Plasma concentrations of atrial natriuretic hormone in acromegaly: Relationship to hypertension

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Abstract. Atrial natriuretic hormone is involved in the control of blood pressure and water-electrolyte balance. In order to assess the relationship between atrial natriuretic hormone and hypertension in acromegaly, 34 subjects were studied, 18 with acromegaly (10 normotensive and 8 hypertensive) and 16 healthy controls. Plasma atrial natriuretic hormone levels, as well as plasma renin activity, aldosterone and growth hormone levels were measured in basal conditions in all subjects. Additionally, plasma renin activity and aldosterone levels were determined after standard stimulation. In hypertensive acromegalic patients, atrial natriuretic hormone plasma concentrations (39.8±3.5 ng/l) were significantly higher than in patients without hypertension (27.9±4.1 ng/l), and in controls (28.6±1.3 ng/l) (p<0.01 in both comparisons). Stimulated plasma renin activity values were decreased in hypertensive acromegalic patients when compared with those in normotensive patients (1.14±0.29 vs 4.03±0.66 μg/l·l·h⁻¹, p<0.01). In acromegaly, atrial natriuretic hormone levels correlated with mean arterial pressure (r=0.58, p=0.01). These results suggest that atrial natriuretic hormone plasma levels are slightly increased in patients with acromegaly and hypertension.

Atrial natriuretic hormone (ANH), a recently discovered bioactive peptide synthesized in the heart, is suggested to play an important role in water-electrolyte homeostasis and blood pressure control (1). ANH possesses diuretic, natriuretic and hypotonic properties (1-3), and is released in response to an increase in atrial pressure or atrial stretch (4), which may be caused by plasma volume expansion (5).

The characteristic features of acromegaly are: sodium retention and volume expansion (6,7). Arterial hypertension frequently develops in patients with acromegaly, but its pathogenesis is not fully understood (7,8). Chronic growth hormone (GH) excess, leading to sodium-water retention is probably the main cause (8,9). However, the potential for development of hypertension is not directly related to GH blood levels (7,8,10).

In recent studies, normal (11,12) or markedly increased ANH (13) levels were found in patients with acromegaly. The aim of this study was to determine plasma levels of ANH in acromegalic patients and determine whether ANH concentrations are related to the presence of hypertension.

Patients and Methods

Eighteen patients with active acromegaly were studied. The diagnosis of acromegaly was established by the presence of typical clinical signs and elevated serum GH levels not suppressible by an oral glucose load (7). Patients were divided into a hypertensive (N=8) and a normotensive (N=10) subgroup. Arterial hypertension was defined according to WHO criteria: a systolic blood pressure over 160 mmHg and/or a diastolic blood pressure over 90 mmHg, as measured in the sitting position, at least three times on two different days. Patients with diabetes mellitus, thyroid disorders, and renal or heart failure were excluded from the study. The signs of moderate cardiac enlargement were usually found on chest X-ray and/or ECG examinations in the patients studied, regardless of the presence or absence of hypertension. The control group comprised 16 age- and sex-matched healthy normotensive subjects. Additional relevant clinical and labo-
All subjects remained on a standard hospital diet, with normal electrolyte supplementation (sodium: 120, potassium: 80 mmol/day). No medication was used for at least one week prior to the study. After night bed-rest, fasting blood samples were obtained for plasma ANH, GH, sodium, potassium, as well as supine plasma renin activity (PRA) and aldosterone determination. The second blood sample, for stimulated PRA and aldosterone estimation, was taken following 3 h in the upright position and 40 mg iv furosemide. Supine blood pressure, for mean arterial pressure estimation, was measured with a mercury sphygmomanometer before blood samples were withdrawn.

Plasma ANH was measured after extraction with the use of a radioimmunological method. ANH was extracted from plasma on Sep-Pak C_{18} mini-columns (Waters Ass, USA). One ml of plasma, diluted to 3 ml with 4% acetic acid, was passed through the methanol-activated columns. After washing with 0.9% NaCl, ANH was eluted with the use of 4 ml of 86% ethanol in 4% acetic acid. The approximate ANH recovery from plasma was 90%, thus results were not corrected for recovery. The reagents used for RIA were purchased from Amersham Int, UK. The between-assay coefficient of variation was 15%.

Serum concentrations of GH were measured after extraction with the use of the double antibody RIA (14). PRA and aldosterone were determined using commercially available RIA kits (ANGIO I and ALDO, Chemapol, Prague, Czechoslovakia). The concentrations of blood sodium and potassium were measured by flame photometry.

Results were compared with the use of t-test or one-way analysis of variance with the subsequent Fisher’s least significant difference multiple range test, as appropriate. Correlations between the data were calculated by linear regression methods. A p-value below 0.05 was considered as significant. Values are expressed as means ± SEM, unless other stated.

**Results**

The mean plasma level of ANH in all the patients with acromegaly was 33.2±3.1 ng/l and did not differ from that of healthy controls, 28.6±1.3 ng/l (Fig. 1). However, hypertensive acromegalic patients exhibited significantly higher plasma ANH concentrations: 39.8±3.5 ng/l, as compared with those in normotensive patients: 27.9±4.1 ng/l (p<0.01) and in the controls (p<0.01) (Fig. 1).

**Table 1.**

Clinical and laboratory data of subjects studied.

<table>
<thead>
<tr>
<th>Group</th>
<th>Number [Female/male]</th>
<th>Age (years) mean [range]</th>
<th>MAP [mmHg]</th>
<th>Na⁺ [mmol/l]</th>
<th>K⁺ [mmol/l]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acromegaly</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertensive</td>
<td>8 [5F/3M]</td>
<td>39.6 [31-54]</td>
<td>120.9±3.1</td>
<td>142±1.3</td>
<td>4.1±0.3</td>
</tr>
<tr>
<td>Normotensive</td>
<td>10 [7F/3M]</td>
<td>36.5 [23-49]</td>
<td>95.7±1.5</td>
<td>138±1.1</td>
<td>4.1±0.2</td>
</tr>
<tr>
<td>Healthy controls</td>
<td>16 [10F/6M]</td>
<td>39.6 [23-60]</td>
<td>91.8±1.1</td>
<td>138±1.2</td>
<td>4.3±0.3</td>
</tr>
</tbody>
</table>

MAP: mean arterial pressure, Na⁺: serum sodium, K⁺: serum potassium
Table 2.
The results of growth hormone, plasma renin activity (PRA) and aldosterone determinations.

<table>
<thead>
<tr>
<th>Group</th>
<th>Growth hormone μg/l</th>
<th>PRA</th>
<th>Aldosterone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>supine</td>
<td>stimulated</td>
<td>supine</td>
</tr>
<tr>
<td>Acromegaly</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertensive</td>
<td>52.4±10.4</td>
<td>0.30±0.08</td>
<td>1.14±0.29 $^a$</td>
</tr>
<tr>
<td>Normotensive</td>
<td>57.1±8.4</td>
<td>0.49±0.66</td>
<td>4.03±0.66</td>
</tr>
<tr>
<td>Healthy controls</td>
<td>2.9±0.8</td>
<td>0.49±0.10</td>
<td>2.77±0.56</td>
</tr>
</tbody>
</table>

$^a$ p<0.01 vs normotensive acromegalic patients
Values are expressed as means ± SEM

The remaining results are shown in Table 2. Although basal PRA did not differ between the groups studied, stimulated PRA was significantly decreased in the hypertensive as compared with the normotensive patients. Aldosterone levels, although slightly lower in the hypertensive patients with acromegaly, were not significantly different from the other groups under study. Serum GH concentrations, highly elevated in acromegaly, were similar in the normotensive and hypertensive subgroups.

ANH levels in all patients with acromegaly correlated positively with mean arterial blood pressure: r=0.58 (p=0.01), as well as negatively with the stimulated PRA: r=−0.46; however, this correlation was on the border of significance (p=0.057). ANH levels and mean arterial pressure did not correlate with GH concentrations (r=−0.26 and r=−0.08, respectively).

Discussion
The results obtained in this study seem to indicate that ANH plasma levels are increased only in hypertensive patients with acromegaly. Cardiovascular disorders are often noted in acromegaly, and are, in fact, the leading cause of mortality from this disease (15). Arterial hypertension is seen in many patients, with a prevalence of 30-60% (7,8,10). Hypertension development is dependent mainly on disease duration and the patients' age, but not directly on blood GH concentrations (10,16,17). Cardiomegaly is another frequent pathological finding in acromegalic patients and results mainly from heart muscle hypertrophy (18-20). Some acromegalic patients develop a unique form of cardiomegaly (acromegalic heart disease), apparently independent of hypertension or circulatory failure (21).

ANH secretion is altered in patients with heart muscle hypertrophy or cardiac enlargement owing to cardiac dilatation. Increased ANH levels were observed in congestive heart failure (22,23), and the hormone concentrations correlated with atrial pressure and dimension (4,23). Patients with heart failure were excluded from our study, and since no correlation has been reported between cardiomegaly and hypertension in acromegaly (17,18), it is unlikely that major heart dysfunction is the primary cause of increased ANH levels in hypertensive patients with acromegaly.

ANH secretion in essential hypertension is not definitely established: both increased or normal levels of this hormone have been found (2,3,24). However, in some types of secondary hypertension, with volume expansion and low plasma renin activity, high ANH blood concentrations were described (25). In hypertensive acromegalic patients the plasma renin activity usually is lower than in normotensive patients (26,27), a finding confirmed in this study. PRA suppression in acromegaly may be due to body fluid overload (6,7). This phenomenon may also be responsible for the elevation of the plasma ANH levels. In the study of Czekalski et al. (13), as in our study, ANH levels and PRA were inversely correlated.

McKnight et al. (11) found normal ANH plasma levels in 8 patients with acromegaly, but only in two of them hypertension was noted. However, a
blunted response to saline infusion was shown in the acromegalic patients, and the authors suggested that both facts may have reflected pathological lack of compensatory ANH response to chronic sodium retention and acute sodium loading (11). Different results were obtained in the study of Czekalski et al. (13), who found about 5-fold higher ANH plasma levels in 8 patients with active acromegaly (3 hypertensive) than in the controls, but in another 8 acromegalic patients (after successful therapy) ANH concentrations were normal. The relatively small number of patients in both of these studies did not make it possible to subdivide acromegalic patients according to the presence or absence of hypertension. Recently, Deray et al. (12) found that ANH levels were not elevated in a larger group of acromegalic patients, and that ANH responded normally to isotonic saline infusion. However, all the patients were normotensive during their study. In the present study, the difference between ANH levels in hypertensive and normotensive acromegalic patients or controls, although significant, was of far less magnitude than that observed by Czekalski et al. (13).

It is a matter of discussion whether elevated plasma ANH levels in hypertensive disorders reflect a compensatory reaction in view of its hypertensive properties (2,3,28). In the patients with acromegaly and high blood pressure reported here, ANH concentrations, although significantly elevated in the subgroup as a whole, were within normal limits in most subjects. Thus, as in essential hypertension, plasma ANH increase may not exhibit important physiological significance.

Increased GH levels are not directly related to development of hypertension in acromegaly. In a previous study (10) and in the present no correlation between serum GH and blood pressure was observed, nor did a reduction of GH levels influence blood pressure values in hypertensive patients (17). Other factors influencing sodium pump and water/electrolyte balance may also contribute to the development of hypertension in acromegaly. In our previous studies we have found that hyperinsulinemia (29) and raised sodium pump inhibitor/digoxin-like substance activity (27) are related to hypertension in patients with acromegaly.

In conclusion, the results obtained in the present study suggest that plasma concentrations of atrial natriuretic hormone are slightly increased in patients with acromegaly and arterial hypertension.

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References


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