Nature Reviews Immunology | AOP, published online 13 March 2015; doi:10.1038/nri3835

Lifestyle Concepts & Emotions/Alamy

ANTIBACTERIAL IMMUNITY

A pinch of salt

> immune cells entering infected and/or inflamed skin are exposed to a high-salt environment

We are all familiar with the negative effects of a diet high in salt — from increased risk of cardiovascular disease to worsening of autoimmune disease — so why have humans evolved to store high levels of salt in the body, particularly in the skin? New evidence points to a role for salt in contributing to cutaneous antibacterial defences.

In patients with bacterial skin infections, ^{23}Na magnetic resonance imaging and ^{23}Na spectroscopy showed that, independently of the diet, the skin of the infected leg had marked Na^+ accumulation compared with the contralateral uninfected leg and that this was decreased after antibiotic treatment. Furthermore, mice with skin wounds had an increased salt concentration in the affected skin compared with intact skin. Thus, in both humans and mice, immune cells entering infected and/or inflamed skin are exposed to a high-salt environment.

To test the effect of this *in vitro*, lipopolysaccharide (LPS)-activated bone marrow-derived mouse macrophages were cultured in high-salt medium (with a 40 mM increase in NaCl concentration), which increased nitric oxide synthase 2 (*Nos2*) expression and the production of nitric oxide (NO) compared with culture in normal-salt medium. Increased *Nos2* transcription was associated with increased histone H3 lysine 4 trimethylation of the *Nos2* gene in the presence of high salt levels.

Next, the authors showed that high salt levels augment macrophage activation by increasing LPS-induced activation of p38 mitogen-activated protein kinase (MAPK) and of nuclear factor of activated T cells 5 (NFAT5), of which *Nos2* is a known target gene. Decreasing or increasing NFAT5 levels in LPS-stimulated macrophages inhibited or promoted, respectively, the increased NO production in a high-salt environment.

The increased NO production by macrophages in high-salt medium promoted the elimination of intracellular *Escherichia coli*, and of *Leishmania major* infection in a p38 MAPK- and NFAT5-dependent manner. In an *in vivo* model, mice fed a high-salt diet had improved resolution of a footpad infection with *L. major* compared with mice fed a low-salt diet, and this correlated with increased salt concentration in the skin and increased levels of *Nfat5* mRNA and NOS2. This beneficial effect was mitigated in mice with a myeloid cell-specific deletion of *Nfat5*.

So a 'pinch' of endogenous salt really could be good for you in terms of skin defence. However, given the health risks of increasing salt in the diet, local application of salt to infected tissues might be more suitable as an approach to therapeutically target this pathway.

Kirsty Minton

ORIGINAL RESEARCH PAPER Jantsch, J. *et al.* Cutaneous Na^+ storage strengthens the antimicrobial barrier function of the skin and boosts macrophage-driven host defense. *Cell Metab.* http://dx.doi.org/10.1016/j.cmet.2015.02.003 (2015)