Brief Report

Lack of elevation of urinary albumin excretion among patients with chronic syndromes of inappropriate antidiuresis

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Abstract

Background. A recent study has revealed that acute and chronic administration of the vasopressin V2 receptor (V2R) agonist dDAVP induced a marked increase of urinary albumin excretion (UAE) in healthy rats and humans (Bardoux P et al. Nephrol Dial Transplant 2003; 18: 497–506). The occurrence of an elevation of UAE among patients with chronic syndromes of inappropriate antidiuresis has not been reported.

Methods. We looked for the elevation of UAE in 24-h urine samples of the following patients: nine chronic SIADH patients, two patients with acute post-operative SIADH, three patients of the same family with nephrogenic syndrome of inappropriate antidiuresis (NSAID) and two patients with hyponatraemia due to surdosage of dDAVP in the setting of central diabetes insipidus.

Results. There was no elevation of UAE in our patients (whether they presented with hyponatraemia or not), apart from a patient treated with supra-physiological doses of dDAVP. When she received 80 μg/day of dDAVP, her UAE was 42 mg/day. In this patient, UAE returned to the normal range (20 μg/day) when doses of dDAVP were tapered (20 μg/day).

Conclusion. The present study shows that chronic V2R stimulation generally does not result in a rise in UAE. The discrepancy between our results and those of the above-mentioned study could be explained by a dose-dependent effect of V2R stimulation on UAE.

Keywords: antidiuresis; AVP; microalbuminuria; nephrogenic syndrome of inappropriate antidiuresis; SIADH

Introduction

A recent study has revealed that vasopressin induces a marked increase in urinary albumin excretion (UAE) in healthy rats and humans [1]. In normal Wistar rats and humans (healthy or patients with diabetes insipidus), acute administration of the vasopressin V2 receptor agonist dDAVP increased UAE significantly and reversibly. Chronic dDAVP administration (during 1 week) was also performed in normal Wistar rats and was accompanied by an increase in UAE. This albuminuric effect seems to result from increased glomerular leakage and requires functional vasopressin V2 receptors (V2R).

We decided to study the effect on UAE of chronic V2R stimulation in humans. To address this question, we measured UAE between two groups of patients: chronic syndrome of inappropriate antidiuretic hormone (SIADH) from various conditions on the one hand and nephrogenic syndrome of inappropriate antidiuresis (NSIAD) on the other hand. SIADH is an emerging entity recently described by Feldman et al. in two male newborn babies, characterized by an X-linked gain-of-function mutation of the V2R leading to free water retention and hyponatraemia [2]. We recently described a large family with NSIAD caused by a missense mutation of the V2R gene [3]. The diagnosis was first made in a hyponatraemic elderly male (index patient). Affected males from the family had hyponatraemia and most of the women with the mutation had an abnormal response to water loading.

Subjects and methods

We measured UAE in 24-h urine samples of the following patients:

- Nine patients with chronic SIADH (defined as SIADH lasting for at least 2 days), without following comorbidities associated with the elevation of UAE: diabetes mellitus, arterial hypertension and systemic inflammatory response syndrome. We also excluded patients with macroproteinuria and patients treated by angiotensin-converting enzyme inhibitors or angiotensin II receptors antagonists (in rats, these drugs blunted the dDAVP-induced rise in UAE) [1]. These exclusion criteria were also considered for the other groups of patients. Criteria used for the diagnosis of SIADH are the following: decreased effective
osmolality (<275 mOsm/kg of water), urine osmolality >100 mOsm/kg of water during hypotonicity, clinical euvołaemia, urinary sodium >30 mmol/l with normal dietary salt intake, normal thyroid, renal and adrenal function and no recent use of diuretic agents.

- Two patients with acute post-operative SIADH to evaluate the effect of a non-sustained stimulation of V2R.
- Three NSAID patients from the above-mentioned family, bearing the mutated AVPR2 gene responsible for NSAID. Relationships between the members of the family and their genotypes are shown in Table 1.
- One patient with chronic hyponatraemia due to surdosage of dDAVP. This young female patient had central diabetes insipidus since a hypotalamic surgery for Rathke’s pouch exeresis. This surgery was complicated by a lesion of the hypothalamic thirst centre. Indeed, she complained of thirst, was drinking 2 l/day and—for unclear reasons—took high doses of intranasal dDAVP (20 µg four times a day), resulting in chronic hyponatraemia. During an in-hospital stay, we progressively tapered the doses of dDAVP (10 µg two times a day), which allowed a normalization of natraemia.
- One patient with acute hyponatraemia under treatment with dDAVP for central (pituitary) diabetes insipidus, linked to a traumatic lesion of pituitary stalk. This patient also received intravenous hypotonic fluids, since he had a transient alteration of consciousness.

Results

There was no elevation of UAE in our patients (whether they presented with hyponatraemia or not), apart from the patient treated with supra-physiological doses of dDAVP. When she received 80 µg/day of dDAVP, her UAE was 42 mg/day. In this patient, UAE returned to the normal range (21 mg/day) when doses of dDAVP were tapered (20 µg/ day) (see Table 1).

Discussion

The present study shows that chronic V2R stimulation generally does not result in a rise in UAE.

Our data are not in accordance with the article of Bardoux, showing that the dDAVP-induced rise of UAE in normal rats was greater after a prolonged treatment (1 week in their protocol) than that after a single injection. Their study suggested that dDAVP-dependent albuminuria might progressively worsen with the prolonged exposure to the hormone.

The lack of elevation of UAE after prolonged exposure to excessive levels of ADH (chronic SIADH patients) or chronic stimulation of V2 receptors (NSAID patients) may be due to the fact that the stimulatory effect of V2R stimulation on UAE could be transient. In the study of Bardoux, the stimulatory effect of acute dDAVP infusion was indeed transient—in rats and in humans—and UAE returned to values close to basal levels within a few hours after the acute infusion. This could represent an escape from the effect of vasopressin on UAE, by analogy with the well-known ‘vasopressin escape’, a process that counters water-retaining action of vasopressin [4]. Nevertheless, in rats submitted to a dDAVP during 1 week, a six-fold increase in UAE was shown.

Nevertheless, the most likely explanation for the discrepancy between our results and those of Bardoux is a dose-dependent effect of V2R stimulation. Indeed, doses of dDAVP used in Bardoux’s protocol for acute infusion in human subjects (0.3 µg/kg over a 20-min infusion) are supra-physiological and could result in a more intense stimulation of V2R than the chronic stimulation obtained from gain-of-function mutation of the V2R gene or from SIADH. Whether doses of dDAVP infused during 1 week in rats by Bardoux (8.33 ng/h, 200 ng/day) are supra-physiological is likely but uncertain, since plasma levels of dDAVP cannot be measured directly. In an experimental model of SIADH, the infusion rate of AVP of 10 mU/h was sufficient to cause maximal antidiuresis and severe hyponatraemia (SNa+ <120 meq/l). Infusion of dDAVP at a rate of 1 ng/h resulted in antidiuresis and hyponatraemia equivalent to the AVP infusion of 10 mU/h. With this infusion rate of AVP, AVP levels were still in the physiological range, but were significantly elevated (8.4 ± 0.4 µU/ml). AVP levels increased linearly with higher infusion rates of AVP; for example, an infusion rate of 50 mU/h resulted in AVP levels of ~30 µU/ml, which are supra-physiological. So it is likely that the infusion rate of dDAVP of 8.33 ng/h represents a supra-physiological dose [5].

The observation of our patient is of particular interest to discuss the dose-dependent effect of V2R stimulation on UAE. Indeed, UAE was elevated when this patient received supra-physiological doses of dDAVP and returned to the normal range (with a diminution of UAE of 50%) when she received conventional doses.

The two subgroups of patients in our series may be different from one point: only V2R are stimulated in NSAID patients and in patients treated with dDAVP (like in healthy patients or patients with diabetes insipidus studied in Bardoux’s article), whereas V1 receptors (V1R) are also stimulated in chronic SIADH.

Just as for stimulation of V2R, there are also arguments in favour of a relationship between stimulation of V1R and elevation of UAE. Basal levels of AVP in diabetic patients showing microalbuminuria were significantly higher compared to diabetics without any complications [6,7]. In two trials [7,8], OPC21268 administration—a nonpeptide V1R antagonist—resulted in a decrease of UAE in patients with type 2 diabetes mellitus, suggesting that V1R blockade could represent a novel therapeutic option in the prevention of the progression of diabetic nephropathy. However, our results do not support a significant role of V1R chronic stimulation in an increase of UAE.

The present study has several limitations: first, AVP levels were not measured; measurement of AVP is not mandatory for the diagnosis of SIADH, but the degree of increase of AVP levels could have added weight to the speculative dose-dependent effect mentioned above. Another limitation is the lack of a second measurement of microalbuminuria for the majority of patients.
Table 1. Urine parameters in patients with different syndromes of inappropriate antidiuresis

<table>
<thead>
<tr>
<th>Name/sex/age</th>
<th>Diagnosis</th>
<th>Natraemia</th>
<th>24-h microalbuminuria</th>
<th>Urine osmolality (mOsm/kg)</th>
<th>Creatiniuria (g/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Index patient/M/74</td>
<td>NSAID/hemizygous</td>
<td>143</td>
<td>6 mg</td>
<td>761</td>
<td>1.3</td>
</tr>
<tr>
<td>IP’s daughter/F/49</td>
<td>NSAID/heterozygote</td>
<td>NP</td>
<td>14 mg</td>
<td>625</td>
<td>1.4</td>
</tr>
<tr>
<td>IP’s grandson/M/24</td>
<td>NSAID/hemizygous</td>
<td>NP</td>
<td>6 mg</td>
<td>774</td>
<td>1.5</td>
</tr>
<tr>
<td>M/57</td>
<td>SIADH/SCLC</td>
<td>130</td>
<td>5 mg</td>
<td>635</td>
<td>1.1</td>
</tr>
<tr>
<td>F/39</td>
<td>SIADH/oxcarbazepine</td>
<td>134</td>
<td>6 mg</td>
<td>177</td>
<td>0.7</td>
</tr>
<tr>
<td>M/66</td>
<td>SIADH/idiopathic</td>
<td>130</td>
<td>14 mg</td>
<td>489</td>
<td>ND</td>
</tr>
<tr>
<td>F/48</td>
<td>SIADH/post-hypothalamic surgery</td>
<td>127</td>
<td>16 mg</td>
<td>558</td>
<td>1</td>
</tr>
<tr>
<td>F/83</td>
<td>SIADH/idiopathic</td>
<td>13 mg</td>
<td>13 mg</td>
<td>574</td>
<td>0.8</td>
</tr>
<tr>
<td>M/48</td>
<td>SIADH/idiopathic</td>
<td>125</td>
<td>&lt;13 mg</td>
<td>331</td>
<td>1</td>
</tr>
<tr>
<td>M/70</td>
<td>SIADH/pharynx neoplasia</td>
<td>121</td>
<td>24 mg</td>
<td>267</td>
<td>0.9</td>
</tr>
<tr>
<td>M/82</td>
<td>SIADH/stroke</td>
<td>131</td>
<td>6 mg</td>
<td>293</td>
<td>1.1</td>
</tr>
<tr>
<td>M/64</td>
<td>SIADH/idiopathic</td>
<td>128</td>
<td>13 mg</td>
<td>311</td>
<td>0.7</td>
</tr>
<tr>
<td>M/59</td>
<td>Acute post-operative SIADH</td>
<td>127</td>
<td>13 mg</td>
<td>407</td>
<td>1.2</td>
</tr>
<tr>
<td>F/67</td>
<td>Acute post-operative SIADH</td>
<td>127</td>
<td>18 mg</td>
<td>532</td>
<td>1</td>
</tr>
<tr>
<td>M/37</td>
<td>Acute hyponatraemia related to treatment with dDAVP and intravenous hypotonic fluids</td>
<td>131</td>
<td>&lt;14 mg</td>
<td>579</td>
<td>1.9</td>
</tr>
<tr>
<td>F/36</td>
<td>Hyponatraemia due to ‘over-treated’ central diabetes insipidus (dDAVP 20 µg qid)</td>
<td>124</td>
<td>42 mg</td>
<td>429</td>
<td>1</td>
</tr>
<tr>
<td>Same patient with normal natraemia (dDAVP 10 µg bid)</td>
<td>137</td>
<td>21 mg</td>
<td>781</td>
<td>1.1</td>
<td></td>
</tr>
</tbody>
</table>

M = male; F = female; IP = index patient; SCLC = small cell lung carcinoma; NP = measurement of natraemia not performed the same day that 24-hour urine sample; ND = not defined.

Note that index patient’s cousin (NSAID–hemizygous) was not included because of diabetic nephropathy and treatment with angiotensin-converting enzyme inhibitors.

In conclusion, the present study shows that chronic V2R stimulation generally does not result in a rise in UAE among patients with chronic syndromes of inappropriate antidiuresis. The discrepancy between our results and those of the above-mentioned study could be explained by a dose-dependent effect of dDAVP on UAE. Further studies—using appropriate animal models as a first step—are needed to investigate this hypothesis.

Conflict of interest statement. None declared.

References

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