Vasopressin V2 receptors, ENaC, and sodium reabsorption: a risk factor for hypertension?

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1Institut National de la Santé et de la Recherche Médicale, UMRS 872, Paris, France; 2Université Pierre et Marie Curie, Université Paris Descartes, Paris, France; and 4Service de Néphrologie, Hôpital du Sacré-Coeur, Université de Montréal, Montréal, Quebec, Canada

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Bankir L, Bichet DG, Bouby N. Vasopressin V2 receptors, ENaC, and sodium reabsorption: a risk factor for hypertension? Am J Physiol Renal Physiol 299: F917–F928, 2010. First published September 8, 2010; doi:10.1152/ajprenal.00413.2010.—Excessive sodium reabsorption by the kidney has long been known to participate in the pathogenesis of some forms of hypertension. In the kidney, the final control of NaCl reabsorption takes place in the distal nephron through the amiloride-sensitive epithelial sodium channel (ENaC). Liddle’s syndrome, an inherited form of hypertension due to gain-of-function mutations in the genes coding for ENaC subunits, has demonstrated the key role of this channel in the sodium balance. Although aldosterone is classically thought to be the main hormone regulating ENaC activity, several studies in animal models and in humans highlight the important effect of vasopressin on ENaC regulation and sodium transport. This review summarizes the effect of vasopressin V2 receptor stimulation on ENaC activity and sodium excretion in vivo. Moreover, we report the experimental and clinical data demonstrating the role of renal ENaC in water conservation at the expense of a reduced ability to excrete sodium. Acute administration of the selective V2 receptor agonist dDAVP not only increases urine osmolality and reduces urine flow rate but also reduces sodium excretion in rats and humans. Chronic V2 receptor stimulation increases blood pressure in rats, and a significant correlation was found between blood pressure and urine concentration in healthy humans. This led us to discuss how excessive vasopressin-dependent ENaC stimulation could be a risk factor for sodium retention and resulting increase in blood pressure.

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VASOPRESSIN WAS FIRST IDENTIFIED as a pressor hormone and later recognized to be also a potent antidiuretic hormone. Today, these early historical discoveries have been expanded by the identification of different receptor types. V1a receptors (V1aR), abundantly expressed in vascular smooth muscle cells, and signaling through calcium and phosphatidylinositol transducer pathways, are responsible for the pressor effects. V2 receptors (V2R), expressed mainly in principal cells of the renal collecting duct (CD), and signaling through cAMP, mediate the antidiuretic actions of the hormone (113).

Vasopressin is elevated in some forms of human hypertension (26, 92, 111) and in animal models of hypertension (see reviews in Refs. 91 and 108). This hormone has long been suspected to play a role in blood pressure control because of its vasoconstrictive effects, well demonstrated in vitro. However, the studies trying to evaluate the contribution of V1aR-dependent effects in hypertension are inconclusive [either in favor of (27, 35, 70) or against (59, 98)].

Excessive sodium reabsorption by the kidney is known to participate in the pathogenesis of some forms of hypertension. Among the genes responsible for monogenic forms of blood pressure disorders identified to date, the majority either mediate renal sodium transport in the distal part of the nephron or are involved in its regulation. Loss of function of the corresponding proteins leads to salt-wasting states with hypotension (48), and gain of function to salt-retaining syndromes and hypertension. Liddle’s syndrome, a severe and hereditary form of early onset hypertension, is due to gain-of-function mutations in the genes coding for either the β- or γ-subunits of the epithelial sodium channel, ENaC (41, 93). Patients exhibiting this syndrome have strongly increased ENaC activity (53, 82). If a permanent activation of ENaC is sufficient to induce severe hypertension, more subtle stimulation of ENaC by hormones or mediators could participate in essential hypertension (77).

ENaC is expressed in several excretory organs including the salivary glands, colon, and kidney. In the salivary glands and colon, aldosterone is the main hormone regulating ENaC abundance and activity. However, in the principal cells of the CD, vasopressin regulates ENaC activity, in addition to aldosterone. Vasopressin and V2R agonists thus not only increase water permeability of the CD but also stimulate sodium reabsorption (88, 90, 99). Accordingly, excessive vasopressin-dependent ENaC stimulation could potentially be a risk factor for sodium retention and an increase in blood pressure. This
sodium-retaining effect of vasopressin may probably be additive to that occurring upstream, on the Na-K-Cl cotransporter (NKCC) in the thick ascending limb and on the Na-Cl cotransporter (NCC) in the distal convoluted tubule (31, 64, 65, 74). The hormone levels required for these actions in the different parts of the distal nephron may differ and may exhibit significant species differences (5, 55). Moreover, even if vasopressin also influences NKCC and NCC activity, ENaC in the CD is the last transporter where a final regulation of sodium excretion can occur.

Vasopressin and aldosterone are released in response to different stimuli and act in different ways. The action of aldosterone is obviously linked to the need to conserve sodium. The renin-angiotensin-aldosterone system (RAAS) is stimulated by a low-sodium diet, and aldosterone increases sodium reabsorption in the distal nephron, as it does in the gut. In contrast, vasopressin is not known to be secreted in response to low sodium intake. It is secreted in response to increases in plasma osmolality, and mostly to hypernatremia, usually indicating a water deficit. Thus, why is renal ENaC regulated and activated by vasopressin? This review presents experimental and clinical data demonstrating the role of renal ENaC in water conservation at the expense of a reduced ability to excrete sodium and explains how this vasopressin-dependent function might contribute to salt-sensitive hypertension.

Vasopressin, ENaC, and Urinary Sodium Excretion

In the rodent and human kidney, ENaC is most abundantly expressed in the luminal membrane of connecting tubule cells and in principal cells of the CD, mainly in its cortical and outer medullary parts. The activity of this channel is considered to be the limiting step for sodium reabsorption in these segments. In the rodent and human kidney, the same cells express the V2R on their basolateral membrane, and aquaporin-2 (AQP2), the vasopressin-regulated aquaporin, on their luminal membrane (Fig. 1A). This coexpression of V2R, AQP2, and ENaC is also observed in the amphibian urinary bladder, often used as a model of the mammalian CD. A number of other mediators possess specific receptors and have been shown to act specifically on the same cells, including prostaglandins, dopamine, bradykinin, endothelin, and α2-adrenergic agonists.

Different time course and mechanism of vasopressin and aldosterone effects on ENaC. The major action of hormones involved in ENaC regulation is an alteration in channel density at the apical membrane (20). Most of the effect of aldosterone on sodium membrane transporters occurs over hours and involves the synthesis of specific proteins. Acute aldosterone-mediated ENaC activation by rapid, nongenomic mechanisms has been observed in isolated rabbit principal duct cells (112) and cortical CD cell lines (see review in Ref. 43), but the relevance of these effects in vivo are unknown. On the contrary, the rapid effects (minutes) of vasopressin on its target tissues are well established and can be reversed quickly because of the short biological half-life of the hormone. Sustained high vasopressin levels (for days) may also induce a long-term regulation of ENaC as explained below.

In several cell and tissue models, the addition of vasopressin or cAMP agonists induces a rapid increase in ENaC activity.

**Fig. 1.** Diagrams depicting the influence of AVP on ENaC in the collecting duct (CD) and the resulting potential consequence on urinary sodium excretion. A: vasopressin, binding to basolateral V2 receptors (V2R), not only increases water permeability through aquaporin-2 (AQP2) but also stimulates sodium reabsorption through the epithelial sodium channel (ENaC). Several other mediators, binding to their own receptors, induce a negative regulation of V2R-mediated effects by accelerating the degradation of cAMP by phosphodiesterases. The effect of AVP on water permeability seems to be more intense and/or to require a lower level of AVP than the effect on sodium transport (see text and Figs. 5 and 6). B: the amount of sodium reabsorbed under the influence of vasopressin in the CD is quantitatively small compared with that reabsorbed in other parts of the nephron. However, it may result in a very significant change in sodium excretion. If vasopressin stimulates sodium reabsorption by only one-tenth of its basal value (from 5.0 to 5.5%), this will reduce sodium excretion by half (from 1.0 to 0.5%). Thus even a modest stimulation of ENaC activity by vasopressin could have a large impact on sodium excretion in vivo. C, cortex; OS, outer stripe; IS, inner stripe; IM, inner medulla; PCT and DCT, proximal and distal convoluted tubule, respectively.
The increase in sodium transport occurs mainly by increasing channel density at the apical membrane through targeting and fusion of ENaC-containing vesicles (21). The translocation of ENaC to the apical membrane is facilitated by a vasopressin-induced increase in expression of an ubiquitin-specific protease (Usp10) that stabilizes sorting nexin 3 (18). On removal of a V2R agonist, ENaC is endocytosed from the membrane surface and reorganized into recycling vesicles, with a mechanism similar to that described for AQP2 regulation (21). Aldosterone also increases the abundance of ENaC at the apical membrane, mainly by decreasing ENaC internalization through the synthesis of SGK1, a kinase that negatively modulates the action of Nedd4–2 (28, 36, 96). Recent data suggest that the regulation of sodium transport is probably not only accounted for by changes in apical channel density but also by proteolytic maturation of its subunits and changes in open probability of the channel (19, 50, 83). The present models of proteolytic regulation of ENaC comprise intracellular action of furin and furin-like convertases at the Golgi and final activation by membrane-bound proteases or soluble proteases present in the extracellular milieu (49, 83). Furin and prostasin have been identified as activators of ENaC by releasing inhibitory peptides from the α- and γ-subunits that increase the channel open probability. Additional proteases can process the γ-subunit (CAP2, kallikrein, elastase . . .). However, the identification of tissue-specific proteases and the mechanisms of regulation of these proteases remain to be elucidated (50). It has been shown that aldosterone reciprocally regulates the expression of prostasin and protease nexin-1, an endogenous prostasin inhibitor (66). Our recent findings suggested that prostasin could be involved in the effect of vasopressin on ENaC (87), favoring the increase in channel open probability observed by Bugaj et al. (19) in the isolated murine CD.

In addition to the differing kinetics of the action of aldosterone and vasopressin, these two hormones also differ by their long-term effects on the abundance of ENaC subunits. In most aldosterone-sensitive tissues, aldosterone regulates the abundance of ENaC subunits at both the mRNA and the protein level (4, 32, 79). Surprisingly, however, in the kidney aldosterone does not increase the abundance of β- and γ-subunits (the 2 subunits in which gain-of-function mutations induce Liddle’s syndrome) and has only a very modest effect on the α-subunit (4, 32, 58, 106). In contrast, administration of vasopressin or the V2R agonist dDAVP in rats has been shown to increase significantly the abundance of the mRNA coding for these two subunits and of the corresponding proteins (Fig. 2, A and B) (30, 34, 68, 87). Salt-sensitive Brattleboro rats (SBH) rats, known to have higher vasopressin secretion and higher urine osmolality than their salt-resistant counterparts (108, 109), also have a higher abundance of β- and γ-subunits in kidney cortex (67). Moreover, changes in dietary salt intake in SBH rats did not modify ENaC subunit abundance, while an increase in water intake significantly lowered ENaC expression (67) (Fig. 2C) without affecting serum aldosterone level (67, 87). As shown in Sprague-Dawley rats, the vasopressin-induced increase in ENaC subunit abundance allows more intense sodium reabsorption in the CD upon acute stimulation by dDAVP (68) (Fig. 3A).

Studies of in vitro perfused cortical CD or of cell lines derived from amphibian bladder have shown that vasopressin and aldosterone exert synergistic actions on ENaC-mediated sodium transport (19, 22, 44, 78, 102). As illustrated in Fig. 3, B and C, the acute effect of vasopressin on sodium reabsorption in cortical CD from rats or mice is markedly potentiated by chronic stimulation of mineralocorticoid receptors (19, 90). The different mechanisms of action described above could account for at least some of the synergism between aldosterone and vasopressin. Moreover, it was shown in vitro that phosphorylation of Nedd4–2 by SGK1 or PKA, triggered by aldosterone or vasopressin, respectively, is a central point of convergence for ENaC regulation by the two hormones (94, 95). In this review, we purposely focused mainly on the influence of vasopressin on ENaC. However, because of the synergism observed in vitro, vasopressin may have only a modest effect on ENaC activity in vivo in situations in which aldosterone levels are very low.
Effects of ENaC stimulation by vasopressin on renal sodium excretion in vivo. Could the V2R-mediated effects on ENaC and sodium reabsorption demonstrated in vitro contribute to sodium retention in vivo? A theoretical calculation suggests that it should, as explained in Fig. 1B. Recent observations in vivo confirm that vasopressin significantly reduces sodium excretion. The acute administration of the potent and selective V2R agonist dDAVP not only increased urine osmolality and reduced urine flow rate but also reduced sodium excretion in rats (75) and humans (10) (Fig. 4). In patients with nephrogenic diabetes insipidus (DI) due to loss-of-function mutations of either AQP2 or V2R, dDAVP was unable to increase urine osmolality. However, it reduced sodium excretion in those with AQP2 mutations but not in those with nonfunctional V2Rs (10) (Fig. 4). In the isolated erythrocyte-perfused rat kidney (allowing good oxygenation of the medulla and thus operation of the concentrating mechanism), addition of dDAVP to the perfusate increased urine osmolality and decreased both urine output and fractional sodium excretion (52). This suggests that the effect observed in vivo is due to an intrarenal mechanism. The effect of dDAVP on sodium excretion is probably due, in large part, to a V2R-dependent ENaC-mediated increase in sodium reabsorption in the CD because prior administration of amiloride prevented the antinatriuretic but not the antidiuretic effect of dDAVP in water diuretic healthy subjects (16).

Besides these recent demonstrations of a direct negative V2R influence on natriuresis, several previous studies in normal rats and healthy humans showed that sodium was excreted faster or with a higher fractional excretion rate when hydration and thus urine flow were increased above normal, suggesting that a low urine flow impaired sodium excretion to some extent (2, 3, 12, 17, 23, 51, 63) (Table 1).

The effect of vasopressin on sodium reabsorption probably requires a higher hormone concentration than the effect on water reabsorption and is detectable only when urine osmolality reaches a certain threshold, as observed in vitro and in vivo in rats and humans. In the isolated, perfused rat cortical CD, a relatively high vasopressin concentration in the bath was needed to significantly stimulate sodium flux while water flux responded to much lower concentrations (Fig. 5A) (5, 90). In normal rats, acute V2R antagonist administration increased urine flow rate and sodium excretion dose dependently, but the effect on sodium was of much lesser magnitude than that on urine flow rate and sodium excretion dose dependently, but the effect on sodium was of much lesser magnitude than that on water flow rate and sodium excretion (3).

In normal life (without any intervention), a fall in sodium excretion or fractional excretion is observed only when urine osmolality rises above a certain threshold (~500–600 mosmol/kgH2O) (Fig. 6) (12, 63), suggesting that in humans also, a higher level of vasopressin is required to influence sodium reabsorption than water reabsorption. Moreover, these data reveal that a reduction in the efficiency of sodium excretion with increasing urine concentration occurs in about one-third of the urine samples obtained from healthy individuals in their usual lives.

When vasopressin levels reach pharmacological levels or are inappropriately high, a natriuretic action progressively compensates and even largely overrides the antinatriuretic V2R-
mediated effect. This vasopressin-induced natriuresis is mostly due to V1aR-mediated actions (5, 47, 75). This explains why vasopressin has often been described to be natriuretic. However, the level of vasopressin required to induce this V1aR-dependent natriuretic effect is probably not often reached in normal conditions (75).

It is important to stress that the intensity of the urine concentration process resulting from vasopressin action on the CD does not depend solely on the plasma level of vasopressin. Several hormones and mediators are known to interfere with the cellular effects of vasopressin by acting on phosphodiesterases that promote the degradation of cAMP in CD cells (Fig. 1A) (5). Thus, for a given vasopressin level, the intensity of vasopressin’s effects on water and sodium reabsorption will depend on the level of all other mediators acting simultaneously on the same cells. For example, it is well established that prostaglandins counteract the antidiuretic action of vasopressin, whereas nonsteroidal anti-inflammatory drugs (NSAID) potentiate it. Although less often mentioned, these mediators also influence its antinatriuretic action in the same way. This may, at least in part, explain the well-known sodium retention induced by NSAID in vivo (42) as also observed in the isolated kidney in vitro (52). Activation of V1aR in the apical membrane of CD principal cells and in interstitial medullary cells is known to stimulate prostaglandin production and may thus attenuate V2R-mediated effects (5, 75). Bradykinin has also been shown, both in isolated, perfused rat CD and in transgenic mice, to attenuate vasopressin action on water and sodium transport (99) and urine concentration (1).

**Table 1. Influence of urine concentration on sodium absolute or fractional excretion in 1 rat study and 5 different human studies**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Species</th>
<th>Conditions</th>
<th>Measurement</th>
<th>Low Urine Concentration</th>
<th>High Urine Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>17</td>
<td>2 Groups of rats</td>
<td>Increase in water intake or infusion of dDAVP for 5–7 days. Urine collected for 2 × 24-h periods.</td>
<td>FE Na, %</td>
<td>1.19 ± 0.12</td>
<td>0.73 ± 0.03</td>
</tr>
<tr>
<td>3</td>
<td>9 Healthy volunteers</td>
<td>Acute water diuresis followed by infusion of 25 pg·min⁻¹·kg⁻¹ AVP for 2 h.</td>
<td>Na excretion rate/GFR, μmol/100 ml</td>
<td>61 ± 9</td>
<td>26 ± 3</td>
</tr>
<tr>
<td>2</td>
<td>12 Healthy volunteers</td>
<td>Same subjects submitted to high or low oral hydration for 3 h on 2 different days, 3 wk apart.</td>
<td>FE Na, %</td>
<td>2.14 ± 0.28</td>
<td>1.42 ± 0.16</td>
</tr>
<tr>
<td>23</td>
<td>8 Healthy volunteers</td>
<td>Acute hypertonic iv sodium load in the same subjects submitted to either a high or a low oral hydration, on 2 different days, 2 wk apart.</td>
<td>Increase in Na excretion rate after the NaCl load, mmol/ h</td>
<td>10.9 ± 2.6</td>
<td>5.8 ± 2.7</td>
</tr>
<tr>
<td>12</td>
<td>12 Normal subjects during normal life</td>
<td>Urine collected in 7–8 successive micturitions per subject over a 24-h period. Comparison of urine samples produced with the 20% highest and 20% lowest urine flow rate.</td>
<td>Na excretion rate, mmol/h</td>
<td>10.1 ± 1.1</td>
<td>3.2 ± 0.4</td>
</tr>
<tr>
<td>63</td>
<td>66 Normal subjects with free food and fluid intake</td>
<td>Individual spot urine samples. Subjects were divided a posteriori into 2 groups according to their urine concentration (urinary-to-plasma creatinine concentration ratio below or above 140).</td>
<td>FE Na, %</td>
<td>0.9 ± 0.3 (SD)</td>
<td>0.4 ± 0.2 (SD)</td>
</tr>
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</table>

Values are means ± SE, except where stated otherwise. FE Na, fractional sodium excretion; GFR, glomerular filtration rate.
experimental vs. basal: *P < 0.05, **P < 0.01, ***P < 0.001.

Water Conservation at the Expense of Less Efficient Salt Excretion

Sodium and water conservation or excretion are often associated. A highly effective control mechanism keeps sodium concentration in plasma and extracellular fluids within narrow limits. Vasopressin is a critical hormone in this homeostatic regulation because the osmoreceptor neurons that influence vasopressin release are most sensitive to extracellular sodium concentration. An increase in plasma sodium concentration will stimulate vasopressin release, which will in turn promote water reabsorption, but also impair to some extent the ability of the kidney to excrete sodium because of vasopressin’s effect on ENaC. This regulatory pathway is counterbalanced by the pressure-natriuresis mechanism. An increase in extracellular fluid volume due to water and sodium retention induces an increase in blood pressure, which, in turn, reduces isosmotic sodium and water reabsorption in the kidney and allows readjustment of the extracellular fluid volume. Note that during pressure-natriuresis, sodium and water excretions are increased simultaneously and to the same extent (83). This pathway brings sodium balance back to normal, at the expense of an increase in blood pressure (40). All individuals are not equally sensitive to salt excess. “Salt-sensitive” subjects exhibit larger changes in blood pressure than “salt-resistant” subjects when submitted to abrupt changes in salt intake (62, 105). Presumably, the osmoreceptor-vasopressin-thirst system may play a role in the magnitude of salt-dependent changes in blood pressure. The influence of aldosterone on ENaC activity in both the colon and kidney suggests a role for this channel in sodium conservation. However, the fact that, in the kidney, ENaC is also regulated by vasopressin suggests that ENaC may, in addition, play a role in water conservation.

As explained above, low levels of vasopressin probably act only, or mostly, on water permeability, whereas with higher levels of vasopressin, sodium reabsorption is also stimulated and promotes additional water reabsorption. These differences in vasopressin’s influence on water and sodium handling may be due to the different distribution of AQP2 and ENaC along

Fig. 5. Vasopressin or V2R activation affects sodium excretion to a much lesser extent than water excretion. A: dose-dependent influence of vasopressin (AVP) on water permeability and net sodium flux of isolated, perfused rat cortical CDs. The water permeability response was more sensitive to low vasopressin levels than the sodium transport response. The maximum effect on water permeability was reached for vasopressin concentrations that elicited only a fraction of the maximum effect on sodium transport. Adapted from Ref. 44, and reproduced from Ref. 5. B: dose-dependent influence of dDAVP on water and sodium excretion rates in conscious rats. On day 1 (basal), all rats were injected intraperitoneally (ip) with vehicle only. On day 2 (experimental), rats received an ip injection of dDAVP at one of the doses indicated in the abscissa. BW, body wt. Urine was collected for the next 6 h. The V2R agonist induced a marked decline in urine flow (top) and rise in urine osmolality (not shown) already close to maximum with the smallest dose used. In contrast, the reduction in sodium excretion rate was much more progressive (thin line) and reached its maximum at 2 mg/kg. Adapted from Ref. 75. Paired t-test, experimental vs. basal: *P < 0.05, **P < 0.01, ***P < 0.001.

Fig. 6. Relationship between urine concentration and sodium excretion in healthy subjects. A: 12 healthy volunteers collected their urine in multiple fractions throughout a 24-h period (6–9 samples/subject) during their usual activities and while maintaining their usual fluid and food intake. The resulting 92 urine samples were divided into quintiles (Q) according to decreasing urine flow rates. In the first three quintiles, urine flow rate (V) declined sharply without affecting sodium excretion rate (Na), suggesting an ability of the kidney to regulate independently water and sodium excretion. For urine flow rates below 80 ml/h and urine osmolality (Uosm) above 140 (which corresponds to ~600 mosmol/kgH2O; slope traced freehand). Adapted from Ref. 63.
the CD. Even modest increases in water permeability will favor water reabsorption along the entire CD, including its medullary portion lying in a hyperosmotic environment. However, in the cortex, osmotic equilibration with the surrounding interstitium likely occurs relatively early along the collecting system (connecting tubule and initial cortical CD). Thus, in later sections of this collecting system within the cortex and outer medulla, more water can be reabsorbed only if solutes are reabsorbed (89). ENaC-mediated sodium reabsorption creates an osmotic driving force that allows an additional (isosmotic) reabsorption of water (89). Such isosmotic water and sodium reabsorption in the cortex leaves sodium concentration in the lumen unchanged (68) but concentrates all other solutes in the tubular fluid and thus favors final urine concentration. As recalled earlier, vasopressin is not secreted in response to a sodium deficit. Thus its ability to regulate ENaC activity and abundance is not likely related to the need to conserve sodium. Rather, based on the observations listed above, we propose that the action of vasopressin on ENaC is intended to conserve water by allowing more water to be reabsorbed from the CD, thus enhancing the concentration of other solutes and reducing the amount of water required for their excretion. Water conservation is favored at the expense of less efficient sodium excretion.

Interestingly, a similar improvement in water conservation occurs with urea (Fig. 7). Although the kidney needs to excrete a relatively large daily load of urea (on a normal protein intake), the vasopressin-dependent urea transporter UT-A1, located in the terminal inner medullary CD (54), allows significant amounts of urea to be reabsorbed. This improves urea accumulation in the medullary interstitium and favors overall urine concentration (33), but results in less efficient excretion of urea (like for sodium with the effect on ENaC), as illustrated by the fall in fractional excretion of urea with declining urine flow rate (8). Thus vasopressin’s actions on ENaC in the cortex and outer medulla, on the one hand, and on UT-A1 in the inner medulla, on the other, can be viewed as two independent and additive means to improve water conservation (Fig. 7). The less efficient urea excretion due to vasopressin action is compensated for by an increase in plasma urea level that allows more urea to be filtered (8, 17). The less efficient sodium excretion may secondarily induce pressure-natriuresis. This concept is also supported by the finding of reduced blood pressure dipping at night (hence a relative nocturnal hypertension) in subjects in whom sodium and water excretion during the daytime is an abnormally low fraction of the total 24-h excretion (6, 7, 37). When subjects are in a steady state, the influence of urine flow rate on diuresis/natriuresis is not discernible in 24-h urine because the nighttime period compensates for changes occurring during the daytime period (or vice versa in rats which are active mostly during the nighttime).

**Water Conservation and Blood Pressure: Pathophysiological Observations**

The data reported above demonstrate that vasopressin’s effects on ENaC result in better water conservation but less efficient sodium excretion. This effect of vasopressin on so-
diuretic hormone (80). Moreover, complex specific tissue inter-
actions were shown between V2 and V1a effects, at the
epithelial and vascular levels (25). Acute regional vasodilator
and hypotensive effects of dDAVP mediated by endothelial
V2R and NO production have been reported in healthy humans
and animals (15, 45, 97, 101, 103).

In summary, several local or peripheral compensatory mech-
anisms may offset the vasopressin/ENaC-mediated effect on
blood pressure. The resulting increase in blood pressure
is likely small and does not reach pathological values. However,
in the presence of other aggravating factors, vasopressin could
contribute to sodium retention and become one of the multi-
determinants of salt-dependent hypertension.

Vasopressin and blood pressure: effects of gender, ethnic
background, and geographic location in humans. Men are
known to be more susceptible to hypertension than women.
Studies have shown that men have higher vasopressin levels
than women and that the antidiuretic effect of a given dose of
vasopressin is stronger in men than in women (76). This could
contribute to their greater susceptibility to hypertension.

It is conceivable that a higher urine concentration, especially
during the daytime, may induce a temporary sodium and water
retention that favors a rise in blood pressure. In young normo-
tensive Americans (age range 18–40 yr), a significant positive
correlation was observed between systolic or pulse pressure
and mean 24-h urine concentration in men but not in women
(11) (Fig. 8). Over the whole range of urine concentration,
systolic and pulse pressure were significantly higher in African
Americans (AA) than in European Americans (EA) (Fig. 8).
Now, AAs show a greater susceptibility to develop hyperten-
sion than EAs. Some studies suggest that they have higher
vasopressin levels and/or higher urine osmolality (11, 24) and
are less able to dilute urine after a water load (104). AAs also
have a less active RAAS. This has been proposed to be part of
corrective mechanisms involved in maintaining sodium bal-
ance in response to sodium retention (85). As proposed earlier,
there may be a balance between the RAAS and the osmore-

### Table 2. Influence of chronic dDAVP infusion on blood pressure in conscious rats

<table>
<thead>
<tr>
<th></th>
<th>Systolic blood pressure measured by tail-cuff method, mmHg</th>
<th>Basal</th>
<th>dDAVP (1 wk)</th>
<th>Recovery</th>
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<td><strong>Wistar Rats with 2 Kidneys (13)</strong></td>
<td></td>
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<td>Rats with no pretreatment</td>
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<td>132 ± 3</td>
<td>132 ± 4</td>
<td>124 ± 3*</td>
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<td>Rats with ACEI pretreatment</td>
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<td>106 ± 2</td>
<td>112 ± 2*</td>
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<tr>
<th></th>
<th>Systolic blood pressure measured by tail-cuff method, mmHg</th>
<th>Basal</th>
<th>dDAVP (2 wk)</th>
<th>dDAVP (4 wk)</th>
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<tr>
<td><strong>Uninephrectomized Sprague-Dawley Rats (34)</strong></td>
<td></td>
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<tr>
<td>Control rats (no dDAVP)</td>
<td></td>
<td>125 ± 3</td>
<td>131 ± 7</td>
<td>189 ± 8</td>
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<tr>
<td>Experimental rats (dDAVP)</td>
<td></td>
<td>125 ± 3</td>
<td>142 ± 4*</td>
<td>207 ± 3*</td>
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<th></th>
<th>Mean arterial pressure measured continuously over 24-h by intra-arterial catheter, mmHg</th>
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<th>dDAVP (2 wks)</th>
<th>Recovery</th>
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<td></td>
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<td>107 ± 2</td>
<td>117 ± 2</td>
<td>108 ± 3</td>
</tr>
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</table>

Values are means ± SE in all 3 studies, dDAVP was infused continuously at the following doses: top and middle, 0.6 μg·day⁻¹·kg body wt⁻¹ ip; bottom, 2 ng·min⁻¹·kg body wt⁻¹ iv. Top: the ACE inhibitor was perindopril (10 ng·kg⁻¹·day⁻¹) mixed with powdered food and started 10 days before the experiment. Middle: dDAVP was given only in rats in the experimental group, but both groups were subjected to the DOCA-salt treatment. Comparison with the previous period: *P < 0.05, †P < 0.01.
because nicotine is a potent stimulator of vasopressin release may be partially responsible for some of these adverse effects. A rise in vasopressin levels is known to be an aggravating risk factor for high blood pressure and cardiovascular events. Smoking is known to be an aggravating risk factor for high blood pressure (69), suggesting an association during evolution between better water conservation (an essential function in heat adaptation) and higher blood pressure. Nephrolithiasis has been repeatedly found to be associated with high blood pressure (69), suggesting that a common factor such as high urine concentration favors the simultaneous occurrence of the two diseases. Smoking is known to be an aggravating risk factor for high blood pressure and cardiovascular events. A rise in vasopressin levels may be partially responsible for some of these adverse effects because nicotine is a potent stimulator of vasopressin release (46, 84).

Taken together, these observations regarding gender and ethnic differences, and associations of high blood pressure with climate, urolithiasis, or smoking, support the notion that hypertension is favored by high urine concentration and hence by the balance between the antidiuretic/antinatriuretic action of vasopressin and the counteracting effects of other humoral factors acting on the CD.

**Water conservation and blood pressure: evolutionary aspects.** In ancestral times, salt intake was low and it was appropriate to conserve simultaneously salt and water. Reabsorbing sodium to conserve water had no adverse consequences. The present Western-type diet provides significantly more sodium and less potassium than prehistoric food. The typical balance between the RAAS and the thirst-vasopressin system is still the same although water conservation is no longer crucial. To date, conserving water and sodium simultaneously is less necessary, at least in Western countries. Moreover, natural selection during human evolution may have favored the survival and expansion of subjects with a good ability to conserve water, even if the price to pay was a poor, or rather a delayed capacity to excrete sodium. Poor water conservation increases the risk of dehydration and death within a few days, whereas a poor sodium excretory capacity has only long-term adverse effects by raising blood pressure and favoring cardiovascular diseases later in life, usually after the age of reproduction, thus without influence on natural selection.

Moreover, changes in diet from the hunter-gatherer civilization to present living conditions probably makes aldosterone and the renin-angiotensin system less important than it was in primitive humans. In this context, and without enough time for significant evolutionary changes, we hypothesize that the osmoreceptor-vasopressin-thirst axis has reached a greater influence in the overall regulation of water and salt homeostasis.

**Conclusion**

In conclusion, the studies reviewed above suggest that the effects of vasopressin on renal ENaC abundance and activity are part of a mechanism that contributes to water conservation at the expense of less efficient sodium excretion. Vasopressin, which is elevated in some forms of hypertension, could contribute to a rise in blood pressure, not by its V1A-R-mediated effects (that actually facilitate sodium excretion) but by its V2R-mediated effects. High salt intake would probably not affect blood pressure in salt-sensitive individuals did the kidney dispose of larger amounts of water to excrete the salt. In Western countries, with a long life expectancy, relatively high levels of salt intake and less risks of dehydration, it might be appropriate to reduce, even if only modestly, the spontaneous tendency to conserve water (i.e., to concentrate urine) that occurs at certain times of the day, to accelerate sodium excretion after each intake. It is, however, difficult to increase fluid intake deliberately above what natural thirst commands. Even subjects with recurrent, painful nephrolithiasis often do not succeed in raising their urine output above the recommended amount of 2 liters/day (9, 73). In this context, it will be interesting to see whether newly designed “aquaretics” (selective vasopressin V2R antagonists) (29, 38) are able to reduce salt-sensitive hypertension with fewer side effects than classic diuretics. Interestingly, V2R antagonists have been shown to increase sodium excretion in cirrhotic patients (39). It is conceivable that hyponatremic heart failure or cirrhotic patients, resistant to classic diuretics, may increase their sodium...
excretion if the diuretic is associated with a small dose of a vasopressin receptor antagonist, promoting a moderate increase in urine flow rate. Finally, it will be interesting to see whether tolvaptan treatment in patients with polycystic kidney disease (100) will prevent or retard the development of hypertension, in addition to reducing cyst expansion.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

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