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Worth one's salt: the master dysnatremia equation

Fish, birds, amphibians, reptiles, and mammal share the interesting physiological fact that their plasma salt concentration ($[Na^+]_{pw}$) is virtually identical, amounting to ~ 9 g/l. This is the equivalent of a 0.9% salt solution. In humans, the $[Na^+]_{pw}$ is maintained within a very narrow range, where its value varies by only 1% (11). Diseases that perturb the $[Na^+]_{pw}$ are collectively known by clinicians as the “dysnatremias.” Understanding the physiological basis for changes in the $[Na^+]_{pw}$ has remained a major challenge for physiologists and clinicians alike; for unlike the concentration of the majority of substances in plasma, it has been known since the 1950s that the mass balance of Na^+ per se cannot account quantitatively for changes in the $[Na^+]_{pw}$. In addition to the mass balance of Na^+ , the mass balance of K^+ and H_2O play an important role in determining the $[Na^+]_{pw}$. In a landmark paper, Edelman et al. (1) reported for the first time an equation relating the $[Na^+]_{pw}$ to the exchangeable Na^+ , exchangeable K^+ , total body water (TBW) where $[Na^+]_{pw} = 1.11(Na^+ + K^+)/TBW - 25.6$.

Changes in the mass balance of Na^+ , K^+ , and H_2O affected the terms in this equation and therefore the $[Na^+]_{pw}$. In most texts, the equation was simplified to $[Na^+]_{pw} = (Na^+ + K^+)/TBW$ and the slope and y-intercept were ignored.

Until the landmark studies of Nguyen and Kurtz (3, 5–8, 10), the validity of the simplified equation had remained unquestioned despite the fact that it could not account for several clinical and physiological factors that affect $[Na^+]_{pw}$. These factors included: hyperglycemia-induced hyponatremia, the effect of Gibbs-Donnan equilibrium in altering the distribution of Na^+ ions between the plasma and interstitial fluid (ISF), the fact that not all Na^+ -containing salts are completely dissociated in an aqueous solution, the fact that not all exchangeable Na^+ and K^+ is osmotically active, and the effect of osmotically active non- Na^+ and non K^+ osmoles in inducing intercompartmental water shifts (2, 4, 12).

One of the important key insights of the recent elegant studies by Nguyen and Kurtz (3, 5–8, 10) was their recognition that all these factors can be explained quantitatively by the original Edelman equation (1). Specifically, the slope and y-intercept represent the effect of various physiological parameters whose total numeric value is 1.11 and 25.6, respectively. Moreover, these authors have shown that the slope and y-intercept are not invariant mathematical constants. Rather, the value of the slope and y-intercept will change depending on the value of the individual physiological parameters of which they are composed. For example, changing the plasma glucose alters several components in the y-intercept, resulting in a change quantitatively in the $[Na^+]_{pw}$.

In this issue of the *Journal of Applied Physiology*, Nguyen and Kurtz (9) have taken their analysis one step further. The authors have solved the difficult problem of characterizing the quantitative interrelationship between the Gibbs-Donnan equilibrium, the osmolality of body fluid compartments, and the $[Na^+]_{pw}$. Their analysis demonstrates quantitatively how the altered distribution of osmotically active non- Na^+ ions due to the Gibbs-Donnan equilibrium will have a modulating effect on the $[Na^+]_{pw}$ by affecting the distribution of H_2O between the plasma and ISF. Moreover, they validate their model using

empirical data from the literature. The results of their analysis are relevant not only for clinicians but also for physiologists who wish to use their new published “master equation” when teaching students. This equation greatly simplifies the task of conveying to students the quantitative relationship between all known factors that modulate the $[Na^+]_{pw}$.

In the clinical context, patients with a decreased albumin concentration due to renal or gastrointestinal diseases often have alterations in the $[Na^+]_{pw}$. Changes in the plasma protein concentration alter the distribution of Na^+ and non- Na^+ ions in the plasma and ISF as reflected by the changes in the osmolality of these compartments. Mathematically, these changes are accounted for by the terms θ_{pw} and θ_{ISF} in the Gibbs-Donnan correction factor “g.” This new insight demonstrates that just as the y-intercept in the Edelman equation was previously shown to vary in hyperglycemic states, in clinical conditions characterized by hemoconcentration, hemodilution, or hypoalbuminemia, the $[Na^+]_{pw}$ must vary as a result of changes in slope of the Edelman equation (variation in the Gibbs-Donnan correction factor “g”).

In their current paper (9) and previous quantitative analyses of the factors modulating the $[Na^+]_{pw}$, Nguyen and Kurtz have helped us recognize the subtle beauty of how all known factors that modulate the $[Na^+]_{pw}$ are related mathematically. In this way, they have reminded us of the elegant studies performed by Edelman and colleagues over 50 years ago, while providing physiologists and clinicians with indispensable tools for updating our approach to teaching the dysnatremias. Although questions remain that are difficult to study in humans, such as whether the exchangeable osmotically inactive Na^+ and K^+ are essentially fixed or variable, it is likely that future advances in our understanding of the regulation of the physiological parameters uncovered by Nguyen and Kurtz that determine the $[Na^+]_{pw}$ will result from animal studies where these issues can be addressed more easily.

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