Editorial

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Interpretation of the Urine Electrolytes and Osmolality in the Regulation of Body Fluid Tonicity

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The purpose of this editorial is to examine how the kidneys contribute to the regulation of the appropriate partitioning of water between the extracellular (ECF) and intracellular (ICF) compartments. This is synonymous with the renal contribution to the defence of body fluid tonicity and can be evaluated by examining the urinary volume and solute composition. Certain solutes contribute to urine osmolality but do not influence body tonicity. To do the latter, a compound must have a different concentration in the ICF and ECF; otherwise, it will not be a 'particle that counts with respect to tonicity' (i.e. ineffective osmoles such as urea). For a compound to exert a significant osmotic force, its concentration must be in the m.M range. Hence potentially toxic compounds (e.g. ammonium) cannot be physiologically important osmoles which influence body tonicity. One final point needs to be considered: if a compound dissociates, both the cation and anion must either be retained in the same compartment or induce an ion shift across the cell membrane for electrical neutrality (fig. 1). This restriction will become evident when we examine the contribution of dietary potassium chloride in patients with or without a potassium deficit. The above points can be illustrated by the following example – does the excretion of 1 litre of urine containing 150 m.M sodium chloride, 150 raM potassium chloride, 150 mM ammonium chloride and 300 raM urea (total osmolality 1,200 mosm/kg water) lead to a decrease in body tonicity?

Body fluid 'effective' osmolality or tonicity is maintained within very narrow limits. A small rise in tonicity (1–2%) provokes a strong urge to drink [1]; the renal response to hypertonicity is the excretion of urine of minimum volume and maximum tonicity. The converse is true when body tonicity falls. By examining urine composition, it is possible to evaluate the renal response to the defence of body isotonicity. However, this evaluation is complex, and depends in part upon the relative contribution of different urinary solutes. Therefore, we wish to define those renal responses which alter body tonicity. In particular, we shall consider which urinary solutes are important in this regard.

Determinants of Body Fluid Tonicity

Partitioning of fluid between the ECF and ICF compartments is critical for survival. This process depends on restricting particles to either the ECF or ICF because water crosses cell membranes very rapidly to achieve osmotic equilibrium. Although osmolality is a function of the number of particles per unit volume, not all particles are equal in determining compartment volumes. For example, particles such as urea cross cell membranes and achieve equal concentrations in the

ECF and ICF. Hence, urea contributes to osmolality but not to the 'effective' osmolality or tonicity. Glucose is more complicated; its volume of distribution in the ICF compartment varies with specific organs. For example, in the liver, glucose behaves like urea with respect to water shifts; in contrast, in muscle cells, glucose behaves as an 'effective' osmole causing net water movement between ICF and ECF compartments [2]. Since the focus of this paper is on defence of tonicity or effective osmolality, we can ignore the osmotic contribution of urea. The contribution of glucose only achieves importance in markedly hyperglycemic states. The principal solutes in the ECF influencing ECF-ICF water shifts are sodium and its attendant anions, chloride

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Na⁺ -

X[⊖]

urβa« (■

• urea

\\

A''-*

1(a)

JCF_ ^/

³/₈ v_y

Ineffective

ECF

Dissociating

Osmoles

Compounds

Fig. 1. Definition of 'particles that really count with respect to tonicity'. The circle represents a cell membrane. On the left-hand side, we show that particles which cross cell membranes and achieve an equal concentration in the ECF and ICF are ineffective osmoles with respect to tonicity. On the right-hand side, we illustrate that the gain of a cation and an anion can only occur if both these ions can be retained in the same compartment (e.g. NaCl in the ECF, option 1), if the cation can shift so that it and the countermoving anion can be retained in their new compartments (e.g. potassium enters the ICF in exchange for sodium in the ICF, option 2) or if there was a chloride-bicarbonate shift across the cell membrane (option 3).

and bicarbonate. With respect to the ICF, the situation is more complex because (a) the bulk of the anions are polyvalent macromolecules, (b) the activity coefficient for the major cation, potassium, is difficult to determine because of the high ICF protein concentration and (c) there are many organic molecules making significant contributions to the ICF osmolality [3]. Keeping in mind the foregoing considerations, it is possible to analyze the renal response to body fluid tonicity based upon the urinary solute composition. 1

Sodium

Since sodium and its attendant anions chloride and bicarbonate are the principal ECF solutes which determine ECF-ICF water shifts, it is clear that factors which govern the urine sodium:water ratio ($\text{Na}/\text{F}\% \text{O}$) will influence body fluid tonicity. This ratio in turn depends

1 The body particle:water ratio may be altered by processes which are not reflected in the urine solute composition. The generation of a large number of new particles from a much smaller number of macromolecules as would occur with rhabdomyolysis [11] or convulsive disorders [12] can result in hypertonicity and the converse would apply to anabolic processes. The current article deliberately focusses on the renal contribution to body tonicity.

upon factors which affect sodium handling in the nephron (processes principally affecting the numerator) as well as the degree of water abstract

ion in the terminal portion of the nephron (processes affecting the denominator). In simplest terms, since all dietary sodium chloride represents 'particles that count with respect to tonicity' (fig. 1), the excretion of 1 litre of urine with a sodium concentration equal to that in the ECF will not result in a change in the effective osmolality of body fluids (ECF volume would decline). If the urine sodium concentration was much less than isotonic, body tonicity would rise and vice versa.

Urea

As discussed above, urea is not an effective osmole because it does not influence the partitioning of fluid between ECF and ICF compartments. Hence, as pointed out by Goldberg [4] and Rose [5], urinary urea contributes to urine osmolality, whereas it does not contribute to the defence of body fluid tonicity.2 In the example cited above, we should ignore the 300 mmol of excreted urea with respect to changes in body tonicity.

Ammonium

During chronic metabolic acidosis, the urine ammonium concentration can be greater than 150 mM [6]. In which way does the urine ammonium concentration reflect a change in body tonicity? Approximately 1,400 mmol of NH_4 and roughly an equivalent quantity of bicarbonate are produced from only a few millimoles (100 g) of protein each day [7]. To the extent that some of these ions (NH_4 plus bicarbonate rather than urea) are excreted in the urine, they do not reflect a change in tonicity (but they do influence urine osmolality). Thus, the excretion of ammonium does not represent a significant change in total body particles (just the loss of less than

1 mmol of protein because the ammonium concentration in the plasma is always less than 1 mM). Viewed in this way, the excretion of ammonium is not a component of the renal defence of tonicity. Failure of urinary ammonium to act as an effective osmole is illustrated dramatically in the alligator. The urine in this species can contain close to isosmolar ammonium bicarbonate with very little sodium and chloride [8]. In this case, isosmolar urine can be viewed as saline free water containing isosmolar

2 Urine osmolality is very useful in assessing the osmolality of the medullary interstitium together with the water permeability of the medullary collecting duct (ADH action). This is different from an assessment of tonicity!

Table I. Chloride excretion and body tonicity in urines containing ammonium chloride

A. Production of ammonium in the kidney

Protein $\rightarrow$ glutamine

Glutamine $\rightarrow$ kidney

Glutamine $\rightarrow$ $\text{NH}_4^+ + \text{HCO}_3^-$

Net: Protein $\rightarrow$ $\text{NH}_4^+ + \text{HCO}_3^-$

B. Excretion of ammonium

Filter $\text{Na}^+ + \text{Cl}^-$

Cell $\text{NH}_4^+ \rightarrow \text{NH}_3 + \text{H}^+$

Reabsorb Na^+ in exchange for H^+ secretion

NH_3 crosses cell to lumen

Net: Filtered Na^+ reabsorbed and NH_4^+ plus Cl^- are excreted

C. Fate of bicarbonate formed in A 1. Added from renal cell to body

D. Sum A+B+C

Loss of $\text{NH}_4^+ + \text{Cl}^-$ in urine

Gain of HCO_3^- in blood

Loss of some protein (less than 1 mmol)

Virtually no change in tonicity

E. Effect of body buffering

Protein $\rightarrow \text{H}^+ + \text{protein}^-$

$\text{H}^+ + \text{HCO}_3^- \rightarrow \text{CO}_2$

Net: Loss of number of particles (bicarbonate)

For description see text.

concentrations of an ineffective osmole. As in the case of urea, the urinary osmolality would not be useful in assessing the renal contribution to defence of body fluid tonicity without identifying the solutes present and taking into account their influence on ECF-ICF water shifts. Therefore, in our example, we can ignore the contribution of the 150 mM ammonium with respect to body tonicity (see also section on chloride excretion).

Chloride

Chloride is the most abundant anion in the ECF; its excretion leads to a change of body tonicity when sodium chloride is excreted. However the excretion of chloride does not result in an equivalent loss of 'particles that count with respect to body tonicity' in the case of ammonium chloride excretion. The reason for this difference is illustrated in table I. Glutamine metabolism in the kidney results in the production of equimolar concentrations of ammonium and bicarbonate; the ammonium so formed is added to the urine (see ammonium section above), and the bicarbonate is added back to the body. Up to this point, the body has an anion gain (bicarbonate) and a cation loss (ammonium). However, the process by which ammonium first entered the luminal fluid required that filtered sodium be reabsorbed, an equivalent quantity of hydrogen ions be secreted (the sodium-hydrogen ion antiport system) and that ammonia (NH_3) cross the proximal luminal membrane by non-ionic diffusion. Thus, when ammonium chloride is excreted, sodium bicarbonate is added back to the body; the net result of these processes is an 'exchange' of ECF chloride for bicarbonate. Hence, up to this point, the number

of particles in the ECF is not changed – we have merely replaced 150 mmol of chloride with 150 mmol of bicarbonate.

One final point needs to be considered. If the bicarbonate gain were to alkalinize the body and back-titrate body buffers, some of the bicarbonate would be lost as CO₂. Since body buffers are mainly polyvalent anions [for review see reference 9], they would increase their net anionic charge and bicarbonate consumption would lead to a net particle loss.

In summary, only a portion of the chloride excreted along with ammonium represents the loss of ‘particles that count with respect to body tonicity’. It is difficult to quantitate how much of the generated bicarbonate would be converted to CO₂ by a process which resulted in the synthesis of polyvalent (but not monovalent, e.g. lactate) anions without knowing the pH and bicarbonate concentration of the patient.

Potassium

To analyse the effect of urine potassium with respect to the defence of tonicity, let us consider two examples.

Hypokalemia and Potassium Excretion. A subject consumes a low sodium, potassium-free diet and is maintained on a natriuretic agent. ECF volume contraction, secondary hyperaldosteronism and increased potassium excretion ensue. For simplicity, let us assume that this excreted potassium came from the ICF (the potassium content of the ECF is very low). To make this example even simpler, we shall assume that sodium from the ECF is exchanged for this ICF potassium (pathway 1a of fig. 2a). Hence, in this case, the urinary potassium reflects, ultimately, sodium lost from the ECF (this sodium is now in the ICF). Thus, the excretion of potassium represents the loss of an effective osmole and should lead to body fluid hypotonicity (see next section for physiological implications of this excretion). Hypotonicity will persist as long as there is continued release of ADH due to hypovolemia in the example given.

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„” < + da) f v_y

Diet K*

Na+

Na* + Ct-

NH₄⁺

+
-Na⁺

a Kidney
ECF
Muscle
b Reabsorb NaCl
c Excrete Ammonium

Fig. 2. Integration of defence of tonicity and potassium homeostasis. Pathways 1a and 1b in panel a represent urinary excretion of potassium together with a gain of sodium in the ICF and the excretion of potassium of dietary origin, respectively. In panel b, the reabsorption of sodium chloride stimulated by aldosterone will lead to a defence of ECF volume. In panel c, the reabsorption of sodium together with ammonium excretion can be stimulated by aldosterone and thereby lead to a defence of sodium content and thus of ECF volume.

The Excretion of Dietary Potassium Chloride. Does the excretion of exogenous potassium similarly lead to hypo-tonicity or is this excretion independent of the defence of tonicity? To simplify the discussion, let us consider two cases where each person is in sodium balance. When potassium chloride is ingested, both the potassium and chloride need to be retained to increase tonicity. In our first case, the subject is potassium-deficient (sodium has entered the ICF in exchange for potassium). Now when potassium chloride is ingested, the potassium enters the ICF and sodium moves in the opposite direction. Hence, the potassium chloride can be retained (see option 2 of fig. 1). In the second case, the patient has a normal body potassium content and is in potassium balance. Obviously, the daily potassium load must now be excreted and this excretion could occur with no change in sodium balance. In this latter case, chloride is ingested and excreted in equivalent quantities. As shown in figure 2 (process 1b), the simple excretion of dietary potassium does not make a contribution to sodium or body particle balance. In summary, since dietary potassium chloride would influence body tonicity only in states where it was retained and/or led to a change in sodium balance, it follows that (for reasons which are somewhat different than those used for eliminating urea and ammonium chloride from the effective osmole category in our example) dietary potassium which is excreted should also be eliminated from the important urinary constituents which are critical for the renal response which defends body tonicity.

In the example cited at the beginning of this editorial, there will be no change in body fluid tonicity if the urine

potassium was of dietary origin and all the bicarbonate formed due to ammonium excretion was retained as such. In contrast, body tonicity would fall if some or all of the urine potassium had originated from the ICF or if some bicarbonate was titrated. Therefore only a portion of the urine potassium should be added to the sodium in considering the urine 'effective solute' to water ratio.

Integration of Defence of Tonicity and Potassium Homeostasis

The urinary concentration of sodium and 'sodium ion replacements', but not the urine osmolality provides the clearest indication of the renal response for the defence of tonicity. It appears that only potassium which was shifted from the ICF should be regarded as sodium ion replacements. Superficially, the reabsorption of filtered sodium together with the addition of potassium to the urine seems to defend body sodium content and thus the ECF volume. However, on more careful examination, there is insufficient potassium in the ECF to allow a major quantitative flux in this

pathway. In a subject who does not ingest potassium, the ultimate source of urine potassium is potassium in the ICF. Since potassium transport from the ICF to ECF is accompanied by a large sodium movement in the opposite direction (pathway 1a of fig. 2 [10]), the net result appears to be the transfer of ICF potassium to the urine together with the transfer of sodium from the ECF to the ICF. Thus, it appears that this mineralocorticoid action has led to a loss of ECF volume and a disorder

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of ICF cation composition; all the above appear to be to the disadvantage of the individual. However, it is well known that aldosterone action is essential for ECF volume defence (e.g. patients with Addison's disease have ECF volume contraction). We offer the following explanations for this apparent paradox. First, reabsorption of filtered sodium together with the excretion of dietary potassium (pathway 1b of figure 2) contributes to the defence of ECF sodium content. Second, aldosterone enhances distal nephron proton secretion which is associated with an augmented rate of ammonium excretion (the latter may also be augmented by hypokalemia [6], fig. 2). To the extent that these processes are associated with sodium reabsorption, they will lead to defence of ECF volume. Third, an enhanced reabsorption of sodium which is accompanied by chloride and/or bicarbonate would also lead to the defence of ECF volume (fig. 1). Taken together, it is these actions of aldosterone which account for preservation of ECF sodium content and outweigh the loss of sodium into the ICF in exchange for potassium.

Summary

To evaluate urinary solutes in terms of their effect on body fluid tonicity, it is necessary to consider: (1) whether that solute serves as an effective osmole in terms of ECF-ICF fluid shifts, (2) its ability to accumulate in the body even if it is an osmotically effective particle, and (3) the original number of body particles from which it derived. Thus, urea can be excluded since it is an ineffective osmole and only urine cations and anions need be considered. With respect to the former, one must separate the proportion of dietary versus endogenous potassium in this analysis as their effects differ. With respect to urine anions, urine chloride need not contribute to the loss of 'particles that count' when its excretion is accompanied by ammonium (i.e. equivalent to a bicarbonate gain). Thus, in the example cited at the beginning of this article, the excretion of hyperosmolar urine may not change body fluid tonicity if all the urinary potassium was of dietary origin and all the bicarbonate generated was retained as such. Finally, it is necessary to integrate defence of ECF volume (sodium balance), potassium balance, acid-base balance and intercompartmental fluid shifts to understand the overall renal response to defend tonicity (fig. 2). While there is utility in measuring urinary osmolality (assessment of medullary physiology, ADH action, water abstraction, concentrating power), in situations where body fluid tonicity is deranged, it is necessary to evaluate the urine sodium concentration along with the concentration of other solutes which may serve as effective osmoles in the urine.

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