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METABOLISM

Acetate promotes obesity via a gut–brain–β-cell axis

> These data identify increased acetate turnover, parasympathetic activation and hyperinsulinaemia as potential therapeutic targets for obesity

A new study published in *Nature* reports a novel relationship between the gut microbiota and nervous system, which can lead to development of the metabolic syndrome. Gerald Shulman and colleagues report that increased acetate production by gut bacteria in rats fed a high-fat diet (HFD) promotes increased glucose-stimulated insulin secretion (GSIS) via activation of the parasympathetic nervous system, which leads to a vicious cycle of hyperphagia, insulin resistance and obesity.

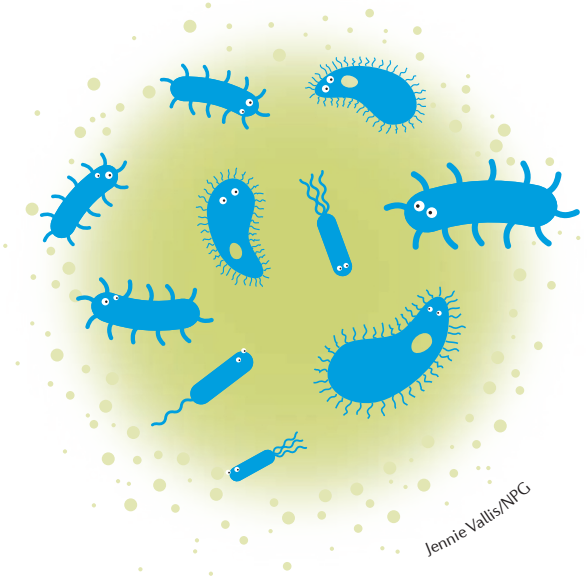
Short-chain fatty acids such as acetate are produced by the gut microbiota. Previous studies have implicated both increased and decreased concentrations of short-chain fatty acids with obesity and the metabolic syndrome; however, the mechanism by which these molecules might exert a metabolic effect has not been characterized. Consequently, the investigators compared whole-body turnover of short-chain fatty acids in HFD-fed rats and chow-fed controls. "We observed that acetate turnover was clearly higher in the HFD-fed animals," comments lead author Rachel Perry, "and the clear question became, why?"

To understand the effect of increased acetate on metabolic pathways, the researchers next examined GSIS in their rat models and found that this secretion was substantially higher in HFD rats compared with chow-fed control rats. The high GSIS could be ameliorated in HFD-fed rats by antibiotic treatment and could also be induced in chow-fed rats by intra-arterial infusion with acetate. Importantly, faecal transplant from HFD rats to chow-fed rats increased acetate turnover and GSIS in the recipient animals, which implies a causal relationship between microbially generated acetate and metabolic dysfunction in these animals.

However, direct application of acetate to isolated islets did not induce GSIS, suggesting an indirect effect of acetate on β cells. The team, therefore, investigated whether acetate might stimulate β-cell insulin secretion via activation of parasympathetic neuronal inputs in the pancreas. In support of this mechanism, severing the vagus nerve or treatment with atropine, which blocks parasympathetic signals in the nervous system, abolished acetate-induced induction of GSIS. Chronic intragastric infusion of chow-fed rats with acetate over 10 days was also found to induce hyperphagia, increase insulin resistance, impair glucose disposal and compromise insulin suppression of hepatic glucose production, all of which were prevented by severing the vagus nerve.

"These data identify increased acetate turnover, parasympathetic activation and hyperinsulinaemia as potential therapeutic targets for obesity," concludes Perry. "Future studies will be needed to identify whether these findings translate to humans, and we plan to study whether increased acetate turnover induces parasympathetic activation and/or hyperinsulinaemia in humans."

Charlotte Ridler



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