of treatment with captopril26 strongly supports the existence of a defect in the renal responsiveness to Ang II. In contrast with this hypothesis, the renin response to saline infusion is not completely restored by 3 days of treatment with enalapril,26 suggesting alternative explanations for the renin behavior. In our opinion, the reduced ANP increase after Ang II infusion could be taken into consideration. The effect of ANP on renin release is still a point of debate (see Reference 10 for review), because controversial data have been obtained in both animals and humans. In fact, ANP has been reported to inhibit25–27 or to have no effect on28–31 both in vivo and in vitro renin secretion. However, considering the possibility that ANP might reduce renin release in vivo,30–32 a blunted Ang II–related ANP increase could play some role in the altered renin response of non-modulators. However, this hypothesis needs to be confirmed by the direct evaluation of the effects of ANP infusion on renin release in non-modulators and modulators.

A limitation of the present study could be a possible misclassification of the patients. The non-modulating phenotype is characterized by 10 different hormonal and hemodynamic characteristics (see References 3 and 4 for review). The most sensitive and specific ones that allow the identification of non-modulators are represented by the criteria we used.34,42 Furthermore, although the use of only one of the procedures seems to be sufficient to discriminate modulators from non-modulators,42 to prevent misclassification we considered as non-modulators only patients showing the simultaneous presence of three positive criteria. Also, because the level of sodium intake is basic for the identification of non-modulating hypertension, sodium intake was carefully controlled during the entire study. Moreover, because the non-modulating phenotype seems to be clearly inheritable22 and normotensive subjects with a parental history of hypertension may show the same characteristics of non-modulating hypertensive patients,43 normotensive subjects with hypertensive heredity were excluded from the study, such as all the potentially confounding factors in the identification of the non-modulating phenotype.

In conclusion, plasma ANP levels during dietary Na+ restriction were similar in non-modulators and modulators. The ANP response to 5 days of dietary Na+ load was also normal in non-modulators. However, non-modulating patients failed to increase ANP levels in response to Ang II infusion during both the low and high Na+ intake. The altered ability of non-modulators to suppress PRA after Ang II infusion could be related to an alteration in Ang II–related ANP secretion.

References

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