New insights into the determinants of serum Na\(^+\) and the risk for dysnatremias

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The serum Na\(^+\) concentration is the primary determinant of plasma osmolality, and, as such, it has key role in regulating the transcellular distribution of water. Typically, osmolality is tightly regulated (between 285 and 290 mosM/kg) and maintained through modulation of arginine vasopressin (AVP) secretion and changes in renal tubular reabsorption/excretion of free water. Thirst plays a secondary role in this process. Thus, it is not surprising that alterations in serum Na\(^+\) (hypo- or hypernatremia) can lead to serious symptoms usually manifested as changes in neurological function. In fact, hyponatremia is the most commonly encountered electrolyte disorder in both hospital (15–30% of patients) and ambulatory (1.7% of patients) settings (8, 9). In nearly all studies, hyponatremia has been found to be a powerful predictor of adverse events and mortality (2, 6–10). However, it has been difficult to determine if hyponatremia is simply a marker of underlying disease severity or a direct mediator of adverse outcomes. A recent study (3) that demonstrated that correction of serum Na\(^+\) in critically ill patients improves outcomes supports, at least partially, the notion that there may be a direct link between hyponatremia and mortality.

Understanding the determinants of serum Na\(^+\) is critically important in determining the etiology of Na\(^+\) disorders as well as leading to effective treatment and prevention. Traditionally, the plasma Na\(^+\) concentration has been thought to be correlated to the ratio of the total exchangeable solutes (primarily made up of extracellular Na\(^+\) and intracellular K\(^+\)) to total body water (4). Thus, hyponatremia results from some combination of the loss of Na\(^+\) and K\(^+\) from the body or from gain of total body water in excess of solute (such as with the condition of the syndrome of inappropriate antidiuretic hormone secretion). Central to the maintenance of normal plasma osmolality and Na\(^+\) is control of the secretion of AVP by hypothalamic osmoreceptors. AVP then alters the renal excretion of water (leading to concentrated urine in its presence and dilute urine in its absence). Once toxicity is restored, AVP secretion ceases in a feedback loop. Recent data have demonstrated that the underlying mechanisms and control of plasma osmolality and Na\(^+\) may be more complex and influenced by individual-specific effects that influence both baseline plasma Na\(^+\) levels and the risk for dysnatremias.

In a recent issue, of the American Journal of Physiology Renal Physiology, Zhang and colleagues (14) demonstrated that the plasma Na\(^+\) contribution has a large individual component. The authors analyzed two large health plan-based cohorts with serial, individual plasma Na\(^+\) levels over time. By doing this, they demonstrated that plasma Na\(^+\) varies to a greater extent between individuals than within an individual over time, similar to that of plasma glucose. This means that serial levels of plasma Na\(^+\) in a specific patient will cluster around an individual “set point” that is unique for that person. What are the possible explanations and implications of this finding?

The first possibility is that determinants of plasma Na\(^+\) may, to some degree, be heritable and genetically determined. This possibility was previously described by Tian and colleagues in 2009 (11). These investigators demonstrated that a loss of function polymorphism in the transient receptor potential vanilloid 4 channel (a postulated element involved in central hypothalamic sensing of plasma tonicity) was highly correlated to the serum Na\(^+\) concentration, with Na\(^+\) being lower in those with the polymorphism. Furthermore, those with the polymorphism were significantly more likely to have hyponatremia. Further data supporting the influence of genetic effects on the serum Na\(^+\) level, at least on a population level, was provided by Wilmot and colleagues (12), who demonstrated the heritability of this parameter in five large cohort studies. Interestingly, heritability was highest in African-Americans and American Indians and was greater in women than in men. A final piece of evidence is that the rise in AVP in response to a hypertonic fluid infusion is more closely correlated in monozygotic twins than in controls.

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Fig. 1. Model for the determinants of the plasma Na\(^+\) concentration. The central osmostat is the primary controller of the individual set point of plasma osmolality and Na\(^+\) levels. Polymorphisms in an osmosensor protein [the transient receptor potential vanilloid 4 (TRPV4) channel] correlate with plasma Na\(^+\) levels. This set point can be influenced by environmental, medical, and age-related physiological changes in water handling. Hyponatremia may result from the interaction of genetic/heritable predispositions as well as nongenetic factors.
gotic twins than in dizygotic twins (13). Other proteins in the pathway of water/tonicity homeostasis could be candidates for individual-based determinants of plasma Na\(^+\). However, another study (5) from this same group found that a functional polymorphism in the vasopressin receptor type 2 (AVPR2) gene did not influence the population level of the serum Na\(^+\) concentration. These limited data implicate the central osmostat as the key overall determinant of an individual’s plasma Na\(^+\) and suggest that any individual may have a specific set point for tonicity. This individual set point determines plasma Na\(^+\) and is defended from perturbations. Thus, some individuals may have a baseline lower plasma Na\(^+\) and be more likely to develop hyponatremia when water homeostasis is disturbed. These data fit with observational experiences demonstrating that those patients who present to the hospital with significant symptomatic hyponatremia often have had preexisting mild degrees of asymptomatic hyponatremia and perhaps a unique susceptibility to this disorder (1).

A second, but less likely, explanation is that there are reproducible set point-independent mechanisms that maintain an individual’s plasma Na\(^+\) within a narrow range over time. These may include environmental determinants, such as access to water or specific dietary habits, as well as medications and disease processes that influence water balance. The latter possibilities seem unlikely since the authors painstakingly attempted to exclude such confounders and the former possibilities are hard to rationalize to the extent that they can control individual Na\(^+\) levels over extended periods of time.

Thus, the authors’ data support the model (shown in Fig. 1) that plasma Na\(^+\) has a large individual-specific set point determined in part by genetically influenced polymorphisms in the hypothalamic osmoreceptor that control both AVP secretion and thirst. Further studies are needed to better define this hypothesis, but the implications for clinical practice are that there are those patients who have a lower plasma osmolality set point and thus lower baseline plasma Na\(^+\) levels compared with others. These patients are perhaps more likely to develop hyponatremia, and, thus, clinicians should be attuned to those patients whenever prescribing medications that alter this axis. Certainly, more data are needed to determine if an individual’s ability to defend changes in osmolality is also individual specific.

DISCLOSURES

M. H. Rosner has served on the advisory board of Otsuka America.

AUTHOR CONTRIBUTIONS

Author contributions: M.H.R. prepared figures; M.H.R. drafted manuscript; M.H.R. edited and revised manuscript; M.H.R. approved final version of manuscript.

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