Evidence in Hyponatremia Related to Inappropriate Secretion of ADH that V₁ Receptor Stimulation Contributes to the Increase in Renal Uric Acid Clearance¹,²

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ABSTRACT
In hyponatremia related to syndrome of inappropriate antidiuretic hormone (SIADH), hypouricemia is explained primarily by the high uric acid clearance rate that results from the decrease in tubular uric acid reabsorption. This modification of tubular handling of uric acid is considered to be induced by the increase in the “effective vascular volume.” This study was designed to determine if V₁-receptor stimulation participates in the development of a high uric acid clearance rate as in SIADH, in which the antidiuretic hormone acts on V₁ and V₂ receptors. Therefore, the urate clearance rate was measured in seven volunteers with 1-desamino-8-D-arginine vasopressin (dDAVP)-induced hyponatremia, with dDAVP stimulating exclusively the V₂ receptors (Group I), and in six patients with SIADH (Group II) during both normo- and hyponatremia. As expected, in both groups, the serum uric acid concentration decreased during hyponatremia, but did so to a larger extent in the patients with SIADH (< -53% versus -29%, P < 0.02). Despite similar levels of hyponatremia (126 ± 5 mmol/L and 125 ± 5.5 mmol/L), of hypoproteinemia (64 ± 5 g/L and 63 ± 5 g/L) and of salt excretion (FNa, 0.66 ± 0.28% and 0.73 ± 0.25%), the urate clearance (8.3 ± 3.3 mL/min) and the fractional excretion of filtered uric acid (5.7 ± 2%) in Group I were not significantly different during hyponatremia than during normonatremia (6.4 ± 1.5 mL/min and 5.4 ± 0.9%). On the other hand, in Group II, both parameters were increased (17.8 ± 2.9 mL/min and 19.6 ± 5.3%; P < 0.001) and both values were higher than in the dDAVP-induced hyponatremia (P < 0.01). Additionally, the administration of a potent V₁-receptor agonist (triglycyl-His-Lys-vasopressin) in a patient with central diabetes insipidus with preexisting dDAVP-induced hyponatremia produced a rapid increase of urate clearance. Because dDAVP acts only on the V₂ receptors, these data suggest that the higher urate clearance observed during hyponatremia related to SIADH is not only the consequence of an increased “effective vascular volume,” but that V₁-receptor stimulation also contributes to it, by a mechanism that remains to be determined.

Key Words: Hyponatremia, urate clearance, V₁ receptor, V₂ receptor, “effective vascular volume”

H yponatremia is typically associated with hypouricemia (1,2) in the syndrome of inappropriate secretion of antidiuretic hormone (SIADH), whereas in hypovolemic hyponatremia, the uric acid concentration is generally normal or increased (2). Hypouricemia is primarily the consequence of an high uric acid clearance related to a decrease in tubular uric acid reabsorption (1,2). Correction of the hyponatremia by water restriction normalizes the uric acid clearance despite the persistent inappropriate secretion of ADH (1,2). It is generally believed that the changes in tubular handling of uric acid observed in the SIADH is secondary to the increase in the “effective vascular volume” associated with this syndrome (2), although the mechanisms of this regulation remain unknown. We had the opportunity to study the uric acid clearance rate in a patient with postoperative central diabetes insipidus who developed hyponatremia after 1-desamino-8-D-arginine vasopressin (dDAVP) administration. In this patient, the uric acid clearance rate was not increased, despite the hyponatremia. This situation differed from the classical SIADH in that water retention was induced by dDAVP. This hormone acts only on V₂ receptors, and has no significant effect on V₁ receptors (3), contrary to the arginine vasopressin (AVP) secreted in the SIADH. This prompted us to investigate the uric acid clearance rate in hyponatremia induced by dDAVP in volunteers. We confirm that, in this model of hypona-

1 Received July 27, 1995. Accepted February 6, 1996.
2 Portions of this work were presented at the 27th Annual Meeting of the American Society of Nephrology and published in abstract form (J Am Soc Nephrol 1994;5:366).
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1046-6573/0705-0805$03.00/0
Journal of the American Society of Nephrology
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tremia, the increase in the uric acid clearance rate is less important than that of classic SIADH, despite a similar increase in the "effective vascular volume".

PATIENTS AND METHOD

Hyponatremia Induced by dDAVP in Volunteers

In seven physicians (aged 25 to 40 yr), dDAVP (Minirin, Ferring, Belgium) was administered by nasal route for 4 days. dDAVP was given at the dose of 20 μg every 8 h. The first day, the subjects were submitted to mild water restriction (10 mL/kg) followed during the subsequent days by a free water intake. The subjects were on a stable food and salt intake diet during all of the procedures (70 to 150 mmol/day). Body weight was determined each morning. Alcohol was prohibited for 5 days before and during the study. Serum electrolytes, protein, creatinine, and uric acid concentrations were measured on the mornings of each day (until Day 5) after an overnight fast. Twenty-four h urine samples were collected during Day 1 and Day 4. None presented neurological symptoms. The fractional excretions of filtered uric acid (F_{uric} [urine]) and sodium (F_{Na} [serum]) in % were calculated as the (urine/serum) concentration of uric acid and sodium multiplied by the (serum/urine) concentration of creatinine multiplied by 100 and were measured each morning between 8 and 10 a.m.

Hyponatremia Related to SIADH

In six asymptomatic patients with SIADH (three related to oat cell carcinoma, one idiopathic, and two related to brain disease) and mild hyponatremia, the same measurements were made as with the volunteers. Uric acid clearance rate was determined during the hyponatremic state and after normalization of the serum sodium by severe water restriction (in 3 to 4 days) (Table 1). These patients were also on stable food and salt intakes (70 to 150 mmol/day) during the normo- or hyponatremic periods. Alcohol was prohibited as with the volunteers.

The fractional excretion of filtered sodium and uric acid were also determined in the morning during several days of mild hyponatremia. All serum and urinary chemical measurements were performed by the hospital clinical laboratory. Uric acid was measured by the uricase method.

Effect of Triglycyl-Lysine Vasopressin (TGLV) on Urate Clearance in a Patient with Central Diabetes Insipidus (CDI) and Hyponatremia Induced by dDAVP

We evaluated the effects of acute V_1-receptor stimulation on urate clearance by triglycyl-lysine vasopressin (TGLV) administration (Glypressin; Ferring, Malmö, Sweden). TGLV acts as a chemical depot or "hormonogen" according to its ability to release slowly the parent hormone lysine vasopres- sin and thus to exert protracted biological effects (at least 4 h) (4,5).

In the subject studied, a 35-year-old man with CDI, serum ADH was not measurable despite mild hypernatremia (148 mEq/L). After providing informed consent, he was submitted to the same protocol as the normal volunteers. Sufficient water intake amounts (>1.5 L/day) were required over 5 days to obtain mild hyponatremia. On Day 4 (Table 2) urine samples were collected between 8 and 10 a.m. and then every 2 h for four consecutive periods after iv administration over 30 min of 7.5 μg/kg of TGLV, dissolved in 100 mL 5% glucose (4). Blood pressure and pulse rate were monitored every 10 min during the test for the first h and then every 30 min. The patient stood up only to void, and drank a volume of water every 2 h that was equivalent to the urine volume voided during the preceding 2 h, to ensure a relatively stable "water" expanded state. Blood was collected in the middle of each collection period for determinations of the same parameters as with the volunteers. The patient fasted after a moderate breakfast eaten at 8 a.m.

Because the patient developed mild hypertension during the first hour after TGLV administration, which could have

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Hyponatremia Induced by dDAVP (N = 7)</th>
<th>Hyponatremia Related to SIADH (N = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Water Restriction</td>
<td>Free Water Intake</td>
</tr>
<tr>
<td>Body Weight (kg)</td>
<td>77 ± 8</td>
<td>80.3 ± 9</td>
</tr>
<tr>
<td>Serum (mmol/L)</td>
<td>138 ± 1</td>
<td>126 ± 5*</td>
</tr>
<tr>
<td>Serum Protein (g/L)*</td>
<td>69 ± 4</td>
<td>64 ± 5*</td>
</tr>
<tr>
<td>Uric Acid (mg/dL)*</td>
<td>5.5 ± 0.6</td>
<td>3.9 ± 0.46</td>
</tr>
<tr>
<td>Creatinine Clearance (mL/min)</td>
<td>119 ± 20</td>
<td>147 ± 28</td>
</tr>
<tr>
<td>Uric Acid Clearance (mL/min)</td>
<td>6.4 ± 1.5</td>
<td>8.3 ± 3.3</td>
</tr>
<tr>
<td>24-h urate excretion (mg)</td>
<td>505 ± 79</td>
<td>475 ± 133</td>
</tr>
<tr>
<td>F_{uric} acid (%)</td>
<td>5.4 ± 0.9</td>
<td>5.7 ± 2</td>
</tr>
<tr>
<td>F_{Na} (%)</td>
<td>0.61 ± 0.15</td>
<td>0.66 ± 0.28</td>
</tr>
<tr>
<td>Urine Flow (mL/min)</td>
<td>0.84 ± 0.4</td>
<td>1.4 ± 0.4</td>
</tr>
</tbody>
</table>

* SIADH, syndrome of inappropriate antidiuretic hormone.
* P < 0.001.
* P < 0.01.
* P < 0.05 compared with values observed during hyponatremia induced by dDAVP.
* Conversion factor in mmol/L = mg/dl × 0.059.
induced some "pressure diuresis" (Table 2), a second test was performed the next morning with a lower dose of TGLV (2.5 μg/kg) injected in the same way. This dose produces an increase in plasmatic antidiuretic activity close to that of endogenous arginine-vasopressin concentrations (4).

The results are presented as mean ± SD, and conventional or paired t tests were used as appropriate. We also used linear regression.

RESULTS

Figure 1 shows the individual data of the volunteers and of the patients with SIADH. The patient with central diabetes insipidus (O) is presented also in the Figure. A few weeks after hypophysectomy for tumor-related Cushing's disease, this patient developed central diabetes insipidus. He presented mild hyponatremia (124 mmol/L) during dDAVP administration, which was associated with a slight decrease in serum uric acid level from an initial level of 3.6 mg/dL to 3 mg/dL, but the fractional uric acid excretion was not modified (F_{uric acid} 1.5% during normonatremia and hyponatremia). Similarly, in the volunteers with dDAVP-induced hyponatremia, we observed a decrease in serum uric acid concentrations from mean value of 5.5 mg/dL to 3.9 mg/dL (−29%) whereas serum sodium concentration decreased to a mean value of 126 mmol/L (−9%). Mean uric acid clearance tended to increase by 30% but this was not significant (6.4 ± 1.5 to 8.3 ± 3.3 mL/min; P < 0.10) (Table 1), and the fractional excretion of filtered uric acid was not modified (5.4 ± 0.9% before and 5.7 ± 2% during hyponatremia). The creatinine clearance rate increased significantly during the hyponatremic state only in the volunteers (119 ± 20 mL/min to 147 ± 28 mL/min; P < 0.05).

In the six patients with hyponatremia related to SIADH, the hypouricaemia observed during the hyponatremic state (125 ± 5.5 mmol/L) was more important (2.1 ± 0.3 mg/dL; a decrease of 53%) than that of the dDAVP-induced hyponatremia (−29%; P < 0.02). There was no significant difference in uric acid levels in both groups during normonatremia (4.5 ± 1.3 mg/dL and 5.5 ± 0.6 mg/dL; not significant [NS]). Uric acid clearance (17.8 ± 2.9 mL/min) and fractional uric acid excretion (19.6 ± 5.3%) increased largely during the hyponatremic state in the patients with SIADH (for both parameters P < 0.001). Both were also significantly higher than the value observed during dDAVP-induced hyponatremia (P < 0.01). There was also a mild increase in absolute 24-h uric acid excretion in the hyponatremic patients with SIADH (from 461 ± 154 mg/24 h to 525 ± 150 mg/24 h; P < 0.01). The mean body weight increase, protein concentrations, fractional excretion of filtered sodium, and the urine flow rate were similar in both hyponatremic groups (Table 1).

Our patient with CDI had no measurable endogenous ADH secretion. When hyponatremia was induced by water retention secondary to dDAVP administration, we observed a mild increase in uric acid clearance (from 7.2 mL/min to 10.8 mL/min) and fractional excretion (from 6.5% to 8%) (Table 2). After TGLV administration, the urate clearance and fractional excretion of uric acid rates acutely increased over at least 4 h (from 10.8 mL/min to 19.8 mL/min and from 8% to 13.6%, respectively) (Table 2). During
Figure 1. Evolution of serum sodium, uric acid concentrations, and fractional excretion of uric acid (FE.uric acid) during water restriction and free water intake in volunteers taking dDAVP (N = 7) or patients with SIADH (N = 6). The patient with central diabetes insipidus who developed hyponatremia after dDAVP intake is presented by an open circle (○). In SIADH patients, the values obtained after the correction of hyponatremia are presented first. The dotted line represents the 95% normal limits. To convert uric acid from mmol/L to mg/dL, we multiplied the number of mmol/L by 0.059.

Figure 2. Positive correlation between FE. Na and FE. uric acid in dDAVP-induced hyponatremia (●) (r = 0.78 + 5.2x; r = 0.78; P < 0.01) and lack of significant correlation between both parameters in the SIADH (○) (r = 0.33; NS).

DISCUSSION

Hyponatremia related to SIADH is typically associated with hypouricemia, a high uric acid clearance rate, and high fractional excretion of filtered uric acid (1,2). It is generally accepted that these changes are the consequence of increased “effective vascular volume.” In hyponatremia associated with a decreased “effective vascular volume,” serum uric acid concentration is normal or increased (2,6). In our study, volunteers with dDAVP-induced hyponatremia presented similar levels of hypoproteinemia and salt excretion than did patients with SIADH, suggesting similar degrees of plasma volume expansion (7). Nevertheless, reduction in serum uric acid levels was clearly less important in the group with dDAVP-induced hyponatremia than in patients with SIADH. The greater decrease in uric acid concentration (−29%) than was expected for the dilution (serum sodium, −9%) observed with dDAVP is probably the result of the mild (although not significant) increase in the uric acid clearance rate (6.4 ± 1.5 mL/min to 8.3 ± 3.3 mL/min; P < 0.10) recorded in this group with stable urinary flow rate (8) and salt excretion (9).

Patients with SIADH served as control subjects because long-acting AVP (Pitressin) is no longer available. However, our data can be compared with those published regarding five volunteers with Pitressin-induced hyponatremia of a similar level (Na, 128 ± 2 mEq/L) than that found in our study (Na, 126 ± 5

the 7.5 μg/kg TGLV test, the patient presented skin pallor of the face and hands for about 90 min, with a concomitant significant increase in blood pressure (120/80 mm Hg to a maximum of 160/100 mm Hg at the end of the TGLV perfusion). No significant modification of pulse rate was observed. With the lower dose of TGLV (2.5 μg/kg), no skin pallor or blood pressure and pulse rate changes could be observed. With the lower dose of TGLV, the urate clearance rate increased from 9.9 mL/min to 16.5 mL/min, and the fractional excretion rate from 8.4% to 11.2%.

In our volunteers, we observed a positive correlation between FFE Na and FFE uric acid (r = 0.78, N = 14; P < 0.01) (Figure 2). These data were collected when our volunteers were hyponatremic (Na < 132 mEq/L) and presented a body weight at least 2% higher than that seen during the normonatremic state. In our patients with SIADH, no significant correlations were observed between these two parameters (r = 0.33; N = 18; NS) when measured during conditions similar to those of the volunteers.
mEq/L) (1). In that study, uric acid clearance was determined after 2 or 3 days of hyponatremia, and increased from 8.7 ± 2.4 mL/min to 19 ± 5.9 mL/min (P < 0.01), a value similar to that observed in our patients with SIADH (17.8 ± 2.9 mL/min). In the patient with CDI and no residual AVP secretion, the development of hyponatremia during dDAVP substitution was associated with a mild increase in uric acid clearance from 7.2 to 10.8 mL/min. TGLV infusion, which slowly releases lysine-vasopressin during at least 4 h (4,5), and thus also newly stimulates the V₁ receptors, was followed by a striking additional increase in uric acid clearance (10.8 to 19.6 mL/min). This enhanced uric acid excretion rate is independent of the blood pressure changes observed with higher doses (7.5 μg/kg) of TGLV because at a lower dose (2.5 μg/kg) and unchanged blood pressure, uric acid clearance remained largely increased (9.9 to 16.5 mL/min).

A transient increase in salt excretion and urinary flow rates, presumably because of “pressure diuresis,” usually follows vasopressin escape (10). Nevertheless, with a low dose of TGLV, the uric acid clearance rate increased despite normal blood pressure, although mild increases in GFR, urine flow rate, and fractional excretion of sodium were noticed. It is known that urate clearance in man results from filtration, reabsorption, secretion, and postsecretory reabsorption (11). Glomerular filtration does not affect final uricosuria, which is in fact primarily dependent on tubular urate secretion and pre- and postsecretory reabsorption (11). Urate clearance normally does not increase significantly during rapid isotonic saline infusion until very high excretion rates for sodium are reached (9,12,13). For example, in one study performed in man, Fₑ[uric acid] after a stable degree of isotonic volume expansion, increased from a mean value of 8% to 9.8% whereas Fₑ[uric acid] increased frankly from a mean of 1% to 4.4% (12). It is known that the relationship between the fractional excretion of urate and fractional excretion of sodium is entirely attributed to their mutual correlation with volume expansion (13).

We noted a positive correlation between Fₑ[uric acid] and Fₑ[uric acid] only in the dDAVP group. Most patients with SIADH have a Fₑ[uric acid] higher than 12% (2) (14,15), and their uric acid clearance is not correlated with salt excretion (Figure 2) (15). The mechanisms for explaining this difference remain to be determined. The variation in urine flow rates in our study are also too small to affect urate clearance (11).

Our observation suggests that, in SIADH, in addition to the increase in “effective vascular volume,” stimulation of V₁ receptors contributes to the development of high uric acid clearance.

In rats, there is no difference in water retention induced by either dDAVP or AVP (7), although some investigators have reported a more negative sodium balance with AVP when fluid intake is forced (16). One could hypothesize that the difference in uric acid clearance rates observed between both hyponatremic models are the results of discrepancies between AVP and dDAVP stimulation of V₁ and V₂ receptors.

We know that dDAVP acts only on the V₂-receptor sites (3), whereas AVP is effective on both V₁ and V₂ receptors. Although it was not measured in this study, endogenous AVP was likely suppressed by the hyponatremic state induced by dDAVP, as observed in animals (7).

The mechanisms underlying our observation remain to be determined. Some possibilities could be suggested. Uric acid reabsorption is situated primarily in the proximal tubule and is indirectly coupled to sodium reabsorption (17,18). In SIADH, hyponatremia is associated with a decrease in proximal sodium reabsorption. It is possible that V₁-receptor stimulation affects systemic and/or intrarenal hemodynamics and thus indirectly influences proximal sodium and urate reabsorption. Another possibility is that AVP induces natriuresis (19,20) by acting on a V₁ subtype or perhaps a novel V₃ receptor (20,21). Some authors have suggested that this receptor could be located in the S₁ nephron segment (22), where uric acid reabsorption is most important (11). It is possible that the decrease in salt reabsorption is more specifically localized in the S₁ nephron segment in the AVP model, whereas in dDAVP-related hyponatremia, salt reabsorption is decreased more distally, which explains why uric acid reabsorption is influenced less in the second situation. However, it must be noted that the normal fractional uric acid excretion rate observed, despite mild hypouricemia during dDAVP-induced hyponatremia, is an unexpected observation. Indeed, induction of a low uric acid concentration is normally associated with a decrease in the uric acid clearance rate and fractional excretion secondary to a fall in tubular uric acid secretion (11). This means that there was probably also some decrease in tubular uric acid reabsorption in this model (23).

ACKNOWLEDGMENTS
This work was supported by a grant from the Fonds National de la Recherche Scientifique (FNRS) (1-5.175.94 F; 1.5.193.96 F).

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