Plasma atrial natriuretic peptide: its relationship to changes in sodium intake, plasma renin activity and aldosterone in man

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Summary

1. Plasma levels of immunoreactive atrial natriuretic peptide (IrANP), plasma renin activity, aldosterone and vasopressin were measured in 11 normotensive subjects on a low (10 mmol/day), a normal (150 mmol/day) and a high (350 mmol/day) sodium intake.

2. Plasma levels of IrANP increased significantly with increasing dietary sodium intake with levels (means ± SD) of 3.9 ± 2.1 pg/ml on the fifth day of the low sodium diet, 6.1 ± 3.4 pg/ml on the fifth day of the normal sodium diet and 11.4 ± 4.6 pg/ml on the fifth day of the high sodium diet.

3. Plasma renin activity and aldosterone decreased significantly with increasing sodium intake whereas plasma vasopressin was highest on the high sodium intake.

4. These results suggest that the atrial peptides may be a new and important component in the overall control of sodium and water balance during increased sodium intake.

Key words: aldosterone, atrial natriuretic peptide, sodium intake, vasopressin.

Abbreviation: IrANP, immunoreactive atrial natriuretic peptide.

Introduction

Recently, a family of peptides with potent natriuretic and vascular relaxant effects has been isolated from mammalian atrial tissue (see [1-3] for reviews). In animals [4, 5] and man [6-9] it has now been demonstrated that expansion of the extracellular fluid volume is associated with increased circulating levels of immunoreactive atrial natriuretic peptides (IrANP). Furthermore, bolus injections or infusions of the human atrial natriuretic peptides into normal subjects [10-12] leads to a marked natriuretic and diuretic effect. These observations in conjunction with the presence of specific atrial peptide binding sites in renal tissue [13-16] suggest that the atrial peptides may be involved in the control of sodium and water balance. However, in man, physiological changes in extracellular volume usually result from changes in dietary sodium intake. We therefore investigated the effect of changes in dietary sodium intake on the plasma levels of IrANP in a randomized study in young adult normotensive subjects. Plasma renin activity, aldosterone and vasopressin were also measured in an attempt to clarify the relationship between these and the atrial peptides in the maintenance of sodium balance during changes in dietary sodium intake.

Materials and methods

Subjects and protocol

Eleven normotensive subjects aged 20–24 years (five males, six females) were randomly allocated to three controlled sodium intakes. Measurements were made on the fifth day of a 10 mmol/day sodium diet, the fifth day of a normal sodium diet [10 mmol/day plus 14 Slow sodium tablets/day (CIBA; 10 mmol/tablet)] and on the fifth day of a
high sodium diet (10 mmol/day plus 34 Slow sodium tablets/day). All food and drink was supplied by the metabolic kitchen; throughout the study subjects went about their usual activities, but were discouraged from taking vigorous exercise. On the last day of every diet 24 h urine collections were made for measurement of sodium, potassium and creatinine excretion. On the fifth day of each diet, blood was taken from the antecubital fossa in subjects who had been sitting upright for 10–15 min between 09.00 and 12.00 hours. All subjects were of normal body build and none was obese. Informed consent was obtained. No subject was on any drug treatment and none of the female subjects was on the oral contraceptive pill. Supine blood pressure was measured with an ultrasound sphygmomanometer (Arteriosonde, Roche) with automatic recorder. Supine blood pressure was taken as the mean value of five readings at 1–2 min intervals.

Blood collection and assay methods

Blood was collected into tubes containing ethylenediaminetetra-acetic acid (potassium salt) and centrifuged immediately at 4°C. For measurement of IrANP, the plasma was removed, kept on ice and extracted immediately on Sep-pak cartridges as described previously [6].

Plasma renin activity [17], aldosterone [18] and arginine vasopressin [19] were measured by radio-immunoassay as described previously. Plasma and urinary electrolytes were measured by flame photometry.

Statistics

All results are given as means ± SD. Both paired Student's t-tests and Wilcoxon signed rank non-parametric tests were used for statistical analysis and \( P < 0.05 \) in both tests was taken as statistically significant. Spearman rank correlation was used to analyse the degree of association between IrANP and other variables. All \( P \) values are two-tailed.

Results

On the fifth day of the low sodium diet mean plasma IrANP was 3.9 ± 2.1 pg/ml with a urinary sodium excretion of 22.9 ± 8.1 mmol/24 h. On the fifth day of the normal sodium diet mean plasma IrANP was 6.1 ± 3.4 pg/ml with a urinary sodium excretion of 112.1 ± 46.2 mmol/24 h and on the fifth day of the high sodium diet mean plasma IrANP had increased to 11.4 ± 4.6 pg/ml with a urinary sodium excretion of 296.8 ± 82.9 mmol/24 h. Individual values on the low, normal and high sodium intake are shown in Fig. 1.

In the majority of, but not in all, subjects there was a consistent increase in the plasma levels of IrANP from the low sodium to the high sodium diet. On the high sodium intake, there was a small increase in plasma sodium and a decrease in packed cell volume in comparison with the values on the normal or low sodium intake. There was also a small increase in plasma vasopressin with increasing sodium intake. There were the expected changes in both plasma renin activity and plasma aldosterone, furthermore, urinary volume and creatinine measurements indicate a good compliance for the completeness of collections and urinary sodium changed in accordance with the dietary sodium intake. Full details of these measurements on the fifth day of each diet are shown in Table 1.

A detailed correlation analysis between plasma IrANP and these other measurements was not carried out across all three diets because of intercorrelations between each of these variables on the different diets. For instance, there was a significant correlation \(( r = 0.6; \ P < 0.05)\) between plasma levels of IrANP on the high and low sodium intake. Nevertheless, when all individual values were
Plasma atrial natriuretic peptide and Na⁺ balance

**TABLE 1. Plasma and urinary measurements on the fifth day of a controlled low, normal and high sodium intake in normal subjects**

*P < 0.05; **P < 0.01; ***P < 0.005 vs high sodium intake (paired Student’s t-tests/paired Wilcoxon rank sum tests). Number of measurements 11 or as given in parentheses.

<table>
<thead>
<tr>
<th>Dietary sodium intake</th>
<th>Low</th>
<th>Normal</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>IrANP (pg/ml)</td>
<td>3.9 ± 2.1***</td>
<td>6.1 ± 3.4**</td>
<td>11.4 ± 4.6</td>
</tr>
<tr>
<td>Plasma renin activity (ng of ANG I h⁻¹ ml⁻¹)</td>
<td>6.9 ± 3.6***</td>
<td>1.9 ± 1.1*</td>
<td>0.7 ± 0.8</td>
</tr>
<tr>
<td>Plasma aldosterone (pmol/l)</td>
<td>1324.7 ± 745.7***</td>
<td>562.0 ± 404.2***</td>
<td>154.2 ± 79.8</td>
</tr>
<tr>
<td>Arginine vasopressin (μ-units/ml)</td>
<td>0.23 ± 0.15*</td>
<td>0.32 ± 0.15 *</td>
<td>0.45 ± 0.28 *</td>
</tr>
<tr>
<td>Plasma sodium (mmol/l)</td>
<td>138.1 ± 2.4*</td>
<td>139.1 ± 1.4*</td>
<td>141.3 ± 2.4</td>
</tr>
<tr>
<td>Plasma potassium (mmol/l)</td>
<td>3.9 ± 0.3</td>
<td>3.8 ± 0.3</td>
<td>3.8 ± 0.3</td>
</tr>
<tr>
<td>Plasma creatinine (μmol/l)</td>
<td>84.5 ± 14.8</td>
<td>83.7 ± 14.4</td>
<td>75.8 ± 9.6</td>
</tr>
<tr>
<td>Plasma total protein (g/l)</td>
<td>73.4 ± 5.3**</td>
<td>68.8 ± 5.0</td>
<td>67.3 ± 4.6</td>
</tr>
<tr>
<td>Packed cell volume</td>
<td>0.41 ± 0.02 (8)</td>
<td>0.40 ± 0.02* (9)</td>
<td>0.38 ± 0.04 (9)</td>
</tr>
<tr>
<td>Urinary sodium (mmol/24 h)</td>
<td>22.9 ± 8.1** (10)</td>
<td>112.1 ± 46.2** (10)</td>
<td>296.8 ± 82.9 (10)</td>
</tr>
<tr>
<td>Urinary potassium (mmol/24 h)</td>
<td>48.8 ± 16.2 (10)</td>
<td>54.9 ± 16.6 (10)</td>
<td>57.1 ± 10.9 (10)</td>
</tr>
<tr>
<td>Urinary creatinine (μmol/l)</td>
<td>11.7 ± 3.5 (10)</td>
<td>11.8 ± 3.8 (10)</td>
<td>12.6 ± 3.4 (10)</td>
</tr>
<tr>
<td>Urinary volume (litres)</td>
<td>1.39 ± 0.9</td>
<td>1.35 ± 0.5 (10)</td>
<td>1.91 ± 1.1</td>
</tr>
<tr>
<td>Lying systolic blood pressure (mmHg)</td>
<td>117.8 ± 15.4</td>
<td>120.1 ± 14.7</td>
<td>118.4 ± 14.2</td>
</tr>
<tr>
<td>Lying diastolic blood pressure (mmHg)</td>
<td>74.2 ± 10.9</td>
<td>73.7 ± 3.1</td>
<td>73.0 ± 6.8</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>67.3 ± 6.5***</td>
<td>68.5 ± 6.3</td>
<td>69.0 ± 6.4</td>
</tr>
</tbody>
</table>

**FIG. 2.** Plasma levels of IrANP vs plasma renin activity in 11 subjects on all three controlled dietary sodium intakes. Mean values for low (△), normal (△) and high (▲) sodium intake.

**FIG. 3.** Plasma levels of IrANP vs plasma aldosterone in 11 subjects on all three controlled dietary sodium intakes. Mean values for low (△), normal (△) and high (▲) sodium intake.

plotted against plasma renin activity (Fig. 2) or aldosterone (Fig. 3) there was a trend for an inverse relationship (i.e. high values of IrANP being associated with low values of plasma renin or aldosterone). By contrast there was no apparent relationship between plasma IrANP and plasma vasopressin (results not shown).

Correlation coefficients were, however, calculated between the plasma levels of IrANP and these other measurements at each of the three respective dietary intakes. On each on the three controlled sodium intakes there was no statistically significant correlation (|r| < 0.34) between plasma ANP and plasma renin activity, plasma aldosterone or vasopressin.

These results therefore clearly indicate that changes in sodium intake over a realistic physiological range induce corresponding but opposite changes in both the renin–aldosterone system and in the plasma levels of atrial natriuretic peptides.
Discussion

The present results demonstrate that, in a controlled and randomized study of sodium alteration, by the fifth day of a low, normal and high sodium intake there was a progressive increase in circulating IrANP with increases in dietary sodium intake (Fig. 1). Plasma levels of ANP increased 1.56-fold from a low (10 mmol/day) to a normal (150 mmol/day) sodium intake and approximately threefold from the low to a high (350 mmol/day) sodium intake. These observations therefore suggest that the atrial peptides could be an important factor in the excretion of sodium, particularly under conditions of high dietary sodium intake.

The mechanisms through which changes in sodium intake could influence the plasma levels of ANP are as yet unclear. The increased levels on a high sodium diet could reflect either a decrease in metabolic clearance or an increase in secretion from atrial tissue. Whilst the present study cannot distinguish between these two possibilities, it is more likely that the increased levels represent increased cardiac secretion. Several studies have suggested that increases in atrial pressure lead to release of atrial peptides [4, 5]. Although it is not clear whether increased sodium intake in man increases intra-atrial pressure, experiments have clearly demonstrated that changes in dietary sodium intake in dogs are associated with corresponding changes in atrial pressure [20, 21]. In the present study the decrease in packed cell volume and plasma total protein and the increase in body weight with increasing sodium intake (Table 1) are consistent with an increase in blood volume, which is likely to cause a rise in atrial pressure and thereby increase the release of atrial peptides. This is consistent with more recent work where a close association was found between ANP release and intra-atrial pressure after graded levels of saline infusion in normal subjects [22]. Other factors, however, could also be of potential importance in the control of ANP release from the heart (e.g. osmotic, volume and/or neuronal factors). For example, in animal experiments it has recently been demonstrated [23] that neuronal mechanisms could be important in the release of IrANP in response to volume expansion.

The increases in plasma IrANP with increasing dietary sodium intake does not necessarily imply a direct cause–effect relationship in increasing urinary sodium excretion on the higher salt intake. However, the finding of specific atrial peptide binding sites in the glomerulus and in the collecting ducts, in conjunction with the knowledge that infusion of the peptides causes a natriuresis, strongly suggests that the atrial peptides may contribute to the increased urinary sodium. This notion is strengthened by the recent demonstration that infusion of the α-human atrial natriuretic peptide in normal subjects which achieved changes in plasma levels within the physiological range increased renal sodium and water excretion [24].

The atrial peptides could also influence the excretion of sodium through their inhibitory effects on the renin–angiotensin–aldosterone system. The atrial peptides are potent inhibitors of basal and angiotensin II-induced release of aldosterone from isolated adrenal cells [25, 26], in both animal experiments [26–28] and with infusion of the human peptide in man [29, 30]. In the present study with the changes in sodium intake, high levels of circulating atrial peptides were associated with low values of plasma aldosterone and plasma renin activity (Figs. 2 and 3). Interestingly, the adrenal sensitivity to angiotensin II varies with the state of sodium balance [31], and it is possible that the changes in the plasma levels of ANP might at least in part be responsible for this change in adrenal sensitivity.

As yet, little is known about the relationship between circulating atrial peptides and antiuretic hormone. The atrial peptides inhibit vasopressin-stimulated adenylate cyclase [32] and thereby could potentially block some or all of the renal actions of vasopressin. Atrial peptides also inhibited the actions of vasopressin on water reabsorption in the toad urinary bladder [33]. These observations suggest that the diuretic actions of the atrial peptides might be related to inhibition of vasopressin activity. In the present study we found a small but consistent increase in circulating vasopressin levels with increasing sodium intake, possibly reflecting the increase in plasma sodium (Table 1). Although plasma levels of IrANP also increased with increasing sodium intake there was no direct relationship with plasma vasopressin. Furthermore, in a recent study infusion of α-human atrial natriuretic peptide in normal subjects had no effect on the plasma levels of vasopressin [34]. Therefore, although it would not be unreasonable to presume a mutual interaction between the atrial peptides and vasopressin [35], the nature and physiological significance of this relationship clearly requires further investigation in particular during changes in water balance.

In summary, the present study, therefore, in conjunction with previous work strongly suggests that the atrial peptides are an important component in the overall control of sodium and water balance, particularly under conditions of increased sodium intake. A better understanding of the physiology of human atrial peptides in the control of sodium and water balance should lead to a greater pathophysiological insight into the raised levels of these pep-
tides [36–39] found in many cardiovascular/renal conditions associated with sodium and water retention.

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References