Impaired vasopressin suppression and enhanced atrial natriuretic hormone release following an acute water load in primary aldosteronism

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Abstract

The release of arginine vasopressin (AVP) and atrial natriuretic hormone (ANH) and their involvement in renal water and electrolyte metabolism in primary aldosteronism in humans were studied. An oral acute water load (20 ml/kg body weight) was given to each of 12 patients before and after surgical removal of their aldosterone-producing adenoma(s). Plasma AVP and ANH were measured simultaneously, and renal water and electrolyte metabolism and tubular functions were determined. The same water load was given to seven normal subjects and the same parameters were determined. In the presence of mineralocorticoid excess before the operation, plasma AVP was relatively low compared with plasma osmolality (Posm), but was not suppressed in response to decreases in Posm after the water load. Baseline plasma ANH was high and increased further after the water load; urinary dilution and diuresis both remained normal. After the operation, baseline plasma AVP was normal and decreased in response to the decrease in Posm after the water load, with normal urinary dilution and diuresis. Baseline plasma ANH was normal, and did not increase after the water load. The ratio of urinary K and Na clearances and distal tubular reabsorption of Na increased before the operation. These results suggest that there are perturbations of AVP and ANH release in primary aldosteronism, despite the normal urinary dilution after a water load.

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Introduction

It is well known that primary mineralocorticoid excess is associated with sodium retention, extracellular fluid expansion leading to hypertension, and, frequently, hypokalaemia and a tendency toward hypernatraemia. Hypokalaemia per se has been found to impair the ability of the kidney to concentrate urine, leading to a decrease in body fluid (1).

It is likely, therefore, that the release of arginine vasopressin (AVP) and atrial natriuretic hormone (ANH), related to water and electrolyte homeostasis, might be distorted in mineralocorticoid excess. Hypernatraemia may stimulate AVP release, but increases in blood volume and hypertension may attenuate AVP release and enhance ANH release.

Urinary excretion of AVP has been reported to increase in response to osmotic stimuli in patients with mineralocorticoid excess (2). Moreover, AVP release is known to increase in deoxycorticosterone acetate salt-hypertensive rats and to play an important part in the development and maintenance of hypertension (3, 4). In contrast, plasma AVP has been reported to be reduced in primary aldosteronism due to volume expansion (5). Furthermore, hypokalaemia may attenuate the AVP responses to osmotic stimuli (6).

ANH has been shown to increase in patients with mineralocorticoid excess (7) and to have a pivotal role in escape from the sodium-retaining effect of mineralocorticoids (8, 9). Moreover, there are interactions between AVP and ANH release: AVP enhances ANH release, while ANH attenuates AVP release (10, 11). However, the release of AVP and ANH and their interaction in renal water and electrolyte metabolism during the condition of chronic mineralocorticoid excess remain unknown.

In order to clarify these problems, acute water loading tests were carried out before and after adrenalectomy in patients with adrenal aldosterone-producing adenomas. Plasma AVP and ANH were measured simultaneously, and renal water and salt metabolism and tubular functions were investigated concomitantly.

Subjects and methods

The studies were carried out in 12 patients (aged 25–66 years; four men and eight women) with
aldosterone-producing adenomas before and after adrenalectomy were 8.7% and 9.1% for A VP and ANH. The lowest detectable levels for AVP and ANH in the RIAs were 0.4 and 7.5 pg/tube respectively. Plasma aldosterone and renin activity were determined using conventional commercial kits.

Other measurements and calculations
Plasma (Posm) and urine osmolality (Uosm) were determined by an Advanced Instrument osmometer (3D2; Needham Heights, MA, USA), and plasma and urinary sodium and potassium concentrations by flame photometry (Hitachi flame photometer, 205D). Plasma and urinary creatinine concentrations were determined using an autoanalyser. When maximally diluted urine was obtained, creatinine (Ccr), Na (CNa), K (CK), osmolar (Cosm), and free water (CH₂O) clearances were calculated using conventional formulae. The water excretion ratio was calculated as the ratio between total urine volume excreted during 2 h after the water load and ingested water volume.

The proximal tubular reabsorption rate (PTR) and the distal tubular reabsorption rate (DTR) for Na were calculated by the following formulae respectively (14, 15):

\[
PTR = \left[\frac{Ccr - (CNa + CH₂O/Ccr)}{Ccr} \right] \times 100 (\%)
\]

\[
DTR = \frac{CH₂O/(CNa + CH₂O)}{Ccr} \times 100 (\%)
\]

Plasma protein concentration was measured using a refractometer.

Statistical analyses of the data were performed by one- and two-way analyses of variance for repeated measurements of the same variables. Analysis of covariance was also used. Statistically significant differences were calculated by Dunnett’s test (within group) and t-test (between groups). In each study, the initial value was used as the baseline value, and all data were expressed as means ± s.e.

Results
Baseline plasma osmolalities (Posm) in patients with aldosterone-producing adenomas before surgery (+MCE) and after surgery (−MCE), and in normal controls were 287.7 ± 1.5, 284.7 ± 1.4 and 285.2 ± 1.2 mOsmol/kg respectively. After acute water load, Posm decreased gradually and significantly and reached nadirs of 280.6 ± 0.9 in +MCE patients, 276.0 ± 0.7 in −MCE patients, and 280.0 ± 1.1 mOsmol/kg at 60 min in normal subjects (P<0.01). Thereafter, Posm gradually increased to baseline values. There were no significant differences in Posm among the groups (Fig. 1A). Baseline plasma AVP values in patients before and after surgery, and in normal subjects were 2.6 ± 0.5, 2.4 ± 0.5 and 2.9 ± 0.7 pmol/l respectively. Before operation (+MCE), plasma AVP did not change after water loading, but decreased to nadir values at 30 to 90 min (1 pmol/l) and
### Table 1 Profile of the patients with primary aldosteronism on admission.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>SBP (mmHg)</th>
<th>DBP (mmHg)</th>
<th>SNa (mmol/l)</th>
<th>SK (mmol/l)</th>
<th>SCI (mmol/l)</th>
<th>UNa (mmol/l)</th>
<th>UK (mmol/l)</th>
<th>UCI (mmol/l)</th>
<th>UK/Na</th>
<th>UV (ml/day)</th>
<th>CCr (ml/min)</th>
<th>PRA (ng/(l·s))</th>
<th>PAC (pmol/l)</th>
<th>Daily medication at the time of the examination</th>
</tr>
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<td>58</td>
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<td>F</td>
<td>164</td>
<td>104</td>
<td>147</td>
<td>3</td>
<td>106</td>
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<td>1000</td>
<td>71</td>
<td>UD</td>
<td>720</td>
<td>Nifedipine (30 mg)</td>
</tr>
<tr>
<td>3</td>
<td>38</td>
<td>M</td>
<td>152</td>
<td>88</td>
<td>145</td>
<td>4</td>
<td>110</td>
<td>136</td>
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<td>86</td>
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<td>66</td>
<td>M</td>
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<td>32</td>
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</tr>
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<td>143</td>
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<td>109</td>
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</tr>
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<td>98</td>
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<td>98</td>
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<td>113</td>
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<td>114</td>
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<td>F</td>
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<td>UD</td>
<td>2240</td>
<td>Nisoldipine (5 mg)</td>
</tr>
</tbody>
</table>

**Average**

- SBP, systolic blood pressure; DBP, diastolic blood pressure; SNa, serum Na concentration; SK, serum K concentration; SCI, serum Cl concentration; UNa, urine Na concentration; UK, urine K concentration; UCI, urine Cl concentration; UK/Na, urinary K/Na concentration ratio; UV, urine volume/day; CCr, creatinine clearance; PRA, plasma renin activity; PAC, plasma aldosterone concentration; UD, undetectable (less than 0.01 ng/(l·s)).
Table 2: Profile of the patients after removal of adrenal tumour(s).

<table>
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<tr>
<th>Patient</th>
<th>SBP (mmHg)</th>
<th>DBP (mmHg)</th>
<th>SNa (mmol/l)</th>
<th>SK (mmol/l)</th>
<th>SCI (mmol/l)</th>
<th>UNa (mmol/l)</th>
<th>UK (mmol/l)</th>
<th>UCl (mmol/l)</th>
<th>UK/Na</th>
<th>UV (ml/day)</th>
<th>CCr (ml/min)</th>
<th>PRA (ng/(l·s))</th>
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<td>5.5</td>
<td>110</td>
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<tr>
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<td>0.27</td>
<td>1300</td>
<td>56</td>
<td>0.65</td>
<td>100</td>
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<td>144</td>
<td>3.3</td>
<td>107</td>
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<td>0.76</td>
<td>1000</td>
<td>—</td>
<td>UD</td>
<td>740</td>
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<td>1800</td>
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<td>100</td>
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</tr>
<tr>
<td>s.S.</td>
<td>± 4.5</td>
<td>± 2.4</td>
<td>± 0.6</td>
<td>± 0.2</td>
<td>± 0.7</td>
<td>± 12.2</td>
<td>± 4.2</td>
<td>± 14.4</td>
<td>± 0.05</td>
<td>± 110</td>
<td>± 5.3</td>
<td>± 0.06</td>
<td>± 50</td>
<td>Nifedipine (40 mg); propranolol (30 mg)</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1.
increased to the initial level at 150 min in –MCE subjects. In normal subjects, AVP gradually decreased, reached the nadir at 90 min (1.3 ± 0.4 pmol/l) and returned to the initial level at 150 min (P<0.05–0.01). There were significant differences between +MCE patients and normal subjects (60 and 120 min), and between +MCE and –MCE patients at 30 and 90 min (P<0.05; Fig. 1B). When baseline plasma AVP and Posm values were compared with those at the time of maximum diuresis (4th sampling period), plasma AVP was significantly decreased in –MCE patients and normal subjects (P<0.05 to 0.01), but not in +MCE patients: Posm decreased significantly in all groups (P<0.01). The slopes of the calculated regression lines in –MCE patients and normal subjects (0.188 ± 0.039 and 0.297 ± 0.103), and the osmotic thresholds of AVP release (272.0 ± 2.5 and 272.3 ± 2.4 mOsmol/kg) were comparable (Fig. 2). Baseline plasma protein concentration in the +MCE and –MCE patients and normal subjects were 71 ± 2, 72 ± 3 and 70 ± 2 g/l respectively. Protein concentrations were significantly decreased at 30 min and thereafter in the +MCE and –MCE patient groups and at 60 min and thereafter in normal subjects (P<0.01). There were no significant differences among the three groups (Fig. 3A).

Baseline plasma ANH in +MCE and –MCE patients and normal subjects were 34.2 ± 7.7, 11.4 ± 2.6 and 17.2 ± 3.4 pmol/l respectively. Plasma ANH in +MCE and –MCE patients and normal subjects.
patients and in normal subjects increased gradually to a plateau at 90 min \( (P<0.01) \); plasma ANH did not increase significantly in \( -\)MCE patients during water loading. There were significant differences between the \( +\)MCE and \( -\)MCE groups throughout the study \( (P<0.05) \), but no differences were noticed between \( -\)MCE patients and normal subjects or between \( +\)MCE patients and normal subjects (Fig. 3B).

Uosm decreased significantly in the second urine collection period and thereafter, and reached the nadirs in all three groups in the 4th or 5th sampling periods \( (P<0.05–0.01) \). Uosm gradually returned to the initial value in the final period. Urine flow significantly increased in the 3rd period and thereafter \( (P<0.05–0.01) \) and reached peak values in the 3rd or 4th period in all the groups. Cosm increased significantly in the 2nd period and thereafter \( (P<0.05–0.01) \). CH\( _2 \)O changed from negative values to positive ones in the 3rd period and thereafter. There were no significant differences in all these parameters among the groups (Fig. 4A–D).

There were also no significant differences in CNa and CK among the groups. However, the CK/CNa ratio in the \( +\)MCE patient group was significantly greater than those in the \( -\)MCE patients and normal subjects \( (P<0.05; \text{Table 3}) \). There were no significant differences among the three groups in the proximal tubular reabsorption of Na. The distal reabsorption of Na tended to be increased in \( +\)MCE patients compared with normal subjects, but significantly decreased in \( -\)MCE patients \( (P<0.05, \text{Table 3}) \). The water excretion ratio was significantly smaller \( (P<0.05) \) in \( +\)MCE and \( -\)MCE patients than in normal subjects, but also smaller in \( +\)MCE than \( -\)MCE patients (Table 3).

**Discussion**

The present study clearly shows that, in patients with aldosterone-producing adenomas in a state of mineralocorticoid excess (\( +\)MCE), plasma AVP was normal at baseline and did not decrease in response to a decrease in Posm after the acute water load. Plasma ANH was relatively increased at baseline and increased further in response to the water load. Urinary dilution and diuresis occurred normally after the water load, whereas the water excretion rate was slightly impaired. In contrast, after surgery (\( -\)MCE patients), plasma AVP was normal at baseline and decreased normally in response to a decrease in Posm. Plasma ANH was normal at baseline, but did not increase in response to the water load. However, water diuresis and urinary dilution after the water load were normal.

The CK/CNa ratio and the distal tubular reabsorption of Na were increased in \( +\)MCE patients compared with \( -\)MCE patients. The proximal tubular reabsorption of Na did not change, irrespective of the presence or absence of hyperaldosteronism.

To our knowledge, this is the first report showing that there is impaired AVP suppression in response to a decrease in plasma osmolality after an acute water load in \( +\)MCE patients, despite the presence of normal urinary dilution, and that impaired AVP suppression is restored to normal after removal of the adrenal tumour.

The exact mechanisms whereby osmoregulation of AVP release is impaired, but urinary dilution in response to water load is preserved in \( +\)MCE patients, remain unexplained by the present study.

With regard to failing suppression of AVP after the water load, several factors may play a part. First, a chronically slightly increased basal Posm and serum
sodium concentration may render AVP less responsive to an acute decrease in Posm after the water load. Secondly, an increment of osmolality in the cerebrospinal fluid (CSFosm) as a result of an increase in serum sodium may enhance AVP secretion. CSFosm has been reported to lag behind Posm after an acute osmotic challenge (16, 17). Thirdly, an activation of the brain renin–angiotensin system (RAS) in +MCE subjects (18), in spite of a suppressed peripheral RAS, may stimulate AVP release (19, 20). It is also possible that antihypertensive drugs taken by the patients in the +MCE state may have affected AVP release, although such effects have not yet been reported in patients taking calcium antagonists, or α- or β-receptor blocking agents.

Normal urinary dilution after water load in the +MCE state is also difficult to explain. First, it is possible that the increased plasma ANH levels that further increased during water load in +MCE patients, inhibited the effect of relatively high AVP levels on urinary osmolality (21–23). Secondly, the inhibitory effect of high plasma concentrations of ANH on tubular sodium reabsorption and an ANH-induced increase in medullary blood flow in +MCE patients may have had an effect on the medullary osmotic gradient between interstitial fluid and the lumen of the collecting duct. Thirdly, the suppressed peripheral RAS (24) and increased renal prostaglandin formation as a result of hypokalaemia (25, 26) may also have impaired the effect of AVP on urine osmolality.

In spite of a normal decrease in Usom in response to the water load in +MCE patients, AVP exerted some restraining effect on water excretion, as the water excretion ratio was smaller in +MCE patients than in −MCE patients and in controls. It is possible that the increase in distal tubular reabsorption of Na and in the urinary CK/CNa ratio in +MCE patients during the water load was due to increased aldosterone secretion, and that plasma volume expansion because of enhanced Na reabsorption was also the cause of ANH stimulation (7).

In conclusion, these results suggest that perturbation of the osmoregulation of AVP release is present in a state of mineralocorticoid excess, but the simultaneous increases in ANH release alleviate the distortion of renal water metabolism. It remains unknown whether abnormalities of the osmoregulation of AVP release play a part in the development of +MCE-induced hypertension.

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References


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