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NEUROIMMUNOLOGY

# Dietary salt-induced deficits

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Consumption of a high-salt diet (HSD) has been associated with a greater likelihood of developing cognitive dysfunction, cerebrovascular diseases and stroke, but how the excessive intake of salt deleteriously affects brain function is not clear. Now, Faraco *et al.* show in mice that consumption of a HSD induces accumulation of T helper 17 ($T_H17$) lymphocytes in the gut, leading to a rise in the level of interleukin-17 (IL-17) in plasma, which in turn drives neurovascular dysfunction and cognitive deficits.

The authors fed mice a diet containing an 8-fold to 16-fold higher level of salt than was present in the normal mouse diet. After 12 weeks of consuming this HSD, the mice performed poorly in the novel object recognition task, the Barnes maze and nesting behaviour, reflecting impairments in nonspatial memory, spatial memory and limbic function, respectively. Changes in resting cerebral blood flow (CBF) can impair cognitive function and, here, consumption of the HSD for 8 and 12 weeks was associated with respective reductions in resting CBF in the cortex and the hippocampus. Together, these data indicate that, in mice, consumption of high levels of salt leads to changes in resting CBF that precede or coincide with the development of cognitive deficits.

Acetylcholine (ACh) acts on cerebral blood vessels to cause a local increase in CBF by promoting nitric oxide (NO) production. The authors found that CBF in mice that were fed a HSD was less sensitive to ACh than CBF in mice that were fed a normal diet. Moreover, microvascular preparations from HSD-fed mice showed decreases in NO levels at rest and in response to ACh. Thus, a HSD may influence CBF by affecting the production of NO by endothelial cells.

How does the excessive intake of salt impair NO production? In mice fed a HSD for 8 weeks, there was a rise in the number of $T_H17$ cells in the small intestine and an increase in plasma IL-17 levels resulting from this expanded cell population. Moreover, mice lacking lymphocytes or the gene encoding IL-17 that were fed a HSD performed as well as wild-type mice fed a normal diet in the novel object recognition test and showed normal levels of NO production and of inhibitory phosphorylation of endothelial NO synthase (eNOS). By contrast, systemic administration of IL-17 to mice fed a normal diet induced eNOS inhibition as well as the deficits in CBF and cognition associated with consumption of the HSD.

Together, these findings indicate that, in mice, excessive salt intake induces a $T_H17$ lymphocyte response in the small intestine that impairs cognition through disruption of NO production and CBF.

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**ORIGINAL ARTICLE** Faraco, G. *et al.* Dietary salt promotes neurovascular and cognitive dysfunction through a gut-initiated TH17 response. *Nat. Neurosci.* **21**, 240–249 (2018)