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Ode to Salt: Commentary on "Skin Sodium Accumulates in Psoriasis and Reflects Disease Severity"

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Abstract

"Skin Sodium Accumulates in Psoriasis and Reflects Disease Severity" (Maifeld et al., 2021) showed that skin sodium ion (Na^+) is increased in patients with a PASI > 5. Na^+ concentration as well as its content were increased in these patients, supporting the proposed mechanism that increased Na^+ concentrations enhance IL-17 expression from $CD4^+$ cells. These data initially were generated using a noninvasive technique, sodium (^{23}Na) magnetic resonance imaging, and then were verified using ^{23}Na spectroscopy and atomic absorption spectrometry in ashed-skin biopsies in humans and also using mouse models of psoriasis. These findings suggest a novel pathologic mechanism for psoriasis development and target for treatment.

Sodium ion (Na^+) signals multiple essential processes in the body, including cardiac and nerve activity, vascular tone, and blood volume. Thus, it is not surprising that plasma Na^+ is tightly controlled. Although the skin is in contact with the plasma, skin electrolyte concentrations often differ from those in plasma, suggesting that local mechanisms govern skin electrolyte concentrations. Noninvasive techniques such as sodium (^{23}Na) magnetic resonance imaging (^{23}Na-MRI) have shown that skin sodium is increased in a variety of systemic and skin conditions, including aging (Kopp et al., 2013), renal disease (Dahlmann et al., 2015; Kopp et al., 2018; Schneider et al., 2017), hypertension (Kopp et al., 2013; Wiig et al., 2013), systemic sclerosis (Kopp et al., 2017), and atopic dermatitis (Matthias et al., 2019). The observational study by Maifeld et al. (2021) adds to this body of knowledge, showing that skin Na^+ level is proportional to psoriasis severity (PASI > 5). The investigators also use animal models and in vitro approaches to show that (i) the skin Na^+ and water profile are different between psoriasis and allergic contact dermatitis models, (ii)

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CONFLICT OF INTEREST

The author states no conflict of interest.

Na^+ concentrations directly influence IL-17 expression, and (iii) findings from ^{23}Na-MRI are confirmed using complementary models such as ^{23}Na spectroscopy.

This study is innovative in several ways. First, ^{23}Na-MRI is a significant advance over previous experimental techniques because it is noninvasive and also allows localization of signals within tissues. Second, careful controls were done, comparing Na^+ with potassium ion (K^+) concentrations and using chromium-51 EDTA to differentiate intracellular water (H_2O) from extracellular H_2O, thus confirming that not only Na^+ content but also Na^+ concentrations are elevated in psoriasis. Because immune pathways are activated by Na^+ concentrations, this is an important finding. In this respect, psoriasis may be different from skin Na^+ content owing to dietary salt loading because one recent report that measured the Na^+-to-K^+ratio in salt loading showed that Na^+concentration likely remains unchanged (Rossitto et al., 2020). Interestingly, a similar profile to dietary salt loading was seen in the contact dermatitis mouse model, suggesting a different inflammatory pattern that may correlate with the spongiosis seen in allergic contact dermatitis.

The study also has some limitations, and these are acknowledged by the authors. First, this is an observational study, so causality is difficult to assess. Second, the study site for the ^{23}Na-MRI study was the calf, an area where edema might be found in some patients, and this might be a confounding factor. Finally, dietary Na^+ was not measured in these patients, and this also might confound the results if dietary Na^+ intakes happened to be different in patients with more severe psoriasis from the intakes in their less severely affected counterparts.

Similar to any important report, this work raises as many questions as it answers. An obvious question concerns the presence of elevated skin Na^+ in both lesional and nonlesional skin, seen both in human patients with psoriasis and in the imiquimod mouse model. If there is a direct line between skin Na^+ and immune cell activation, one might expect increased skin Na^+ to localize to sites of psoriasis lesions. The finding that increased skin Na^+ does not predict the sites of skin lesions suggests that some additional factor(s) are at play. Perhaps both increased skin Na^+ and minor trauma are required to induce skin psoriasis lesions.

These studies do not identify the etiology of increased skin Na^+. Skin Na^+ may be increased by binding to skin glycosaminoglycans (reviewed in Selvarajah et al. [2018]). Alternatively, skin Na^+ may be governed by a counter-current exchange for urea (Nikpey et al., 2017). If the latter mechanism is dominant, it may be useful to determine whether skin eccrine glands or ducts play a role in regulating skin Na^+ because the eccrine gland is known to have robust transport mechanisms for both electrolytes and small molecules such as urea (Baker and Wolfe, 2020).

This work also focuses on immune regulation as the target that is regulated by skin sodium. However, other cells, including keratinocytes (KCs) and skin neurons, also should be considered as possible targets. KCs possess Na^+-selective channels such as epithelial sodium channel (Brouard et al., 1999; Mauro et al., 2002; Xu et al., 2015) and Na^+-permeable nonselective transient receptor potential and other cation channels (Mauro et al., 1993; Yang et al., 2017) that direct KC differentiation and inflammation. Extracellular Na^+

concentrations are known to modulate nerve excitability and signal amplitude, which have been linked to psoriatic inflammation (Riol-Blanco et al., 2014; Zhao et al., 2019) and itch (Fowler and Yosipovitch, 2020; Jurcakova et al., 2018). These experimental findings may have clinical relevance because loss of nerve function changes the clinical manifestation of psoriatic lesions (Zhu et al., 2016).

Finally, this study has implications for psoriasis therapy. Low-salt diets might decrease psoriasis severity by lowering skin Na^+. However, this therapeutic option may be limited because compliance with low-salt diets is difficult to obtain (Burgermaster et al., 2020). Depending on the mechanism of skin Na^+ retention, drugs that are used to modify systemic Na^+ levels may be useful in decreasing skin Na^+ in psoriasis as well. Whether lowing skin Na^+ modifies psoriasis severity will need to be tested in future studies.

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Clinical Implications

- Skin sodium ion (Na^+) regulation is likely directed by mechanisms distinct from those that regulate plasma Na^+.
- Increased skin Na^+ concentrations exacerbate IL-17–related inflammation in psoriasis.
- Decreasing skin Na^+ may improve psoriasis, especially in patients with a PASI score >5.