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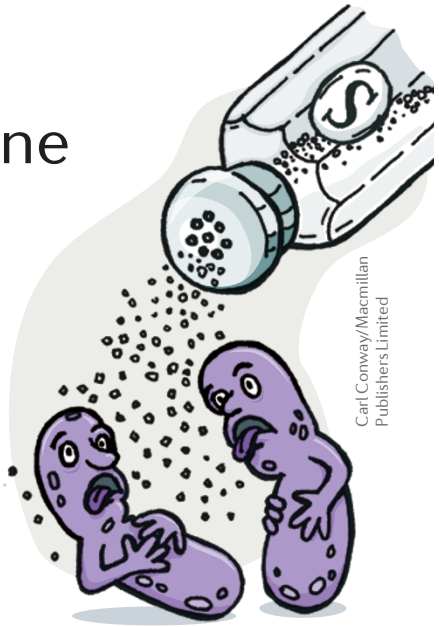
> Microbiome-mediated mechanisms could represent a novel route by which salt acts upon the body

HYPERTENSION

Salt: the microbiome, immune function and hypertension



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Previous studies have demonstrated a role for pro-inflammatory T cells — particularly T helper 17 (T_H17) cells — in the development of hypertension. The generation of pathogenic T_H17 cells is regulated by specific gut microbiota and can be stimulated by a high-salt environment, but the effects of salt on the gut microbiome are unknown. New research now shows that a high-salt diet (HSD) affects the abundance of intestinal bacteria in mice, with depletion of *Lactobacillus murinus*. Treatment of mice with *L. murinus* reduced T_H17 cell numbers and prevented salt-sensitive hypertension, while a pilot study in humans showed that a high-salt challenge reduced intestinal survival of *Lactobacillus* spp., increased T_H17 cell numbers and increased blood pressure. "Our results extend the existing knowledge on the effects of HSD to another compartment of the body — the microbiome," say researchers Dominik Müller and Nicola Wilck. "In addition to the known direct effect of salt and the ionic microenvironment on T_H17 cells, microbiome-mediated mechanisms could represent a novel route by which salt acts upon the body, particularly the immune system."

Müller explains that the effect of salt on the immune system and hypertension has been a long-standing focus of his research. "Increasing evidence suggests that the microbiome is shaped by diet, with possible consequences for the host organism and the immune system — it is interesting that the microbiome has been overlooked with regard to diets rich in salt," adds Wilck. To assess the effect of a HSD on the composition of the microbiome, the researchers performed 16S ribosomal DNA sequencing of faecal pellets from mice fed a normal-salt diet (NSD) or a HSD, which identified *L. murinus* as the species most strongly altered in response to a HSD. *In vitro* studies confirmed the ability of NaCl to inhibit the growth of *L. murinus* and several human-associated *Lactobacillus* spp.

To assess the effects of *L. murinus* depletion on physiological responses, the researchers administered *L. murinus* to two mouse models of disease — experimental autoimmune encephalomyelitis (EAE) and salt-sensitive hypertension. In mice with EAE, a disease that has been linked to alterations in the gut microbiome, administration of a HSD increased numbers of intestinal T_H17 cells and exacerbated the disease course. Administration of *L. murinus* by oral gavage normalized T_H17 cell numbers and attenuated disease severity. To assess the mechanisms for this effect, the researchers investigated the presence of indole metabolites. *Lactobacillus* spp. can metabolize tryptophan to indole metabolites, and in accordance with the depletion of *L. murinus*, the researchers noted lower levels of indole metabolites in faeces of mice fed a HSD — an effect that was reversed by *L. murinus* supplementation. *In vitro,* the indole metabolite ILA significantly reduced T_H17 polarization, suggesting that salt alters T_H17 cells by affecting the abundance of *L. murinus* tryptophan metabolites. In mice with salt-sensitive hypertension, administration of *L. murinus* reduced blood pressure and T_H17 cell frequencies compared with levels in mice fed a HSD.

Finally, the researchers assessed the applicability of their findings in mice to humans by administering slow-release NaCl tablets (equating to 6 g NaCl per day on top of their normal eating habits). This salt challenge increased blood pressure from baseline and induced a significant increase in the number of peripheral blood lymphocyte T_H17 cells. Use of full shotgun metagenomic sequencing of faecal samples demonstrated a loss of *Lactobacillus* spp. in response to the salt challenge, which is in line with the findings in mice and highlights the microbiome as a salt-sensitive compartment. Müller says that they are planning further studies to assess the mechanisms that underly the effect of *Lactobacillus* spp. on T_H17 cells. "We are also aiming to perform controlled clinical studies in humans with hypertension and multiple sclerosis to test the effect of *Lactobacillus*-containing probiotics on these diseases," he adds.

Susan J. Allison

ORIGINAL ARTICLE Wilck, N. *et al.* Salt-responsive gut commensal modulates T_H17 axis and disease. *Nature* http://dx.doi.org/10.1038/nature24628 (2017)