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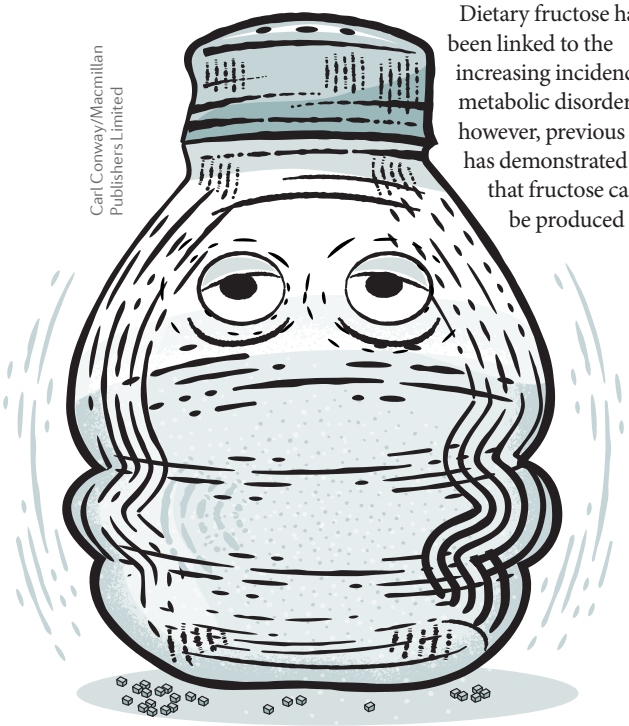
METABOLISM

High salt intake as a driver of obesity

> salt intake should be closely monitored in a variety of populations

The negative effects of high salt intake are typically thought of in terms of the effects of salt on blood pressure; however, long-term ingestion of a high-salt diet is also associated with obesity, insulin resistance and metabolic syndrome through unknown mechanisms. In new findings, Miguel Lanaspa and colleagues demonstrate that high salt intake activates the aldose reductase–fructokinase pathway in the liver and hypothalamus, leading to the production of endogenous fructose and the development of leptin resistance. "We show that salt, despite the fact that it does not provide any calories, can in fact stimulate appetite via the endogenous production and metabolism of sugar," says Lanaspa. "Our findings challenge the dogma that salt restriction should be recommended only for the management of high blood pressure and lead us to propose that salt intake should be closely monitored in a variety of populations."



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Dietary fructose has been linked to the increasing incidence of metabolic disorders; however, previous work has demonstrated that fructose can be produced endogenously through activation of aldose reductase and the polyol pathway. Lanaspa explains that in addition to the increase in dietary fructose, salt intake has also increased over the past few decades. He and his colleagues therefore initiated their study to first test whether increasing dietary salt intake could be linked to the increasing incidence of metabolic syndrome and to determine whether dietary salt is able to induce the production of endogenous fructose. "Although obesity and the metabolic syndrome are commonly thought to be caused by increased caloric intake, the mechanisms driving hyperphagia, reduced leptin sensitivity and increased caloric consumption are not well understood," explains Lanaspa. "Of interest, one of the most important ways of activating the polyol pathway is by raising tonicity, and we therefore hypothesized that increased salt intake would result in the activation of this pathway, leading to endogenous fructose production with deleterious metabolic effects."

To investigate the effect of high salt intake on endogenous fructose production, the researchers administered a 1% hypertonic NaCl drinking solution or sucralose (to ensure equal volume intake) to mice for 30 weeks. Mice receiving the salt solution had significantly higher serum and urine osmolality than mice receiving sucralose and had significantly increased expression of the osmosensitive transcription factor TonEBP (also known as NFAT5), which is known to activate the rate-limiting enzyme of the polyol pathway, aldose reductase. In addition to increased TonEBP expression, liver levels of sorbitol and fructose were significantly greater in salt-treated mice. Although body weight did not initially differ between salt and sucralose-treated mice, by week 13, mice on the high-salt diet began to gain weight, becoming obese and insulin-resistant, and had fatty liver and elevated blood pressure. In response to salt treatment, fructokinase-deficient mice, which are unable to metabolize fructose, had similarly increased osmolality and levels of sorbitol and fructose as salt-treated wild-type mice, but were protected from obesity and metabolic syndrome. Further investigation revealed a difference in energy intake between salt-treated fructokinase-deficient mice and wild-type mice: fructokinase-deficient mice on a high-salt diet ingested 40–50% less energy than similarly treated wild-type mice. Subsequent analyses demonstrated that salt-treated wild-type mice had significantly greater plasma leptin levels than salt-treated fructokinase-deficient mice and sucralose-treated wild-type mice but exhibited leptin resistance, indicating that high salt-induced hyperphagia is driven by leptin resistance through mechanisms downstream of fructose metabolism.

To assess the relevance of their findings in humans, the researchers analysed longitudinal data from a cohort study of 13,000 healthy adults in Japan. "We found that high baseline salt intake could predict the development of features of metabolic syndrome, including diabetes and fatty liver, even after adjusting for total caloric intake," explains Lanaspa. "Our future work will determine whether reducing salt intake can prevent or even treat metabolic syndrome."

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ORIGINAL ARTICLE Lanaspa, M. A. et al. High salt intake causes leptin resistance and obesity in mice by stimulating endogenous fructose production and metabolism. *Proc. Natl Acad. Sci. USA* https://doi.org/10.1073/pnas.1713837115 (2018)