Water-Free Na⁺ Retention: Interaction with Hypertension and Tissue Hydration

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Key Words

Osmotically inactive Na⁺ storage • Osmotically neutral Na⁺/K⁺ exchange • Skin • Muscle • Extrarenal regulation • Electrolyte balance • Osmolality • Glycosaminoglycans • Sodium reservoirs

Abstract

Electrolyte and body fluid homeostasis in higher vertebrates is believed to be fully understood. The paradigm is that Na⁺ is restricted mainly to the extracellular fluid and K⁺ to the intracellular space, where both ions act to hold water and thereby control the extracellular and intracellular fluid volume by their osmotic activity. Na⁺ accumulation thus inevitably leads to water retention. The constancy of the extracellular volume is the task of the kidneys, which control the total body Na⁺ content. More recent data from balance studies in humans have questioned this traditional view, suggesting that large amounts of Na⁺ can be accumulated without accompanying water retention by osmotically inactive Na⁺ retention, or by osmotically neutral Na⁺/K⁺ exchange. Besides the control of the body Na⁺ content by the kidneys, redistribution of body electrolytes hence provides an extrarenal regulatory alternative in the maintenance of body fluid volume and blood pressure control.

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The Two-Compartment Model of Na⁺ Balance

A phenomenological analysis from mid-20th century Na⁺ balance studies in humans provides a widely accepted framework for the relationship between Na⁺ and water retention in the organism [1]. The idea is that after abrupt increases in dietary salt intake from a low- to a high-salt diet, only about one-half of the excess intake is excreted within ≈ 20 h. The remainder is retained in the extracellular fluid and exerts osmotic activity, resulting in thirst and ADH-mediated water retention which subsequently returns plasma osmolality to normal at the cost of a higher effective circulating volume and body weight. On subsequent days, a progressively greater fraction of the excess intake is excreted, until a new steady state is achieved in which renal Na⁺ excretion matches intake. The same sequence occurs in reverse if Na⁺ intake is reduced. Thus, a high-NaCl diet is characterized by Na⁺ retention and increases of extracellular volume, and a low-NaCl diet by decreases in volume and Na⁺ excretion. This view is based on the two-compartment model of Na⁺ balance. Na⁺ and its accompanying anions are the principal extracellular osmoles and act to hold water in the extracellular space; conversely K⁺ salts account for almost all the intracellular osmoles and act to hold water within the cells. Although the cell membrane

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is permeable to both Na^+ and K^+ , these ions are able to act as effective osmoles because they are restricted to their respective compartments by the activity of the Na^+, K^+ -ATPase pump in the cell membrane. Accumulation of 140 mmol Na^+ thus must inevitably lead to 1 l extracellular volume retention to maintain isosmolality in this functional two-compartment model.

Startling Data from Long-Term Balance Studies in Humans: Na^+ Accumulation May Not Lead to Volume Retention

More recent data have questioned this traditional view, suggesting that large amounts of Na^+ can be accumulated without accompanying water retention. The possibility of water-free Na^+ retention during dietary NaCl excess in humans was addressed in long-term Na^+ balance study performed by Heer et al. [2]. The authors observed cumulative Na^+ balances $\approx 1,800$ mmol in the subjects on a high-NaCl diet. This Na^+ accumulation coincided with only distinct increases in plasma volume. Contrary to the prediction of the traditional model, expecting more than 10 l water retention to accompany the Na^+ load, no increase in the extracellular fluid volume or body weight occurred. Similar data were obtained from balance studies in Afro-American and Caucasian girls ingesting a low- or a high-NaCl diet [3], where average Na^+ accumulation within the last 2 weeks of the study was 640 ± 83 mmol in the Afro-American girls, and 300 ± 90 mmol in Caucasians. Neither group showed changes in body weight during the study, although this sodium load should have led to a 4–5 or 2–2.5 l volume retention in the subjects. No changes in the serum $[\text{Na}^+]$ were found. In line with these findings, observations from three cosmonauts during a 135-day long-term Na^+ balance study during a terrestrial space station simulation study provided additional evidence for water-free Na^+ retention [4]. In these long-term time series, where salt intake was not controlled but continuously monitored, individual changes in the total body Na^+ content occurred that displayed a monthly change pattern with an amplitude of 500–700 mmol. These oscillations paradoxically were inversely correlated with body weight, and further Na^+ loss or Na^+ gain from –1,000 to +3,000 mmol did not coincide with weight loss or weight gain as predicted by the traditional concept of Na^+ accumulation in the extracellular fluids. Finally, evidence from short-term balance experiments in elite athletes has supported the idea of a dissociation between body Na^+ and water balance. Noakes et al. [5]

analyzed the relationship between Na^+ and water balance in 2,135 participants from eight recent endurance events. In a sub-analysis of 18 athletes hospitalized with exercise-associated hyponatremic encephalopathy, the authors assessed both the Na^+ deficit and whole-body fluid excess during the athletes' hospital recovery. Predicted serum Na^+ concentrations based on fluid and electrolyte balance during the races exceeded the measured Na^+ concentrations. The authors concluded that a loss of osmotically active Na^+ unaccounted for by external losses contributed to the development of hyponatremia in the athletes, suggesting a water-free Na^+ escape of osmotically active Na^+ into a hitherto unidentified third compartment.

Where Is the Salt?

The notion of a Na^+ excess relative to water without changes in the serum Na^+ concentration makes clear that plasma and extracellular water cannot be the only sites of Na^+ and water metabolism. As judged from the penetration of $^{22}\text{Na}^+$ and $^{24}\text{Na}^+$ radioisotopes and D_2O into human tissues [6], tissues such as bone, cartilage and connective tissue account for $>50\%$ of the total body Na^+ content and it hence is an attractive hypothesis to speculate that an internal Na^+ escape into extracellular matrix components might be operative to maintain the extracellular volume despite a positive Na^+ balance. In case that Na^+ was bound in a 'third' sodium space to negatively charged interstitial matrix components with polyanionic character such as the glycosaminoglycans (GAGs), or to the bone mineral, this bound Na^+ would not readily equilibrate with the extracellular volume and thus were osmotically inactivated. In case of such osmotically inactive Na^+ storage, isomolality between the extra- and the intracellular space could be maintained without water retention despite considerable body Na^+ retention which could escape osmocontrol and its associated readjustment of the total body water content. An alternative pathway of internal Na^+ escape, however, is the intracellular volume. As shown originally by Edelman et al. [7] in short-term isotope dilution studies, changes in the serum $[\text{Na}^+]$ concentration reflect changes in the exchangeable fraction of total body Na^+ and K^+ relative to body water ($\text{TB}(\text{Na}_e^+ + \text{K}_e^+)/\text{TBW}$). As indicated by the Edelman equation ($\text{plasma water } [\text{Na}^+] = 1.11 \times (\text{Na}_e + \text{K}_e)/\text{TBW} - 25.6$), Na^+ accumulation in excess over water can be balanced by a corresponding K^+ loss, suggesting that cells may serve

as Na^+ store. In summary, as originally pointed out by Farber and Soberman [8], two distinct mechanisms might explain the startling finding from recent balance studies in humans: an osmotically inactive Na^+ storage mechanism (as characterized by a cation excess relative to water), and an osmotically neutral cation exchange mechanism (as characterized by a replacement of K^+ ions with Na^+ ions).

Evidence for Osmotically Inactive Na^+ Storage from Animal Models

The role of bone as an osmotically inactive Na^+ reservoir has been addressed in the past, and divergent results have been reported [for review, see 9]. Besides the early observations from Nichols and Nichols [10] who showed that the major fraction of the Na^+ removed by dialysis originated from the skin, little was known on the role of the skin Na^+ content during dietary salt surplus or deficit. Evidence from animal experiments suggests that the skin is an important osmotically inactive Na^+ reservoir in rats. The skin is highly vascularized and consists mainly of extracellular matrix with high GAG content. Experiments with rats fed low-salt versus high-salt for several weeks have shown that the skin Na^+ content is most sensitive to dietary intervention [11–13]. Compared with 0.1% NaCl diet, the skin Na^+ content in rats fed 8% NaCl diet was increased by ≈ 35 –45%. Increases in the skin Na^+ content coincided with only moderate or no increase in the skin water content, indicating water-free Na^+ retention. Water-free Na^+ retention in the skin with high-salt diet was not paralleled by skin K^+ loss [13]. The resulting increases in the skin Na^+ -to-water ratio and the skin $(\text{Na}^+ + \text{K}^+)$ -to-water ratio confirmed that the skin is an osmotically inactive Na^+ reservoir, where Na^+ is stored during dietary salt excess and mobilized with long-term salt restriction. This finding draws attention to the potential role of the polyanionic character of the skin GAGs in the regulation of osmotically inactive skin Na^+ storage. GAGs are negatively charged polyanions, and their charge density varies with their sulfation grade. Recent experiments suggest that skin Na^+ storage could be an actively regulated process that involves a modification of the skin GAGs. The mRNA content of dermatan chain polymerization enzymes was increased in the skin from rats after Na^+ storage had been induced by dietary salt loading [12]. Increased gene expression coincided with an increased proteoglycan content in the skin as measured by Western blot analysis. Most recent data from GAG charge density

measurements [13] support the idea that osmotically inactive Na^+ storage is an actively regulated process that involves modification of the polyanionic character of the extracellular matrix. Dietary salt loading led to suppression of the renin-angiotensin-aldosterone system, an increase in the skin $(\text{Na}^+ + \text{K}^+)$ -to-water ratio indicating osmotically inactive Na^+ storage, and an increase in polyanionic character of the reservoir tissue. This sequence suggests that besides the pivotal role of the kidneys in the control of the total body Na^+ content, extrarenal mechanisms are operative in the regulation of body fluid homeostasis and the maintenance of the internal environment.

Water-Free Na^+ Retention in Experimental Models of Salt-Sensitive Hypertension

Extracellular volume control appears to be tightly coupled with blood pressure regulation. The constancy of the extracellular space is mainly, but not exclusively, the task of mineralocorticoid activity. Unlimited Na^+ retention is prevented by the ‘safety valve’ of the escape phenomenon, i.e., the onset of natriuresis despite persistently high mineralocorticoid activity when a hypothetical limiting size of the total body Na^+ content and thereby the extracellular space has been transgressed. The idea is that initial Na^+ and associated volume retention increases blood pressure, which leads to increased distal nephron Na^+ delivery and results in pressure natriuresis that overrides the mineralocorticoid effect. This ‘mineralocorticoid escape’ phenomenon achieves a new steady-state Na^+ balance at the expense of hypertension, and according to this concept, blood pressure increases might be viewed as a compensatory mechanism to maintain volume homeostasis in states of impaired renal Na^+ excretion. Despite the pivotal role of the kidneys in the maintenance of volume homeostasis, volume-independent mechanisms regulating the vascular resistance also contribute to the development of hypertension. In addition to these concepts, recent data suggest that extrarenal volume control by water-free Na^+ retention might contribute to volume and blood pressure homeostasis. Deoxycorticosterone acetate (DOCA) treatment, a favorite animal model of mineralocorticoid-induced salt-sensitive hypertension, led to Na^+ excess in rats, increasing their total body Na^+ content by 40–50% within 5 weeks [14], but only $\approx 20\%$ of the Na^+ accumulated led to volume retention, leading to only moderate increases in the total body water content despite massive Na^+ retention.

The remainder of the Na^+ load was accumulated by osmotically neutral Na^+/K^+ exchange, or by osmotically inactive Na^+ storage without accompanying water retention. Differential tissue analysis revealed distinct mechanisms of this 'internal Na^+ escape'. Water-free Na^+ accumulation by osmotically inactive Na^+ storage was found in the skin, while the skeletal muscle exhibited osmotically neutral Na^+/K^+ exchange. Bone played no significant role in water-free Na^+ retention in the rat DOCA-salt model. In case that extracellular volume is tightly coupled to blood pressure regulation, it has been tempting to speculate that water-free Na^+ retention attenuates blood pressure, as water-free Na^+ accumulation might buffer blood pressure by maintaining the ECV close to normal despite Na^+ retention. In line with this idea, it can be speculated that a reduced osmotically inactive Na^+ storage capacity or reduced osmotically neutral Na^+/K^+ exchange might predispose the organism to pronounced volume retention at a given amount of Na^+ retention, which might contribute to the development of hypertension. Two studies with rats have addressed this hypothesis. In comparison to Sprague-Dawley rats, salt-sensitive Dahl rats showed a reduced water-free Na^+ storage capacity and were unable to increase their skin Na^+ content despite total body Na^+ excess with a high-salt diet [11, 15]. Furthermore, experiments in intact and ovariectomized (OVX) rats showed that experimental menopause aggravated hypertension in the DOCA-salt model, while no differences in Na^+ retention were found. Instead, OVX reduced the osmotically inactive Na^+ storage capacity compared to intact DOCA-salt-treated rats [16]. This reduced osmotically inactive Na^+ storage ca-

capacity was only partially compensated by augmented osmotically neutral Na^+/K^+ exchange, resulting in an impairment to accumulate Na^+ in abundance over water which went along with further blood pressure increase in OVX DOCA-salt-treated rats.

Perspectives

In summary, experimental evidence suggests that considerable amounts of Na^+ escape iso-osmolality compared to serum Na^+ and are accumulated as 'osmotically inactive' in the extracellular matrix during Na^+ retention. It is therefore questionable whether volume retention and its associated changes in body weight are suitable parameters to indirectly estimate Na^+ retention in humans. The total body Na^+ content in dialysis patients, therefore, may be underestimated. Whether local hyperosmolality in osmotically inactive extracellular Na^+ reservoirs links dietary NaCl excess with chronic extracellular inflammation [17] is currently under investigation. Furthermore, whether water-free Na^+ retention to maintain volume homeostasis in states of body Na^+ excess decreases blood pressure by its 'volume-buffering' effect, or increases blood pressure by redistribution of cellular Na^+ and K^+ which may modulate vascular tone, remains to be investigated. The concept of water-free Na^+ retention by osmotically inactive Na^+ storage and/or osmotically neutral Na^+/K^+ exchange may facilitate new research avenues for our current understanding of body volume homeostasis and hypertension.

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