



Response of the body to changes in salt intake

Jens Titze, Department of Nephrology & Hypertension, Friedrich-Alexander-University Erlangen-Nürnberg, Germany

Since the introduction of the brilliant concept of Claude Bernard I that the body comprises two distinct compartments, namely the "milieu interieur" and the "milieu exterieur", the partitioning between the two has been a challenge to the investigators. As the transition from the salty sea to dry land created an enormous challenge to Na⁺ homeostasis because of the need to preserve the precious Na⁺ ion, evolution went along with the development of most effective Na⁺-conserving mechanisms to maintain Na⁺ homeostasis.² The minimal salt requirements in adults to maintain Na⁺ balance can be estimated from subjects in isolated communities generally living a hunter-gatherer existence, where salt intake is between 20 and 40 mmol (1.2 - 2.3 g) per day.³ On the other hand, physical exercise, especially at hot temperature, requires increased fluid and Na⁺ intake. Evaporation of sweat from exposed skin is the predominant mechanism for heat loss in humans. Four hours cycling exercise at 20°C in athletes produces a 3.5 - 4 L sweat loss, producing a Na⁺ loss between 150 - 190 mmol (8.7 - 11 g salt).⁴

Which mechanisms underlie Na⁺ and fluid volume homeostasis? 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. Accumulation of 140 mmol Na⁺ thus must inevitably lead to 1 L extracellular volume retention to maintain isosmolality in this functional two compartment model.⁵ Unlimited increase in the body Na⁺ and water content is prevented by the "safety valve" of the escape phenomenon, i.e., the onset of augmented renal Na⁺ excretion when a hypothetical limiting size of the extracellular space has been transgressed. Under normal conditions, constancy of the extracellular volume therefore is the task of the kidneys which control the total body Na⁺ content and thereby the extracellular fluid volume. Startling data from recent long-term balance studies, where healthy human subjects accumulated large amounts of Na⁺ without significant changes

in their body water content, have challenged this traditional view.^{6, 7} First, the findings were not in line with the prevailing view that the total body Na⁺ content must be rigorously controlled to maintain body fluid homeostasis. Second, the data did not support the notion that Na⁺ retention always leads to commensurate water retention. Finally, the finding of total body Na⁺ retention in excess over that of water, in the absence of parallel changes in the serum Na⁺ concentration, made clear that the extracellular water space could not be the only site of Na⁺ metabolism.

Subsequent experiments in animals have confirmed that large amounts of Na⁺ can be accumulated without commensurate water retention in the organism. Water-free Na⁺ retention is achieved either by osmotically inactive Na⁺ storage, or by osmotically neutral Na⁺/K⁺ exchange. In rats, high dietary salt consumption leads to osmotically inactive Na⁺ storage in the skin.⁸ Other experiments have shown that considerable amounts of Na⁺ are accumulated without commensurate water retention by intracellular Na⁺/K⁺ exchange in the skeletal muscle. The identification of skin and muscle as actively regulated sites of Na⁺ metabolism has led to the hypothesis that these organs could be involved in volume and blood pressure regulation. The idea was that these Na⁺ reservoirs might "buffer" the relationship between total body Na⁺ excess and blood pressure. This hypothesis has been supported in experiments where inherited or acquired salt-sensitive hypertension was found to be associated with a reduced osmotically inactive Na⁺ storage capacity in the skin, predisposing the organism to volume retention at a given body Na⁺ content.⁹ On the other hand, chronic changes in the extracellular matrix associated with osmotically inactive Na⁺ storage may be viewed as an pro-inflammatory response, linking Na⁺ storage with atherosclerosis. Whether water-free Na⁺ retention by Na⁺/K⁺ exchange ameliorates or deteriorates salt-sensitive hypertension is unclear.





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In summary, evidence suggests that the response of the body to changes in salt intake is more complex than we have believed. Recent data indicate that not only the absolute Na^+ content, but also the redistribution of Na^+ in the body and subsequent changes in K^+ and Ca^{2+} distribution may contribute to fluid volume and blood pressure homeostasis. Na^+ accumulation in the body does not inevitably lead to water retention with subsequent weight gain and, hence, may easily escape our notice in the clinical routine. With a high-salt diet, considerable amounts of Na^+ are retained without extracellular volume changes. Whether this phenomenon is a beneficial or an adverse effect of long-term salt consumption awaits further investigation. Understanding the mechanisms involved in kidney-independent regulation of Na^+ balance may provide a new understanding of the relationship between body electrolytes, body fluid volumes, hypertension, and cardiovascular disease.

References

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