Salt is getting under our skin*

Ton J. Rabelink and Joris I. Rotmans

Department of Nephrology, Leiden University Medical Center, Albinusdreef 2, PO Box 9600, 2300 RC, Leiden, The Netherlands

Correspondence and offprint requests to: Ton J. Rabelink; E-mail: t.rabelink@lumc.nl


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Traditionally, the Na$^+$ cation is thought to be largely restricted to the extracellular compartment, while K$^+$ is stored intracellularly. This balance is maintained by the activity of the Na/K-ATPase sodium pump in the cell membrane. As Na$^+$ and its accompanying anions are the principal extracellular osmoles, extracellular accumulation of Na$^+$ inevitably also leads to fluid retention and expansion of the extracellular volume (ECV). In Guytonian physiology, Na$^+$ balance and its regulation by the kidney are predominant determinants of blood volume and thus of blood pressure. In recent years, however, new insight has been shed into this classical physiological paradigm.

Carefully performed balance studies had already indicated that substantial Na$^+$ retention might occur, without the expected fluid retention and weight gain [1]. The Titze group could subsequently show that Na$^+$ can bind to polyanionic proteoglycans and glycosaminoglycans in the interstitium of the skin (Figure 1A). This was shown to function as an osmotically inactive Na$^+$ reservoir, where Na$^+$ was stored during excess dietary Na$^+$ intake, and from which Na$^+$ was released upon Na$^+$ restriction [2]. The first question that comes up is the more teleological issue as to why nature would have devised a system for subcutaneous storage of osmotically inactive sodium. In this respect, it is probably important to realize that the human body is evolutionarily designed to conserve sodium. Indeed, prehistoric man was exposed to sodium-poor and potassium-rich food. Renal tubular transport systems, modulated by aldosterone, typically facilitate sodium retention and kaliuresis [3]. In this context, subcutaneous sodium storage could probably be primarily looked upon as a back-up system to preserve fluid homeostasis. The non-osmotic storage of sodium allows dissociation of sodium and water handling. In line with this concept, the research group previously showed that long-term salt restriction resulted in the loss of skin sodium without the loss of water, which would be an advantage in adaptation to dehydration.

Unfortunately, sodium-conserving physiology is unsuitable for adaptation to our sodium-rich and potassium-poor modern diet. Sodium loading may thus stimulate renal potassium loss through increased distal delivery, while at the same time accumulation of endogenous inhibitors of Na/K-ATPase, such as digitalis-like factor, may lead to intracellular K$^+$ loss. The ensuing potassium depletion has been implicated in the pathogenesis of hypertension through increased vascular smooth muscle cell contractility, endothelial dysfunction and altered cerebral control of blood pressure [3]. Based on the recent study by Titze’s group, one may wonder whether the subcutaneous sodium storage system that was discovered could also be involved in pathophysiological consequences of sodium loading.

In a paper, published in Nature Medicine, they demonstrated that upon salt loading the polyanionic character of the extracellular matrix molecules in the skin is somehow modified, allowing for a higher sodium storage capacity [4]. Although its regulation is not well understood, this may well reflect the physiological Na$^+$ buffering system described before. The investigators, however, also stumble upon a new adaptation mechanism in these circumstances. It appears that such sodium loading is also accompanied by an influx of myeloid cells in the subcutaneous compartment (Figure 1B). These cells express inflammatory markers, such as dendritic cell markers, and notably express the lymphangiogenic cytokine vascular endothelial growth factor (VEGF-C). In line with this observation, sodium loading is associated with lymphangiogenesis and hyperplasia of the pre-existing lymph capillary network. The question is how to interpret this observation. One explanation would be that the buffering capacity of subcutaneous Na$^+$ storage is exceeded and interstitial hyperosmolarity develops. Through an as yet unidentified mechanism this may elicit a subcutaneous inflammatory response. In support of this, it was shown by the investigators that VEGF-C production by the infiltrating myeloid cells was dependent upon a description factor called tonicity-responsive enhancer binding protein (TonEBP), which regulates osmoprotective genes in response to osmotic stress. Although their studies are primarily focused on the skin interstitial compartment, it is quite striking to realize that salt loading aggravates renal fibrosis in animal models of hypertension and renal damage [5]. If such influx of inflammatory cells upon salt loading were to occur in other interstitial compartments as well, this could be of great relevance to our understanding of the relationship between high-salt diet and progressive organ fibrosis.

In their paper, the investigators also explore the relationship between the interstitial inflammatory and...
lymphangiogenic response, and Na⁺ balance and blood pressure regulation. It is suggested that the lymphangiogenic response to sodium loading could act as a defense mechanism against excess Na⁺ storage in the subcutaneous compartment. Indeed, when VEGF-C is blocked and the lymphangiogenic response is reduced during a high-salt diet, the interstitial Na⁺ content increases further. It was previously shown that the water-free Na⁺ retention could also buffer the effects of a high-salt diet on blood pressure, as it would prevent fluid retention and subsequent ECV expansion. In support of this concept, salt-sensitive Dahl rats showed a reduced interstitial Na⁺ storage capacity when compared to salt-resistant rats [6]. To test whether the lymphangiogenic response to interstitial hypertonicity also bears consequences for blood pressure regulation, the effect of depletion of the infiltrating myeloid cells and inhibition of VEGF-C signaling during high salt diet was tested. Both interventions resulted in decreased lymphangiogenesis as well as an increased blood pressure. Although this may be interpreted as a role of this inflammatory and lymphangiogenic response in blood pressure regulation, it should be noticed that neither intervention specifically targets the interstitial lymphatic system but affects the blood (micro)circulation in general as well. For example, VEGF-C inhibition does not solely affect VEGFR-3-mediated lymphangiogenesis, but also acts upon VEGFR-2 on endothelial cells. Interference with this latter receptor, such as occurs with modern anti-angiogenic cancer drugs, also results in hypertension [7].

This does not distract from the fact that the concept that substantial interstitial Na⁺ storage may exist in the skin, as put forward by the Tize group, which opens up an entirely new perspective on the (patho)physiological adaptations to changes in dietary electrolytes. When one will further understand the regulatory processes involved in water-free sodium storage and its quantitative contributions to volume homeostasis, it may also open up new therapeutic avenues in the treatment of hypertension and target organ damage.

Conflict of interest statement. None declared.

References


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