Is the osmotically inactive sodium storage pool fixed or variable?

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Nguyen MK, Kurtz I. Is the osmotically inactive sodium storage pool fixed or variable?. J Appl Physiol 102: 445–447, 2007. First published August 17, 2006; doi:10.1152/japplphysiol.00614.2006.—Recently, there is renewed interest in the role of osmotically inactive Na+ storage during Na+ retention. Although it is well accepted that a portion of the total exchangeable Na+ reservoir is osmotically inactive, there is current controversy as to whether the osmotically inactive Na+ storage pool is fixed or variable during Na+ retention. In this article, we analyze the current scientific evidence to assess whether the osmotically inactive Na+ storage pool can be dynamically regulated. Our analysis supports the assertion that the osmotically inactive Na+ storage pool is fixed rather than variable.

There has been much interest recently in the role of osmotically inactive Na+ storage during Na+ retention and its implications in the pathogenesis of salt-sensitive hypertension. It is well known that not all exchangeable Na+ (Naex) is osmotically active because there is evidence for the existence of osmotically inactive Na+ storage in bone (2, 3). Because the osmotic activity of a solute depends on its ability to move randomly in solution, a portion of Naex is bound in bone and is therefore rendered osmotically inactive.

Although it is well accepted that a portion of Naex is osmotically inactive, there is current controversy as to whether the osmotically inactive Na+ storage pool is fixed or variable in clinical conditions characterized by Na+ retention. Indeed, Heer et al. (6) demonstrated positive Na+ balance in healthy subjects on a metabolic ward without increases in body weight, expansion of the extracellular space, or plasma Na+ concentration ([Na+]p). These authors, therefore, suggested that there is osmotic inactivation of Naex. However, determination of osmotically inactive Na+ storage must be based not only on Na+ and H2O balance, but also on Na+ balance, because changes in Naex are often accompanied by changes in exchangeable K+ (10). In the study of Heer et al., these investigators accounted for Na+ and H2O balance but they failed to account for K+ balance. Therefore, their observation that Na+ retention was not accompanied by osmotically adequate water retention can potentially be explained by concomitant negative K+ balance. Likewise, Farber and colleagues (1, 4) demonstrated that edematous patients with heart disease have a higher total body Na+/H2O ratio than do edematous patients with hepatic or renal disease and suggested the existence of an osmotically inactive Na+ storage pool in patients with heart disease. However, Farber and colleagues also did not account for the modulating effect of K+ on water retention.

Similarly, Titze et al. (14) suggested the existence of an osmotically inactive Na+ reservoir that exchanges Na+ with the extracellular space in human subjects in a terrestrial space station simulation study. In addition, Titze et al. (13) postulated that skin is an osmotically inactive Na+ reservoir that accumulates Na+ when dietary NaCl is excessive. However, these studies also failed to account for K+ balance. In a subsequent study, Titze et al. (12) did take into consideration the fact that K+, as with Na+, exerts osmotic activity and contributes to water retention. Titze et al. (12) reported that skin Na+ retention in deoxycorticosterone acetate (DOCA)-salt rats was not balanced by K+ loss, indicating osmotically inactive skin Na+ storage (12). In this study, Titze et al. (12) suggested that parallel increases in the skin Na+/H2O ratio and skin (Na+ + K+)/H2O ratio indicated Na+ abundance relative to water and hence osmotically inactive Na+ storage in the tissue. However, the assumption that an increased skin (Na+ + K+)/H2O ratio is indicative of osmotically inactive Na+ storage, fails to account for the modulating effect of non-Na+ and non-K+ solutes on the skin (Na+ + K+)/H2O ratio. The skin (Na+ + K+)/H2O ratio is a function of the Na+, K+, and H2O content of the tissue. Although the skin Na+ and K+ content is modulated by only the mass balance of Na+ and K+, the skin water content is a function of the amount of osmotically active Na+ and K+ as well as osmotically active non-Na+ and non-K+ solutes. To the extent that osmotically active non-Na+ and non-K+ solutes determine the amount of water retained in the skin tissue, the quantity of osmotically active non-Na+ and non-K+ solutes will modulate the skin (Na+ + K+)/H2O ratio by altering the denominator in this ratio. Therefore, an increased skin (Na+ + K+)/H2O ratio may simply reflect changes in the mass balance of skin osmotically active non-Na+ and non-K+ solutes relative to that of Na+ and K+. More importantly, to determine the portion of the total skin water content that is due to the osmotically active Na+ and K+, one must first quantify the amount of skin water that is retained by the osmotically active non-Na+ and non-K+ solutes. However, Titze et al. (12, 13) did not account for the amount of osmotically active non-Na+ and non-K+ solutes. In a subsequent study, Titze et al. (12) demonstrated that skin Na+ retention resulted in an increased skin (Na+ + K+)/H2O ratio in saline-treated rats compared with water-treated rats in both control and DOCA rats (Table 1). Given that the serum [Na+] remained unchanged (Table 1; Ref.

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12), if a significant amount of Na\(^+\) were to accumulate in an osmotically inactive form in the skin, then a concomitant increment in the total body (Na\(^+\) + K\(^+\))/H\(_2\)O ratio must also occur (7, 8). However, as shown in Table 1, the increased skin (Na\(^+\) + K\(^+\))/H\(_2\)O ratio in saline-treated rats was not accompanied by an increment in the total body (Na\(^+\) + K\(^+\))/H\(_2\)O ratio (12). Indeed, the total body (Na\(^+\) + K\(^+\))/H\(_2\)O ratio remained constant in saline-treated rats compared with water-treated rats in both control and DOCA rats without a change in the serum [Na\(^+\)], thereby arguing against significant osmotically inactive Na\(^+\) storage in skin or any other tissues during Na\(^+\) retention (7, 8). Interestingly, there was an increment in the total body (Na\(^+\) + K\(^+\))/H\(_2\)O ratio in DOCA rats compared with control rats, but this increased total body (Na\(^+\) + K\(^+\))/H\(_2\)O ratio was associated with an increment in the serum [Na\(^+\)] (Table 1; Ref. 12). Therefore, the increased total body (Na\(^+\) + K\(^+\))/H\(_2\)O ratio in DOCA rats compared with control rats, likely resulted from osmotically active (not osmotically inactive) Na\(^+\) retention in excess of H\(_2\)O, thereby leading to a concomitant increase in the serum [Na\(^+\)].

Furthermore, the determination of osmotically active Na\(^+\) + K\(^+\) retention was calculated based on the serum [Na\(^+\) + K\(^+\)] (12). However, the calculation of osmotically active Na\(^+\) + K\(^+\) retention based on the serum Na\(^+\) + K\(^+\) concentration ([Na\(^+\) + K\(^+\)]) is overly simplistic because it inaccurately assumes that the [Na\(^+\) + K\(^+\)] is equal in the serum, interstitial fluid (ISF), and intracellular fluid (ICF), as demonstrated below:

\[
\frac{\text{Total body Na}^+ + \text{K}^+}{\text{TBW}} = \frac{[\text{Na}^+ + \text{K}^+]_{\text{serum}} \times \text{Vol}_{\text{serum}} + [\text{Na}^+ + \text{K}^+]_{\text{ISF}} \times \text{Vol}_{\text{ISF}} + [\text{Na}^+ + \text{K}^+]_{\text{ICF}} \times \text{Vol}_{\text{ICF}}}{\text{TBW}}
\]

where TBW is total body water, Vol is volume, and total body Na\(^+\) + K\(^+\) represents the total body osmotically active Na\(^+\) + K\(^+\).

If one were to assume that [Na\(^+\) + K\(^+\)]_{serum} = [Na\(^+\) + K\(^+\)]_{ISF} = [Na\(^+\) + K\(^+\)]_{ICF}, then:

\[
\frac{\text{Total body Na}^+ + \text{K}^+}{\text{TBW}} = \frac{[\text{Na}^+ + \text{K}^+]_{\text{serum}} (\text{Vol}_{\text{serum}} + \text{Vol}_{\text{ISF}} + \text{Vol}_{\text{ICF}})}{\text{TBW}}
\]

Therefore,

\[
\frac{\text{Total body Na}^+ + \text{K}^+}{\text{TBW}} = [\text{Na}^+ + \text{K}^+]_{\text{serum}}
\]

However, the determination of osmotically active Na\(^+\) + K\(^+\) retention based on the serum [Na\(^+\) + K\(^+\)] is inaccurate because it is well known that the [Na\(^+\) + K\(^+\)] is not equal in the serum, ISF, and ICF (5, 9). Additionally, the interstitial fluid [Na\(^+\) + K\(^+\)] is greater than the interstitial fluid [Na\(^+\) + K\(^+\)] due to differences in the concentration of non-Na\(^+\) and non-K\(^+\) osmoles in these two compartments (5). Moreover, it is also not known whether alterations in the mass balance of Na\(^+\), K\(^+\), and H\(_2\)O will result in equivalent changes in the plasma, interstitial fluid, and intracellular [Na\(^+\) + K\(^+\)]. Therefore, on the basis of these studies (6, 12–14), it cannot be concluded that the osmotically inactive Na\(^+\) pool is variable during states of Na\(^+\) retention.

Recently, Seeliger et al. (10) performed Na\(^+\), K\(^+\), and H\(_2\)O balance studies of 4-days duration in dogs. Seeliger et al. demonstrated that changes in exchangeable Na\(^+\) were often accompanied by changes in exchangeable K\(^+\) and that Na\(^+\) storage was osmotically active during Na\(^+\) retention. Indeed, these investigators demonstrated that the changes in total body Na\(^+\) and K\(^+\) were proportional to the changes to total body water (10). Therefore, by considering the mass balance of Na\(^+\), K\(^+\), and H\(_2\)O, these researchers demonstrated that Na\(^+\) accumulation occurs in an osmotically active form during Na\(^+\) retention. In summary, there is clear-cut evidence in the literature that the total exchangeable Na\(^+\) exists in both osmotically active and inactive forms. Whether the osmotically inactive exchangeable Na\(^+\) pool can be dynamically regulated has not been demonstrated experimentally thus far. Indeed, current evidence supports the assertion that the osmotically inactive Na\(^+\) storage pool is fixed rather than variable.

REFERENCES


