The importance of distal delivery of filtrate and residual water permeability in the pathophysiology of hyponatremia

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The purpose of this commentary is to suggest that hyponatremia may develop in some patients in the absence of vasopressin action and to illustrate the possible pathophysiology and its clinical implications.

The traditional approach to understanding the pathophysiology of hyponatremia centers on a reduced electrolyte-free water excretion due to actions of vasopressin [1, 2]. In some clinical settings, release of vasopressin is thought to be due to decreased effective arterial blood volume (EABV). Notwithstanding, at least in some patients, the degree of decreased EABV does not seem to be large enough to cause the release of vasopressin [3]. Acutely reducing EABV by as much as 7% in healthy adults has little effect on vasopressin levels; a 10–15% reduction in EABV is required to double plasma vasopressin levels [4]. In a series of patients with thiazide-induced hyponatremia reported by Sonnenblick et al. [5], four patients had a plasma vasopressin level measured, and in three of them, it was either low or below the level of detection. Ghose [6] reported measurements of plasma arginine vasopressin in six patients with diuretic-induced hyponatremia. In three of these patients, it was ~0.4 pg/mL and ~1 pg/mL in the other three patients. Urine osmolality was 300 mosmol/kg H₂O or less in three of five patients in whom the urine osmolality was measured. Oh et al. reported two patients with what these authors called ‘trickle-down hyponatremia’. Both these patients had a low rate of excretion of osmoles, urine osmolality of close to 325 mosmol/kg H₂O and undetectable levels of vasopressin in their plasma [7]. Thaler et al. [8] reported a patient with hyponatremia and low dietary solute intake in whom the urine osmolality was 81 mosmol/kg H₂O and vasopressin level in plasma was below the limits of detection. Of note, 5–10% of hyponatremic patients with the syndrome of inappropriate anti-diuresis have low or undetectable levels of vasopressin in their plasma [9]. Although some patients may have gain-of-function mutations in the V₂ vasopressin receptor [10], the pathophysiology of hyponatremia in this subset of patients remains largely undetermined. It is possible that these examples may reflect the levels of vasopressin that are sufficient to produce a biological effect but are under the level of detection by the available assays for vasopressin. This may be the case especially in females who may have more vasopressin V₂ receptor expression and greater sensitivity to vasopressin-induced anti-diuresis [11]. In healthy human volunteers undergoing water diuresis, an infusion of vasopressin that resulted in a significant reduction in urine flow rate induced no detectable change in plasma vasopressin concentration [12]. It is of interest to note, however, that the urine osmolality in these subjects rose to ~600 mosmol/kg H₂O. Furthermore, studies by Berliner and Davidson have shown that hypertonic urine can be produced in the absence of pituitary anti-diuretic hormone. In these experiments, in dogs undergoing a water diuresis, reducing the glomerular filtration rate (GFR) to one kidney resulted in the production of urine with an osmolality of close to 350 mosmol/kg H₂O, while urine from the contralateral kidney had an osmolality of ~70 mosmol/kg H₂O [13].

There are two factors that may reduce electrolyte-free water excretion sufficiently and lead to the development of hyponatremia even in the absence of vasopressin actions; the volume of filtrate that is delivered to the distal nephron and the volume of water that is reabsorbed in the inner medullary collecting duct through its residual water permeability (RWP) [14]. A brief case example is provided to illustrate the quantitative importance of these factors in the pathophysiology of hyponatremia.

A 71-year-old woman was started on hydrochlorothiazide 25 mg daily for treatment of hypertension. She had ischemic renal disease with an estimated GFR of 28 mL/min (40 L/day). She consumed a low-salt low-protein diet and drank eight cups of water each day to remain ‘hydrated’. She was not taking any other drugs that may be associated with hyponatremia. A month later, she presented to her family doctor feeling unwell. Her blood pressure was 130/80 mmHg, her heart rate was 80 beats/minute, there were no postural changes in her blood pressure or heart rate, and her jugular venous pressure was ~1 cm below the level of the sternal angle. Her plasma Na⁺ concentration (PNa) was 112 mmol/L and her...
urine osmolality was 325 mosmol/kg H2O. A summary of laboratory data in blood and urine is provided in Table 1.

**Distal delivery of filtrate**

The volume of distal delivery of filtrate is the volume of glomerular filtration minus the volume of filtrate that is reabsorbed in the nephron segments prior to the collecting tubule. Recent findings suggest that aquaporin 1 water channels (AQP1s) are not present in the luminal membranes of the majority of descending thin limbs of the loop of Henle in rats, mice and humans [15], and hence, they are likely impermeable to water. Only descending thin limbs of the juxtamedullary nephrons (15% of all nephrons) possess AQP1. Therefore, for 85% of nephrons, the volume of distal delivery of filtrate will equal the GFR minus the volume that is reabsorbed by the proximal convoluted tubule. It has been suggested that ~60% of the GFR is reabsorbed along the proximal convoluted tubule [16]. This is based on a measured ratio of inulin concentration in proximal tubular fluid to plasma [(TF/P)inulin] of ~3 from micropuncture studies in rats in which inulin was infused (Figure 1) [17]. However, these micropuncture measurements were made at the surface of the renal cortex and do not take into account the volume reabsorbed in the more distal part of the proximal convoluted tubule including its pars recta portion and therefore underestimate the fractional reabsorption in the entire proximal convoluted tubule.

Because the entire loop of Henle of the majority of nephrons is impermeable to water, the volume of filtrate that exits their proximal convoluted tubules can be deduced using (TF/P)inulin data obtained with the micropuncture technique from early distal convoluted tubules in rats. Since the lowest measured value is ~6 [18], 5/6 (83%) of the volume that is filtered is reabsorbed in proximal convoluted tubules. This value is close to the estimate of fractional reabsorption in proximal convoluted tubules obtained with measurement of lithium clearance in human subjects [19].

Extrapolated to humans with a GFR of 180 L/day, only ~30 L of filtrate per day (180/6) would be delivered to the loops of Henle if all nephrons were superficial. This number needs to be adjusted downward because juxtamedullary nephrons have AQP1 along their descending thin limbs. If these nephrons are 15% of the total and receive 27 L of GFR per day (15% × 180 L/day), and if 5/6 of their GFR is reabsorbed along their proximal convoluted tubules, 4.5 L/day reach their descending thin limbs. As the interstitial osmolality rises 3-fold (from 300 to 900 mosmol/kg H2O) in the outer medulla, 2/3 or 3 L of the 4.5 L/day are reabsorbed in the descending thin limbs of these nephrons. Therefore, the volume of filtrate delivered to the distal convoluted tubules is likely to be 27 L/day (30 L/day exit the proximal convoluted tubules minus 3 L/day that are reabsorbed in descending thin limbs of the juxtamedullary nephrons).

The volume of distal delivery of filtrate will be reduced if the GFR is decreased or if the fractional reabsorption of NaCl in proximal convoluted tubule is increased. The later will occur in response to decreased EABV. This can be due to a total body deficit of NaCl e.g. diuretic use in a patient who consumes little salt. Even a relatively small decrease in EABV leads to sympathetic activation [3]: β-adrenergic stimulation activates the ren–angiotensin–aldosterone system, both of which will activate proximal tubular reabsorption of sodium and water and therefore reduce distal delivery of filtrate.

To put this in a quantitative perspective, consider the case described above where the patient had a low baseline GFR of 40 L/day. The use of diuretics and the low-salt diet led to a sodium deficit and thereby a mild reduction in EABV. If she were now to reabsorb 90% of her GFR (GFR may be even lower because of the mild reduction in her EABV) in the proximal convoluted tubule instead of 83%, <4 L/day will be delivered distally, this is the maximum urine volume she can excrete. This volume exceeds the usual daily intake of water, but hyponatremia still can develop in such a patient because there is water reabsorption by RWP along the inner medullary collecting duct even in the absence of actions of vasopressin.

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**Table 1.** Laboratory data in blood and urine in the case example

<table>
<thead>
<tr>
<th></th>
<th>Plasma</th>
<th>Urine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na⁺, mmol/L</td>
<td>112</td>
<td>22</td>
</tr>
<tr>
<td>K⁺, mmol/L</td>
<td>3.6</td>
<td>6.1 (0.7)</td>
</tr>
<tr>
<td>HCO₃⁻, mmol/L</td>
<td>28</td>
<td>6.1 (0.7)</td>
</tr>
<tr>
<td>Urea, mmol/L</td>
<td>8</td>
<td>0.02</td>
</tr>
<tr>
<td>Creatinine, mmol/L (mg/dL)</td>
<td>145 (1.3)</td>
<td>60 (1.3)</td>
</tr>
<tr>
<td>Osmolality, mosmol/kg H₂O</td>
<td>240</td>
<td>325</td>
</tr>
</tbody>
</table>

*FENa, fractional excretion of Na⁺.*
Residual water permeability

Two elements are needed for water transport in the medullary collecting duct: an osmotic driving force and a permeability for water. There are two pathways for transport of water in the medullary collecting duct, a vasopressin-responsive system via AQP2 and a vasopressin-independent system called RWP. Data to suggest the presence of vasopressin-independent water permeability has been obtained from studies in Brattleboro rats with hereditary diabetes insipidus [20] and from studies with isolated medullary collecting duct segments where there is no vasopressin added to the bath or the luminal fluid and sufficient time is allowed for the residual effects of vasopressin to disappear [21].

If as calculated above, 27 L/day are delivered to the distal nephron in a normal subject, and since the urine flow rate during maximum water diuresis is ~10–15 mL/min (~15 to 22.5 L/day, if this maximum water diuresis could be maintained for 24 h) [22], somewhat >5 L of water are reabsorbed per day in the inner medullary collecting duct by RWP during water diuresis.

We envision two factors that may affect the volume of water reabsorbed by RWP (Figure 2): the ‘driving force’, where osmotic pressure is generated by the difference in osmolality between the luminal fluid of the inner medullary collecting duct and that of the medullary interstitium, and ‘contraction of the renal pelvis’, where each time the renal pelvis contracts, some of the volume of fluid in the renal pelvis travels in a retrograde direction up toward the inner medullary collecting duct. First, the osmotic pressure generated by the difference in osmolality between the luminal fluid of the inner medullary collecting duct and that of the medullary interstitium, and the ‘contraction of the renal pelvis’, where each time the renal pelvis contracts, some of the volume of fluid in the renal pelvis travels in a retrograde direction up toward the inner medullary collecting duct. The numbers used in the Figure are for illustrative purposes.

Fig. 2. Factors that affect volume of water reabsorption via RWP. The upper cylinder represents the inner medullary collecting duct with bold outlines to indicate its limited capacity for it to dilate. The inverse triangular structure below it represents the renal pelvis. The heavy upward arrow represents fluid that fluxes retrograde to re-enter the inner medullary collecting duct. Two factors may affect the volume of water reabsorbed by RWP. First, the osmotic pressure generated by the difference in osmolality between the luminal fluid of the inner medullary collecting duct and that of the medullary interstitium. Second, contraction of the renal pelvis, as some of the volume of fluid in the renal pelvis that travels in a retrograde direction may be reabsorbed via RWP as it re-enters the inner medullary collecting duct. The numbers used in the Figure are for illustrative purposes.

There are other examples of patients in whom a low distal delivery of filtrate and water reabsorption by RWP may be important factors in the pathophysiology of hypotnatremia. One group is those who exercise and markedly reduce their dietary intake to lose weight [8]. These patients consume a large volume of water, a diet low in salt and protein and their exercise causes a loss of NaCl in sweat. They thus have some reduction in EABV (likely only mild since they are able to continue to exercise), increased re-absorption of NaCl along the proximal convoluted tubule and a modest reduction in distal delivery of filtrate. Therefore, for these patients to develop hyponatremia, in addition to a large water intake, they will need a large volume of water reabsorption in the inner medullary collecting duct via RWP. Perhaps, a larger proportion of the potential urine undergoes retrograde flux and this may present a greater opportunity to reabsorb more of the volume of the distal delivery in the inner medullary collecting duct.

Beer potomania [25] may be, at least in some patients, another example of this pathophysiology. In this setting, there is a very large intake of electrolyte free in the form of beer. In addition, since each liter of urine will have perhaps 10 mmol of Na⁺, a deficit of Na⁺ will develop over a number of days if the intake of NaCl is low, and hence, the volume of distal delivery of filtrate will be low. A low intake of protein contributes by decreasing the number of osmoles delivered to the inner medullary collecting duct, and hence, more water is reabsorbed via RWP.
Although a low distal delivery of filtrate is likely an important factor in the pathophysiology of hyponatremia in patients with congestive heart failure and in those with liver cirrhosis, the fact that the administration of a vasopressin antagonist, at least in some of these patients, results in a water diuresis and a rise in plasma sodium indicates that vasopressin is playing a role in the pathophysiology of their water retention [26, 27].

Understanding this pathophysiology has clinical implications for the management of patients with hyponatremia. Consider if the patient in our case example presented to the emergency department. She would be found to have hyponatremia which would be thought to be due to stimulation of vasopressin release due to low EABV owing to her intake of a thiazide diuretic and hence was given isotonic saline to re-expand her EABV. An infusion of saline that may not seem large (especially if it were given as a bolus) may be sufficient to reduce the fractional reabsorption of filtrate in the proximal convoluted tubule and increase its distal delivery. If the fractional reabsorption in proximal convoluted tubule is decreased to say 83%, of the GFR of 40 L/day, distal delivery of filtrate will increase to ~7 L/day. This exceeds water reabsorption by RWP causing a water diuresis. Because of her small muscle mass, even a modest water diuresis may be large enough to cause a rapid rise in plasma Na⁺ concentration and perhaps increase the risk of developing osmotic demyelination syndrome [28], especially if she is malnourished or potassium depleted [29].

Our plan for therapy would be to hold the intake of hydrochlorothiazide, to restrict water intake and to increase her salt intake. The maximum rate of rise of her plasma Na⁺ should not be allowed to exceed 6 mmol/L/day [30]. The occurrence of a water diuresis would indicate that her EABV has been re-stored to increase her distal delivery of filtrate. If a water diuresis ensues such that the rate of rise of plasma Na⁺ would exceed the maximum allowable rate, we would administer desmopressin (dDAVP) to halt the water diuresis and limit the rate of rise of plasma Na⁺ [31].

Conflict of interest statement. Dr Kamel is on the advisory board for Otsuka, Canada.

References

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