MICROBIOME

A gut microbe turns the dial on sugar intake

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The *Bacteroides vulgatus* metabolite pantothenate induces secretion of the hormones GLP-1 in the gut and FGF21 in the liver, which act on the hypothalamus to reduce sugar intake.

In humans, regulation of food intake is of utmost importance to maintain energy homeostasis. Maladaptation in food preferences can induce inappropriate food intake – for example, dysregulated sugar preference can lead to the increased consumption of sugary foods. This altered food intake behaviour can lead to the development of obesity and other metabolic disorders like type 2 diabetes, a worldwide epidemic whose prevalence is expected to continue rising in the coming decades (1) .

The development and regulation of sugar preference is complex and involves interactions between genetic and environmental factors. In recent years, microbes inhabiting the gut have been highlighted as key mediators regulating host food preferences. Moreover, alterations in the composition of the gut microbiota and its metabolites have been causally demonstrated to be involved in maladaptive food behaviours observed during obesity (2, 3). In this context, the connection between chemical and ecological dynamics of the gut microbiota and the functioning of the brain – referred to as the gut-brain axis – and how it regulates appetite and food intake behaviour represents an important target for treating/managing disease outcomes. However, the exact mechanisms linking gut microbes to host food preferences remain poorly understood.

In this edition of Nature Microbiology, Zhang *et al*. (4) have used cohousing, faecal material transplantation and specific gut microbe supplementation experiments in mice to reveal a mechanism underlying how the gut microbiota interacts with brain activity to modulate sugar preference. Their results indicate an overlooked interplay between the gut microbes and the hormone activity in the liver modulating the brain. The strategic localization of the liver closely connected to the gut and previous demonstration of the role of a specific liver-derived hormone in the regulation of sugar-intake (5) allow them to highlight an extension of the gut-brain axis into a gut-liver-brain axis involved in the regulation of sugar preferences.

Free fatty acid receptors (Ffars) are at the interface of interaction between constituents of the diet and the host metabolism. Ffar4, also known as GPR120, is a human long-chain fatty acid receptor classically associated with lipid metabolism butFfar4 activation was also linked with sugar metabolism in 2005; Ffar4 activation stimulated the secretion of the incretin glucagon-like peptide-1 (GLP-1), which in turn increased circulating insulin (6). Zhang and colleagues reported the downregulation of colonic and blood *Ffar4* expression in different preclinical diabetes models including in genetic or chemically induced type 1 or type 2 diabetes models using $Nod^{-/-}$ and streptozotocin induced diabetic mice or db-db mice, respectively. Interestingly, the authors also revealed a reduced *Ffar4* expression in human peripheral blood leukocytes from diabetic patients. Using different genetic mice models with tissue specific *Ffar4* deletion and overexpression, they demonstrated the role of intestinal Ffar4 in decreasing sugar preference and reducing blood glucose levels. Moreover, the inverse link between Ffar4 and sugar preferences was also confirmed in human subjects through mendelian randomization analysis of sugar intake data and expression quantitative trait locus data of *Ffar4*, as the authors reported an increase in sugar preference in populations with *Ffar4* mutations. These findings pave the way for a potential therapeutic approach in patients with diabetes or in populations with Ffar4 mutations associated with increased sugar preference, as the specific implication of gut Ffar4 offers a target against the dysregulation of sugar-seeking behaviour.

Knowing that gut microbes may be involved in food preference (2, 3), Zhang et *al*. hypothesized a role of gut microbes in Ffar4 mediated sugar preference. Using multiple and complementary approaches including antibiotic treatment, faecal material transplantation and cohousing experiments in mice t, Zhang *et al*. revealed evidence that gut microbes are key mediators of Ffar4-controlled sugar preference. Antibiotic treatment abolished the differences in sugar preferences observed in mouse models with Ffar4 deletion or overexpression whereas faecal material transplantation from these Ffar4 deleted or overexpressed mouse models into wildtype mice

reproduced the sugar preference. Through 16S rRNA amplicon sequencing analysis of faeces samples, the authors identified inverse changes in the abundance of different genera, including *Bacteroides*, between Ffar4 deletion and overexpression in mice. By qPCR quantification of different species of *Bacteroides* from mice faeces samples, *Bacteroides vulgatus* (*B. vulgatus*) was identified as positively correlated with Ffar4 expression. Moreover, the authors highlighted the key role of *B. vulgatus* species specifically in mediating the regulation of sugar preference by supplementing this microbe in gut Ffar4 deleted mice. Furthermore, high-throughput non-targeted metabolomic analysis of *B. vulgatus in vitro* culture revealed the pantothenate as a major metabolite produced by this bacterium. Importantly, these dynamics were not restricted to mice**:** Zhang et al. performed qPCR on faecal samples from healthy and diabetes patients and found that *B. vulgatus* was also decreased in diabetic subjects. Besides, analysis of human plasma samples revealed that pantothenate was reduced with the aggravation of diabetes. Furthermore, administering diabetic mice with *B. vulgatus* or pantothenate reduced sugar preference and fasting glycaemia. Together, these findings highlight how a specific microorganism can have impacts in food sensing and brain signalling, thus providing a promising research avenue towards the development of gut microbe-related therapeutic approaches for a major global health concern.

The regulation of feeding behaviour relies on the bidirectional communication between the gut and the brain feeding regulatory centres through different mediators, such as gut hormones. Zhang *et al*. identified the precise gut–brain mechanism of interaction driving the signalling between *B. vulgatus* and the hypothalamus, a key brain area for the control of metabolic processes including feeding. By exposing intestinal secretory cells to pantothenate or its supplementation in gut Ff4 deleted mice, Zhang et al demonstrated that *B. vulgatus* or pantothenate triggered the secretion of the intestinal-derived incretin GLP-1 inhibiting sugar preference. Previously, activation of GLP-1 receptor has been positively associated with hepatic fibroblast growth factor 21 (FGF 21) production (7), a liver-derived hormone that interacts directly with the hypothalamus to regulate sugar consumption (5). This study uncovered that *B. vulgatus*, pantothenate and GLP-1 agonist effects on sugar preference was abolished in FGF21 deleted mice thereby demonstrating the implication of a gut-liver brain axis through FGF21 in sugar intake. Interestingly, the antidiabetic effects of FGF21 have recently been related to the promotion of beneficial gut bacteria, including *Bacteroides*, and the production of GLP-1 in a diabetic mouse model (8), which reinforces the idea that this triple *B. vulgatus*–GLP-1– FGF21 association is a promising axis to target in diabetes.

In conclusion, Zhang *et al*. elucidated a novel gut–liver–brain connection that regulates sugar preference. By demonstrating the causal role of each mediator of this signalling cascade, that study is pioneering in revealing the mechanisms involved in sugar preference mediated by gut microbes. However, further research is needed to clarify the precise interactions between pantothenate and the host in the hope of establishing a robust prospective microbiota-directed intervention for diabetes and other pathologies, such as eating disorders. In addition, other mechanisms may also be involved in the effects of gut microbes on food preferences. For example, food preferences are also mediated by other brain-related areas, including the reward system. Moreover, Fan *et al*. also highlighted the beneficial effects of *Faecalibacterium praustnitzii* in ameliorating overeating disorders through a gut–vagus nerve– brain axis that governs food preference (9). Investigating the effects of *B. vulgatus* or pantothenate on the reward system as well as on the gut-brain axis nervous connection could be of particular interest.

. That said, the modulation of food preference represents an interesting strategy for therapies that might help address eating disorders. Interestingly, gut microbiota-targeted approaches to address pathologies linked to food intake alterations are becoming an important focus of research. Recently, some bacteria species have been shown to control eating disorders, such as binge eating by modulating the brain reward response (10). In this context, another species of *Bacteroides, B. uniformis,* has been shown to reduce total caloric intake in a rat model of binge eating without affecting sugar preference (10). This opens the exciting opportunity to assess the regulatory effect of *B. vulgatus* in other conditions where sugar overconsumption lies at the core of the pathology, altogether offering a pathway towards effective therapies that target a growing threat to human health and wellbeing including eating disorders or obesity in addition to type-2 diabetes.

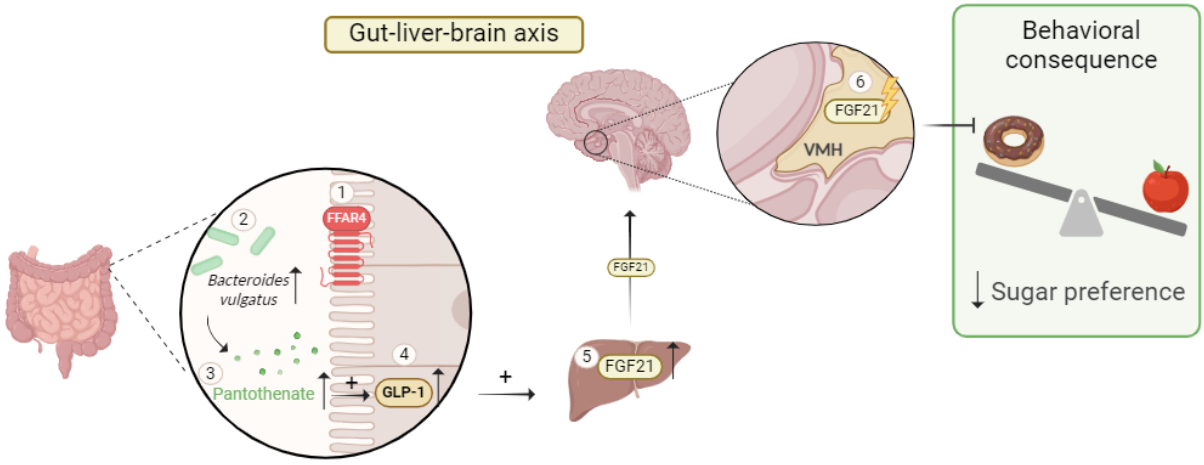

Figure 1 : Pantothenate is a key metabolite of *Bacteroides vulgatus* modulating sugar preference through the gut-liver-brain axis. 1), 2), 3) Intestinal FFAR4 receptor regulates the abundance of *B. vulgatus* and its derived metabolite pantothenate. 4) *B. vulgatus* and pantothenate positively regulate the secretion of GLP-1 by gut endocrine cells. 5) The increase of GLP-1 secretion activates the secretion of hepatic hormone FGF21. 6) FGF21 acts directly in the VMH to regulate sugar intake.

Free-fatty acid receptor 4 (FFAR4); Glucagon-like pepitide-1 (GLP-1); Fibroblast growth factor 21(FGF21); Ventromedial hypothalamus (VMH)

Competing interests

A.E. is inventor on patent applications dealing with the use of *A. muciniphila* and its components in the treatment of metabolic disorders. A. E is inventor on patent applications dealing with gut microbes in food reward dysregulations.

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