Low urine flow reduces the capacity to excrete a sodium load in humans

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Low urine flow reduces the capacity to excrete a sodium load in humans. Am. J. Physiol. 273 (Regulatory Integrative Comp. Physiol. 42): R1726–R1733, 1997.—Recent studies in rats suggest that vasopressin and the resulting urinary concentrating activity reduce the capacity of the kidney to excrete sodium. The present study investigates the influence of the level of hydration on the excretion of a sodium load in humans. Eight healthy male volunteers (18–35 yr) were studied twice, in random order, under either low (LowH) or high (HighH) hydration. They drank throughout the study either 0.25 (LowH) or 2.0 ml water/kg body wt (HighH) every 30 min. After 1 h equilibration, urine was collected for 2 h before (basal) and 10 h after the NaCl load (5 g NaCl in 250 ml, infused intravenously over 30 min). Differences in excretory patterns between LowH and HighH were mostly confined to the first 4 h after the load. The increase in Na excretion after the load was more intense under HighH than under LowH (+10.9 ± 2.6 vs. +5.8 ± 2.7 mmol/h in the first 4 postload h; P < 0.001). Under HighH, urine flow rate (V) increased markedly (+41%), with little change in urinary Na concentration (U_Na), whereas under LowH, V declined slightly and U_Na rose significantly (+33%). The capacity to raise U_Na seemed to reach a maximum at ~280 mM. In both conditions, the changes in U_Na observed after the load were positively correlated with basal U_Na. After the load, urea excretion increased under HighH and decreased under LowH, whereas K excretion was unaffected in either condition. These results show that sodium excretion is facilitated by an abundant water supply. The less efficient sodium excretion occurring at low V is probably due to the influence of vasopressin on water, urea, and sodium movements across the collecting ducts. These observations suggest that, in everyday life, a low water intake could limit the capacity to excrete sodium. Whether this could contribute to salt-sensitive hypertension remains to be evaluated.

A number of studies have examined the capacity of the kidney to excrete a sodium load or to adapt to acute or chronic changes in sodium intake. The interest in this issue is justified by the fact that a reduced capacity to excrete sodium is thought to participate in the pathogenesis of some forms of hypertension or at least to aggravate preexisting hypertension, particularly in “salt-sensitive” subjects (12, 16, 22, 27, 29, 38, 40–43). Despite intensive investigation, the nature of the defect in renal function responsible for an impaired sodium excretion remains unclear. A role for hemodynamic, humoral, and neural factors has been proposed, such as failure to raise glomerular filtration rate, insufficient suppression of the renin-angiotensin-aldosterone system, or enhanced stimulation of the sympathetic nervous system (12, 29). However, little attention has been given to the possible contribution of antidiuretic hormone (i.e., vasopressin) in the renal impairment in sodium excretion.

In recent experiments performed in rats for other purposes, we observed that vasopressin or 1-desamino-8-d-arginine vasopressin (DDAVP; a potent antidiuretic agonist devoid of pressor effects) and/or the resulting urinary concentrating activity had a significant influence on natriuresis. Sodium excretion per unit time was much lower in concentrated urine than in more dilute urine (6). Subsequent studies in rats and humans showed that spontaneous or DDAVP-induced increases in urine osmolality did not involve equivalent increases in the concentration of all urinary solutes but exhibited a preferential concentration of urea at the expense of that of sodium (7).

In humans, the possibility that vasopressin and/or the resulting urinary concentrating activity could influence sodium excretion has been addressed only rarely. Actually, most human studies of renal function requiring periodic urine collections are usually performed after induction of an intense water diuresis to ensure adequate urine sampling. This lowers vasopressin secretion and abolishes the spontaneous urinary concentrating activity prevailing during most of normal life. Accordingly, a possible physiological influence of vasopressin and/or urinary flow rate on sodium excretion could not be observed and interpreted.

The present study was undertaken to evaluate, in humans, the influence of the level of hydration and thus of the intensity of the diuresis, on the capacity to excrete a sodium load. Healthy volunteers were studied twice on two markedly different levels of hydration, each subject thus being his own control. The high level of hydration was comparable to that used in most studies of renal function in clinical investigations, and the low level of hydration consisted in an eightfold lower amount of water intake per unit time.

**SUBJECTS AND METHODS**

**Subjects.** The study was performed in 10 male healthy volunteers aged 22–35 yr (28 ± 2, mean ± SE), weighing 59–76 kg (68 ± 2), and measuring 169–186 cm (176 ± 2). They were all on a free diet and were not taking any medication before or during the study. They had no history of renal disease, diabetes, or hypertension and were normotensive and had normal plasma creatinine at the time of the study. Dipstick urine analysis was negative for blood and proteins. The study was approved by the ethics committee of...
Each subject underwent two tests in a 2- to 3-wk interval in a randomized order under two different conditions of hydration. Each subject’s usual food and fluid intake was kept unchanged before the tests except that subjects were asked to avoid alcohol consumption during the day preceding each test. During that day, 24-h urine (8:00 AM to 8:00 AM) was collected for evaluation of fluid, urea, and electrolyte excretions.

General protocol. After an overnight fast, the subjects were submitted to one of the two hydration protocols (see below), starting at 8:00 AM. After 1 h of equilibration, plasma biochemistry and renal function were studied in each subject for 2 h before (basal) and 10 h after the infusion of a hypertonic sodium chloride solution (experimental) according to the schedule presented in Fig. 1. They were in the supine position. Spontaneous voiding was obtained once per hour for the first 6 h (i.e., 2 h before and 4 h after the load) and then 6 and 10 h after the load. Throughout the study, blood pressure was measured, and a blood sample was collected just before each voiding. The sodium chloride load consisted of 5 g NaCl (85 mmol) dissolved in 250 ml water (2% NaCl solution) and was infused intravenously at a rate of 8.3 ml/min over 30 min. Subjects ate a light breakfast at 8:30 AM and lunch and dinner (each containing 3 g NaCl) at 1:00 and 7:30 PM. Fluid intake was not allowed except for the periodic hydration described below (see Hydration protocol).

During both tests, the first three subjects studied received inulin (Polyfructosan; Inutest, Laevosan, Linz, Austria) and sodium p-aminohippurate (PAH; Nephrostest, Lich, Germany) dissolved in isotonic saline and infused intravenously at a rate of 1 ml/min (concentrations were adjusted to achieve plasma concentrations of ~200 and ~20 mg/l, respectively). It was then realized that the intravenous infusion of fluid associated with the administration of these two indicators had a distinct influence on the hydration status and on the basal urine flow rate (V) of the subjects during the study. It was therefore decided to omit this intravenous inulin and PAH infusion in the remaining seven subjects. During the first of his two tests, one of the subjects could not void appropriately before and during the experiment. Therefore, he was excluded from the study. The whole experiment was completed in nine subjects only (subjects 1-3 with and subjects 4-9 without intravenous infusion during both tests).

Hydration protocol. During the high hydration protocol (HighH), subjects drank 2 ml/kg body wt every one-half hour from 8:00 AM to 8:00 PM. In the low hydration protocol (LowH), they also drank every one-half hour during the entire study, so as to follow the same timing for the two tests, but the amount of water ingested was eightfold lower, amounting to only 0.25 ml/kg body wt. According to this protocol, the average fluid intake per subject was 272 ml/h under HighH and 34 ml/h under LowH. In all other respects, the two tests were carried out with exactly the same procedures and timing.

Measurements, calculations, and statistics. For each of the clearance periods, sodium, chloride, potassium, and urea concentrations were measured in plasma and urine samples with automatic analyzers (Multianalyzer Hitachi 717; Hitachi, Tokyo, Japan). Plasma and urine osmolality were measured with a freezing-point osmometer (Microosmometer Roebling, Berlin, Germany).

The following calculations were performed according to usual formulas: excretion of each solute and of total osmoles for each basal and experimental period (expressed per hour), cumulated excretions in the first 4 h after the NaCl load (expressed as mean per hour), weighted solute concentrations (or osmolality) during the first 4 h after the load (sum of solute concentration in each hourly urine sample times V of the corresponding hour, divided by the total V of the 4 h), and differences in excretion or concentration between experimental (first 4 h) and basal periods (change = experimental – basal).

Results are reported as means ± SE. Comparisons between results observed under LowH and under HighH condition during either the basal or the experimental period (first 4 h) were made by Student’s paired t-test. In some instances, individual data points were analyzed by linear regression (least-square method), and correlation coefficients were calculated by standard methods. Significance was defined as a P value <.05.

After the tests were completed, it was discovered that subject 5 had a very high Na excretion in the 24 h preceding the LowH test (324 mmol/day vs. 132–210 mmol/day, mean 170 ± 10, in the other 8 subjects), suggesting that his Na consumption had been unusually high on that day and markedly greater than on the day preceding his HighH test (Fig. 2A). This marked deviation clearly introduced a bias in the study (see RESULTS). For this reason, data of this subject were not included in the calculations of the means and the statistical evaluation of the results. Accordingly, means and statistics concern eight subjects only. However, in Figs. 2 and 6B, which show individual points, data of this subject were not withdrawn because they provide interesting observations.

RESULTS

All subjects, except subject 5 (see above), exhibited water, Na, Cl, K, and urea excretions within the normal range in the 24 h preceding each test. Moreover, their water and sodium excretions were comparable before the LowH and the HighH studies (except for subject 5) (Fig. 2).

Influence of the salt load in the two conditions of hydration. During the basal period, fluid excretion
recorded in HighH was nearly twice that recorded in LowH (244 ± 50 vs. 137 ± 29 ml/h, n = 8, P = 0.06), but osmolar, Na, Cl, K, and urea excretions were similar (Table 1). After the saline load, Na and Cl excretions rose in the two conditions, but the rise was distinctly greater under HighH than under LowH condition (Figs. 2 and 3). The only subject who did not raise his Na excretion more in HighH than in LowH was the one who had consumed an excessive amount of Na on the day preceding the LowH test (Fig. 2). The mean increase in Na excretion during the first 4 h after the saline load was 10.9 ± 2.6 mmol/h under HighH vs. only 5.8 ± 2.7 mmol/h under LowH (n = 8 subjects; P < 0.01). It is of note that the three subjects receiving an intravenous infusion throughout the whole tests (see SUBJECTS AND METHODS) exhibited the largest increases in V and in Na excretion after the load in both conditions (Fig. 2).

Figure 3 depicts V and urinary Na concentration (U_{Na}) (A and C) and the cumulative changes in water and Na excretions (B and D) observed above control values in the 10 postload hours. During the whole duration of the test, V declined below basal values under LowH and increased above basal values under HighH. There was a clear-cut difference in the pattern of Na excretion between the two conditions. The differences induced by the two levels of hydration were most striking during the first 4 h. They became weaker thereafter. It may be assumed that, after some time, secondary mechanisms came into play to compensate for the disturbances induced by the sodium load, so that the influence of water availability (and resulting antidiuretic hormone level) became less prominent. This is why the statistical analysis (intended to evaluate the direct influence of hydration) was performed on the cumulative changes observed during the first 4 postload hours (Table 1). After 4–6 h, the cumulated values reached a plateau in both conditions (Fig. 3). The fraction of the Na load excreted in the urine in 10 h was 55% under HighH but only 16% under LowH.

Because Na excretion is the product of two terms, U_{Na} and V, it is interesting to see how each of these two terms varies when Na excretion is increased. Under the HighH condition, the additional Na excretion observed during the first 4 h after the load was accounted for by a 41% increase in V, while U_{Na} actually decreased to some extent. In contrast, when water availability was limited under LowH, U_{Na} rose by 33% and V tended to decrease after the load (Fig. 3 and Table 2).

The time course of the excretions of Na, K, and urea is depicted in Fig. 4. With ample water supply, the rise in Na excretion was relatively large and was accompanied by a transient rise in urea excretion. In contrast, with reduced water availability, the rise in Na excretion was partially blunted and urea excretion declined right from the beginning. Remarkably, potassium excretion showed no perturbations after the NaCl load and was not influenced by the level of hydration (Fig. 4). The contrasting situation induced by the differences in water availability during the first 4 postload hours is summarized in Fig. 5. Chloride excretion showed the same pattern of changes as did sodium excretion in

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Table 1. Excretion of water, total osmoles, Na, K, and urea during basal period and change observed during the first 4 h after NaCl load

<table>
<thead>
<tr>
<th></th>
<th>Water, ml/h</th>
<th>Osmoles, mosmol/h</th>
<th>Na, mmol/h</th>
<th>Cl, mmol/h</th>
<th>K, mmol/h</th>
<th>Urea, mmol/h</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HighH</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>244 ± 50</td>
<td>60.0 ± 7.2</td>
<td>16.4 ± 3.4</td>
<td>14.4 ± 3.2</td>
<td>3.54 ± 0.55</td>
<td>29.6 ± 4.6</td>
</tr>
<tr>
<td>Δ</td>
<td>+101 ± 55</td>
<td>+19.7 ± 5.9</td>
<td>+10.9 ± 2.6</td>
<td>+10.9 ± 2.5</td>
<td>-0.84 ± 0.73</td>
<td>+4.4 ± 3.5</td>
</tr>
<tr>
<td>Δ%</td>
<td>+41</td>
<td>+33</td>
<td>+66</td>
<td>+76</td>
<td>-24</td>
<td>+15</td>
</tr>
<tr>
<td><strong>LowH</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>137 ± 29*</td>
<td>63.5 ± 8.3</td>
<td>17.0 ± 2.0</td>
<td>16.1 ± 2.2</td>
<td>4.34 ± 0.62</td>
<td>24.9 ± 3.7</td>
</tr>
<tr>
<td>Δ</td>
<td>-25 ± 26</td>
<td>+3.8 ± 8.3</td>
<td>+5.8 ± 2.7</td>
<td>+5.9 ± 2.8</td>
<td>+0.81 ± 0.83</td>
<td>-4.2 ± 3.1</td>
</tr>
<tr>
<td>Δ%</td>
<td>-18</td>
<td>+6</td>
<td>+34</td>
<td>+37</td>
<td>+19</td>
<td>-17</td>
</tr>
<tr>
<td>Paired t-test on Δ</td>
<td>P &lt; 0.05</td>
<td>P &lt; 0.01</td>
<td>P &lt; 0.01</td>
<td>P &lt; 0.001</td>
<td>NS</td>
<td>P &lt; 0.02</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 8 subjects. Δ, change (experimental minus basal); Δ%, change in % of basal; HighH, LowH, high and low hydration, respectively. Water excretion = urinary flow rate. *Difference between HighH and LowH for basal urine flow rate almost reached statistical significance (P = 0.06).
both conditions. Of note, urea excretion varied in the same direction as that of water. With increased V after the sodium load in HighH, urea excretion rose by 4.4 mmol/h on the average, whereas it declined by about the same amount (4.2 mmol/h) in LowH when V declined.

Additional information provided by observation of individual values. In addition to comparing group means, we examined the individual response to the salt load in each of the subjects in the two conditions of hydration. As is apparent in Fig. 6A, changes in \( U_{Na} \) were variable in HighH. \( U_{Na} \) went down in the subjects with basal \( U_{Na} \). In contrast, in the LowH condition, \( U_{Na} \) rose in all subjects. Nevertheless, the rise was relatively large in those who started with a relatively low basal \( U_{Na} \) (<150 mM) but was only trivial in those with higher basal values (>150 mM). Figure 6B shows that there are significant negative relationships, under both HighH and LowH, between the actual change in \( U_{Na} \) of each subject after the load and its basal \( U_{Na} \). The lower the \( U_{Na} \) in basal period, the larger the rise in \( U_{Na} \) after the load. Note also that, for a basal \( U_{Na} \) in the range of 100–180 mM, \( U_{Na} \) rose after the load under LowH but fell after the load under HighH (points falling above or below the line of zero change, respectively). In no subject did \( U_{Na} \) exceed 300 mM, and in no case did the rise in \( U_{Na} \) observed in 4 h exceed 150 mM above basal value. Note that the largest rise in \( U_{Na} \) in LowH was observed in subject 5, who had been conditioned to excrete a high sodium load in the previous 24 h (shown by an x on Fig. 6B).

### DISCUSSION

The aim of this study was to determine whether the level of hydration, i.e., the amount of fluid available for urine formation, influences the capacity of healthy humans to excrete sodium. The same subjects were studied on two occasions differing only by the amount of water ingested, and the experimental protocol was designed so as to explore renal function within a range of normal physiological regulations. Subjects remained on their usual water and sodium intake before the tests, and they were challenged with a relatively moderate sodium load (less than one-half their usual daily intake). In most previous studies investigating the renal response to a sodium load, the load consisted in a relatively large volume of isotonic sodium chloride (23–27, 39), resulting in a significant volume expansion. In the present study, the sodium load was given as a hypertonic solution to limit the amount of fluid

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**Table 2.** Urinary flow rate, Na concentration, and Na excretion during basal period and during the first 4 h after NaCl load

<table>
<thead>
<tr>
<th></th>
<th>V, ml/h</th>
<th>( U_{Na} ), mM</th>
<th>( U_{Na} ) × V, mmol/h</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HighH</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>244 ± 49</td>
<td>100 ± 17</td>
<td>16.4 ± 3.4</td>
</tr>
<tr>
<td>0-4 h</td>
<td>345 ± 63</td>
<td>81 ± 10</td>
<td>27.4 ± 5.3</td>
</tr>
<tr>
<td></td>
<td>NS</td>
<td>NS</td>
<td>P &lt; 0.01</td>
</tr>
<tr>
<td><strong>LowH</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>137 ± 29</td>
<td>164 ± 24</td>
<td>17.0 ± 2.1</td>
</tr>
<tr>
<td>0-4 h</td>
<td>112 ± 22</td>
<td>218 ± 14</td>
<td>22.8 ± 3.1</td>
</tr>
<tr>
<td></td>
<td>NS</td>
<td>P &lt; 0.01</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 8. V, urine flow rate; \( U_{Na} \), urinary sodium concentration. Statistical significance determined by Student’s paired t-test.
administered by the intravenous route and to vary water availability by the oral route. Moreover, the deliberate alterations in hydration did not involve massive water loading or dehydration.

The results clearly show that, after an acute NaCl load, a significantly larger amount of sodium and chloride can be excreted when abundant water supply is provided regularly before, during, and after the load than when water supply is relatively limited. Besides being influenced by the oral water intake, the capacity to excrete the sodium load was probably influenced by intravenously administered fluid as well. Under both HighH and LowH, the rise in Na excretion in the 4 postload hours was greater in the three subjects who received an intravenous infusion than in the six others who did not (Fig. 2). However, the influence of the different levels of oral hydration was still apparent.

The differences in urinary NaCl and water excretion between the two conditions were most marked during the first 4 h after the load. It is likely that the influence of the different hydration protocols was most pronounced in the first hours and that other mechanisms became preponderant subsequently, interfering with the specific actions of the body fluid/vasopressin system. For this reason, the discussion will focus mainly on the results observed during the first 4 h after administration of the load.

Interferences between water, sodium, and urea excretion. The results reveal that potassium excretion is not influenced by a NaCl load or by changes in the level of hydration (in the reasonable range investigated here). Potassium excretion was remarkably constant with time and equal in both studies. In contrast, the excretion of urea was altered by the NaCl load, and quite differently so according to the availability of water.

Contemporarily with the rise in NaCl excretion, a transient rise in urea excretion was observed at high V (HighH), whereas a marked fall was observed at low V (LowH), leading to a moderate deficit in urea excretion (16.8 mmol in 4 h, i.e., ~17% relative to basal excretion). The decline in urea excretion was relatively close to the concomitant rise in sodium excretion (23.2 mmol in 4 h).

It is usually assumed that the excretion of each solute and of water is regulated independently. This is certainly true on a long-term basis but might be more difficult to achieve during short-term regulation, as shown in the present study. The excretion of a given solute, e.g., sodium, is the product of two terms, \( U_{Na} \) and V. If the kidney could selectively and rapidly increase \( U_{Na} \), a rapid increase in Na excretion could be achieved easily without an increase in V. However, as shown in Fig. 6, the capacity of the kidney to raise \( U_{Na} \) seemed to be limited. No value above 280 mM was observed, i.e., about twice the plasma Na concentration. Note that the largest rise in \( U_{Na} \) after the load under LowH was observed in the subject who showed an unusually high sodium excretion the day before the study. He had probably been preconditioned to concentrate sodium and thus could raise \( U_{Na} \) more rapidly than other subjects after the acute NaCl load.

Why is the capacity to concentrate sodium in the urine limited? The design of the present study does not enable us to analyze the mechanism by which water availability interferes with the capacity to excrete sodium and the associated perturbations in urea excretion. However, a possible mechanism may be proposed, on the basis of the known actions of vasopressin along the nephron and on their integrated consequences on the composition of urine. The only difference between
nontal fluid (because the permeability to urea is low in most of the CD). Altogether, this process should concentrate urea (as well as potassium and other solutes) at the expense of sodium in the CD lumen.

With increasing vasopressin concentration (as is the case with low fluid intake), vasopressin effects on Na reabsorption in the CD become more potent and the imbalance between urea and sodium in the urine is probably accentuated. Accordingly, increases in urine osmolality along the CD are not achieved only by reabsorption of water but also by a more intense reabsorption of sodium needed to amplify the solute gradient present in the renal medulla (2). That potassium excretion remains constant is probably the result of two opposite effects, an increased passive backflux of potassium due to the fall in V and a stimulation of active potassium secretion induced by vasopressin (17).

Influence of vasopressin and/or hydration on sodium excretion in vivo. Because it is well established that vasopressin stimulates sodium reabsorption in the CD in vitro (34), it is logical to assume that it should induce a decrease in overall sodium excretion in vivo. However, this issue remained controversial for several decades. Many studies found that vasopressin was actually natriuretic (3, 4, 10, 21, 31), whereas others showed no influence or a distinct antinatriuretic effect (1, 8, 10, 18, 19). It is now understood that vasopressin induces natriuresis only in some unphysiological situations (acute vasopressin administration during volume expansion or after prior induction of an intense water diuresis by large water loads) (13, 20, 21) or when administered in pharmacological amounts. In the latter case, vasopressin may increase natriuresis by two independent and probably additive mechanisms, binding to oxytocin receptors (9) and stimulation of ANP release (28). It is thus now clear that vasopressin per se is not natriuretic within the physiological range of regulation.

That physiological vasopressin concentration might actually be antinatriuretic in humans and rats is suggested by several studies. In healthy, well-hydrated

the two tests was an eightfold higher water intake in HighH than in LowH throughout the study. It is thus most likely that vasopressin secretion was lower in the HighH than in the LowH condition and that the differences in water, sodium, and urea excretions observed between the two tests might result (directly or indirectly) from the influence of vasopressin on the kidney.

Vasopressin-dependent water reabsorption in the collecting duct (CD) could only concentrate all solutes in parallel. Now, all solutes are not concentrated equally in the urine (Table 3). When urine as a whole is concentrated ~2.3-fold more than plasma, sodium is not at all concentrated, and urea, the most abundant solute in the urine, is concentrated more than 50-fold. Urea concentration in the urine rests on osmotic energy provided by sodium reabsorption along the thick ascending limb and CD and on a complex intrarenal urea recycling process initiated by a selective vasopressin-dependent increase in urea permeability occurring exclusively in the terminal inner medullary CD (5).

In addition to its effects on water and urea permeability, vasopressin also stimulates sodium reabsorption in the CD by increasing the permeability to sodium of the luminal membrane of principal cells (34). The resulting dilution of sodium in the urine enables an additional osmotically driven water reabsorption that is proportional to the amount of sodium reabsorbed and thus should improve the concentration of urea in the lumi-

Table 3. Osmoles, Na, K, and urea in plasma and urine, and urine-to-plasma ratio in 8 healthy subjects

<table>
<thead>
<tr>
<th></th>
<th>Osmoles</th>
<th>Na</th>
<th>K</th>
<th>Urea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma concentration, mosmol/kg H₂O or mM</td>
<td>289 ± 3</td>
<td>141 ± 1</td>
<td>4.2 ± 0.2</td>
<td>5.7 ± 0.5</td>
</tr>
<tr>
<td>Urine concentration, mosmol/kg H₂O or mM</td>
<td>660 ± 49</td>
<td>144 ± 9</td>
<td>53.6 ± 7.1</td>
<td>275 ± 26</td>
</tr>
<tr>
<td>Daily urinary excretion, mosmol/day or mmol/day</td>
<td>890 ± 51</td>
<td>195 ± 14</td>
<td>72 ± 7</td>
<td>368 ± 21</td>
</tr>
<tr>
<td>U/P concentration ratio</td>
<td>2.29 ± 0.18</td>
<td>1.02 ± 0.07</td>
<td>12.4 ± 1.2</td>
<td>51.3 ± 5.7</td>
</tr>
</tbody>
</table>

Values measured in each subject before each of the 2 tests were averaged, and means ± SE of the 8 subjects are shown. Plasma values are those measured in the first blood sample taken at the beginning of the tests. Urine values are those measured in the 24 h preceding the tests. Urine flow rate was 1,420 ± 130 ml/day. U/P, urine to plasma.
volunteers as well as in Brattleboro rats with hereditary central diabetes insipidus, an infusion of vasopressin reproducing physiological plasma levels induced a significant decline in sodium excretion (1, 19). Conversely, the excretion of a sodium load was shown to be improved in both humans and rats by large water loads and resulting water diuresis, which washed out the medullary hypertonicity (23, 24, 32). Finally, we observed in healthy rats and humans that sodium excretion during normal micturitions throughout the day was 30–60% lower in urine samples produced with a low V (suggesting high vasopressin levels) than in those produced with a normal or high V (6, 7).

Perspectives: Possible Relevance in Salt-Sensitive Hypertension

Vasopressin has obviously been assumed to play a role in some forms of hypertension by its vasoconstrictor V1 effects on peripheral vasculature. However, it is also conceivable that this hormone could contribute to hypertension by its V2 effects exerted on the kidney. The present study shows that a low hydration and thus probably an elevated vasopressin secretion, within a physiological range, limits the capacity of the kidney to excrete sodium and could thus be responsible for some sodium retention and resulting hypertension. Several experimental studies in rats support this possibility (30, 33). A limited capacity to excrete sodium and/or a tendency to develop salt-sensitive hypertension on the one hand and increased vasopressin levels or increased tendency to concentrate urine on the other hand seem to be genetically associated in rodents and humans. Sabra SBH rats, a salt-sensitive hypertension-prone strain, exhibit, under a normal salt intake, a higher plasma vasopressin concentration and a more intense urine concentrating activity than the resistant control strain SBN (44, 45). African Americans, who seem to have an intrinsic reduction in the ability to excrete sodium (26), exhibit higher vasopressin levels than Caucasian subjects, and more so in men than in women and in hypertensive than in normotensive subjects, a pattern similar to the relative frequency of hypertension in these different groups (11, 14, 15, 36).

In conclusion, the present study shows that the kidney’s capacity to excrete sodium is limited when water supply is not abundant. According to the design of our study, keeping experimental conditions as close as possible to normal, the results observed in the LowH condition most probably pertain to normal regulations occurring in everyday life. In situations of low diuresis, the reduced capacity to excrete sodium seems to be due to the kidney’s inability to increase UNa selectively and rapidly. These findings suggest that elevated vasopressin levels (due to resetting of thirst and/or vasopressin thresholds) and/or a high tendency to concentrate urine in some individuals could induce temporary sodium retention and thus possibly favor salt-sensitive hypertension. The possibility of selectively suppressing V2 actions of vasopressin with newly developed specific receptor antagonists ("aquaretics") (35, 37) will provide a new experimental approach to investigate this issue.

NOTE ADDED IN PROOF

Vasopressin stimulates sodium reabsorption in the cortical CD not only by increasing the permeability to sodium of the luminal membrane of principal cells (34) but also by stimulating in a rapid, dose-dependent, and reversible manner the Na+-K+-ATPase activity located in the basolateral membrane of these cells (Coutry, N., N. Farman, J. P. Bonvalet, and M. Blot-Chabaud. Synergistic action of vasopressin and aldosterone on basolateral Na+-K+-ATPase in the cortical collecting duct. J. Membr. Biol. 145: 99–106, 1995).

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