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ODE TO SALT:

Commentary on "Skin Sodium Accumulates in Psoriasis and Reflects Disease Severity"

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Abbreviations: MRI, magnetic resonance imaging; PASI, psoriasis area and severity index

ABSTRACT (105 words)

"Skin Sodium Accumulates in Psoriasis and Reflects Disease Severity" (Maifeld et al., 2021) demonstrates that skin Na^+ is increased in patients with a psoriasis area and severity index (PASI) >5. Na^+ concentration as well as content was 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 non-invasive technique, ^{23}Na-Magnetic Resonance Imaging (MRI), and then was 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.

CLINICAL IMPLICATIONS

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

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 skin is in contact with plasma, skin electrolyte concentrations often differ from those in plasma, suggesting that local mechanisms govern skin electrolyte concentrations. Non-invasive

techniques such as ^{23}Na MRI have demonstrated 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; Schneider et al., 2017; Kopp et al., 2018), 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^+ is proportional to psoriasis severity (PASI>5). The investigators also use animal models and in vitro approaches to show that: 1) the skin Na^+ and water profile is different in psoriasis vs. and allergic contact models; 2) Na^+ concentrations directly influence IL-17 expression; 3) 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, as it is non-invasive and it also allows localization of signals within tissue. Second, careful controls were done, comparing Na^+ to K^+ concentrations and using ^{51}Cr-EDTA to differentiate intracellular H_20 from extracellular H_20, thus confirming that not only Na^+ content, but also Na^+ concentrations are elevated in psoriasis. Since immune pathways are activated by Na^+ concentrations, this is an important finding. In this respect, psoriasis may be different than skin Na^+ content due to dietary salt loading, as one recent report that measured the Na^+/K^+ ratio in salt loading demonstrated 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 also might confound the results if dietary Na^+ intakes happened to be different in patients with more severe psoriasis than in their less severely affected counterparts.

Like 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 non-lesional skin, seen both in human psoriatic patients 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 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 if skin eccrine glands or ducts play a role in regulating skin Na^+, as 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 include keratinocytes and skin neurons also should be considered as possible targets. Keratinocytes possess Na^+ selective channels such as ENaC (Brouard et al., 1999; Mauro et al., 2002; Xu et al., 2015) and Na^+ permeable non-selective TRP and other cation channels (Mauro et al., 1993; Yang et al., 2017) that direct keratinocyte differentiation and inflammation. Extracellular Na^+ concentrations are known to modulate nerve excitability and signal amplitude that have been linked to psoriatic inflammation (Riol-Blanco et al., 2014; Zhao et al., 2019) and itch (Jurcakova et al., 2018; Fowler and Yosipovitch, 2020). These experimental findings may have clinical relevance, as 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 as 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.

DATA AVAILABILITY

N/A

CONFLICT OF INTEREST

None

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AUTHOR CONTRIBUTION

The author contributed to the manuscript with the following responsibilities:

Conceptualization: TM; Writing, Review and Editing: TM.

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