DECLARATION OF INTERESTS

The authors declare no competing interests.

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The nerve not taken

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Nutrients entering the gut influence our brains through uncharacterized circuits. In this issue of *Cell Metabolism*, Goldstein et al. (2021) show hypothalamic neurons responding, via distinct neural paths, to nutrients infused in different intestinal segments.

Two nerves diverged in a gut, and sugar took the one less traveled by.

Appetitive behaviors are rapidly adjusted by intestinal sensations elicited by ingested nutrients. Although the taste and smell of foods are salient, nutrients must enter the intestine to influence eating. But how the brain responds to the contents of a meal is not fully understood. In this issue of *Cell Metabolism*, Goldstein et al. (2021) explore how hypothalamic neurons in the brain respond through distinct nerves to macronutrients infused at specific regions of the intestine.

Food intake is the combined consequence of an orchestra of events. At the helm are the agouti-related peptide (AgRP) or hunger neurons in the arcuate hypothalamus. AgRP neurons are active during fasting and, when artificially stimulated, cause voracious feeding. In 2017, two groups discovered that AgRP neuron activity is rapidly suppressed by infusions of macronutrients directly to the stomach of mice (Beutler et al., 2017; Su et al., 2017). Satiety peptides released from the gastrointestinal tract, such as peptide YY and cholecystokinin, suppress activity in AgRP neurons. But what about AgRP responses to nutrients continuing down into different segments the gut? And how do the peptide messengers act to suppress AgRP neuron activity? It is possible that the peptides diffuse onto the bloodstream to act on AgRP neurons, or stimulate peripheral nerves innervating the gastrointestinal tract. Goldstein et al. bring clarity to these questions in this issue of *Cell Metabolism*.

The authors first study where in the gut AgRP neurons detect nutrients. To test this, sugar, fats, and proteins were infused into distinct regions of the intestine while AgRP neuron activity was recorded using fiber photometry. Similar to previous stomach infusions that flow into the intestine, perfusing all three macronutrients directly into the most proximal part of the small intestine, the duodenum, suppressed AgRP activity. In the case of sugar, it is absorbed from the duodenum and transported to the liver via the hepatic portal vein. Delivering sugar directly to the hepatic portal vein suppressed AgRP neuron activity. Thus, it seems that AgRP neurons readily respond to duodenally absorbed sugars in the hepatic portal vein.

A different picture emerged in the ileum. The function of the ileum is to absorb vitamins, bile salts, and remaining nutrients not absorbed by the duodenum and jejunum. Goldstein et al. found that fats

and amino acids did not affect AgRP neuron activity when infused into the ileum. In contrast, sugar in the ileum suppressed AgRP neurons and food intake. This finding is at odds with previous work showing that sugars in the ileum do not condition a flavor preference (Sclafani and Ackroff, 2012). Perhaps ileum sugars change feeding without impacting learning processes, a topic for future study. In fact, the AgRP neuron activity was tightly correlated to food intake across all nutrients and intestine regions. But unexpectedly, fat infusion to the ileum failed to suppress food intake. Infusions of medium- and short-chain fatty acids, more typically present in the ileum, may shed light on this topic.

What road do nutrients take to suppress AgRP activity? Given the fast response of AgRP neurons to intestinal nutrients, the authors examined the role of the primary neuronal pathways from the viscera to the brain. Using surgical denervation, the authors first tested the role of the vagus nerve. The vagus nerve is sensitive to nutrient infusion (Kaelberer et al., 2018; Williams et al., 2016) and required for nutrient-induced suppression of food intake (Sclafani and Ackroff, 2012). But vagal neurons alone do not respond to glucose. They respond rapidly to signals transduced through synaptic and endocrine epithelial signals (Kaelberer et al., 2018). Goldstein et al. found that blunt transection of the vagus through bilateral subdiaphragmatic vagotomies blocked the effect of fat, but not sugar, on AgRP activity, suggesting the vagus nerve relays fat, but not sugar signals, to AgRP neurons. This finding adds to a controversial body of literature on the role of the vagus nerve in sugar detection and preference. While the vagus nerve is not required for conditioned sugar preference (Sclafani and Ackroff, 2012), it is for the development of a sugar preference (Tan et al., 2020) and sugar detection (Buchanan et al., 2020). The rapid evolution of more precise tools would certainly help clarify the role of this cranial nerve in guiding such choices.

Next, Goldstein et al. determined the road sugar takes from the intestine to AgRP neurons. To test whether a nerve fiber contributes to sugar reduction of AgRP neuron activity, the authors turned to spinal fibers. The spinal splanchnic nerve innervates the intestine and reduces food intake when stimulated (Wu et al., 2009). Again, using surgical denervation, the authors found that removal of these spinal afferents blocked the sugar effects on AgRP neuron activity in the ileum, but not the duodenum. This work uncovers an unrecognized role of spinal nerves in linking sugars in the ileum to the hypothalamus.

One unanswered question from this work is how proteins communicate to AgRP neurons to suppress food intake. If a separate path exists for proteins to regulate food intake, might we be able to enhance duodenal fats and ileal sugars to suppress food intake, while turning off duodenal signals from proteins? One can imagine a dietary scenario in which protein cravings are augmented, while staying away from tempting but calorie-dense unhealthy foods.

This article gives a new appreciation for the ileum and splanchnic nerve in conveying sugar stimuli to the brain. Gastrointestinal and vagal pathways are altered in obesity, which can perpetuate overeating. Targeting the vagus nerve has been proposed as a possible treatment for obesity but with mixed results (de Lartigue, 2016). The splanchnic nerve presents a new potential therapeutic target for suppression of carbohydrate intake and weight loss.

Sugar took the one less traveled by, and that might make all the difference.

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DECLARATION OF INTERESTS

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