Sweet taste signaling in the gut

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The taste system plays a critical role in determining whether a food is nutritious and should be ingested or is potentially toxic and should be rejected (1). Considerable attention has focused on the sweet taste of sugar because it is such a potent stimulator of eating in humans and many other animal species. A major advance in our understanding of sweetness perception was the discovery of two G-coupled receptor proteins, T1R2 and T1R3, which dimerize to form a broadly tuned sweet taste receptor (1). Stimulation of the T1R2+T1R3 taste receptor by sugars or artificial sweeteners activates intracellular signaling elements, including α-gustducin, which stimulate peripheral gustatory nerves and, in turn, brain gustatory pathways. The central processing of the sweet taste signal typically activates feeding circuits as well as brain reward systems that promote sweet appetite (2). Brain autonomic centers may also relay information via the vagus nerve to prepare the digestive system for the incoming carbohydrate-rich food (2). Digestive and absorptive processing of the ingested food is further coordinated by sugar sensing in the intestinal tract, which modulates nutrient absorption, hormone release, and gastrointestinal motility, and generates satiation signals to the brain that terminate the meal (3, 4). In this issue of PNAS, Margolskee *et al.* (5) report that the same T1R2+T1R3 sweet taste receptor that initiates sugar ingestion in the mouth also detects sugar in the intestinal lumen and triggers physiological responses that promote sugar absorption and metabolism.

The idea that the gut may have "taste" cells that detect nutrients has been around for at least 25 years (6). A 1996 PNAS article by Höfer *et al.* (7) showing that α-gustducin, the taste signaling protein first identified in Margolskee's laboratory (8), is localized in gut epithelial cells added considerable weight to this idea. More recently, several investigators reported the expression of bitter, sweet, and umami (savory) taste receptors in the gut (9–11). The next important step in this discovery process is to determine the function of these gut taste receptors in digestive and ingestive processing. The new study by Margolskee *et al.* (5) describes one function of the T1R2+T1R3 sweet receptor in the gut.

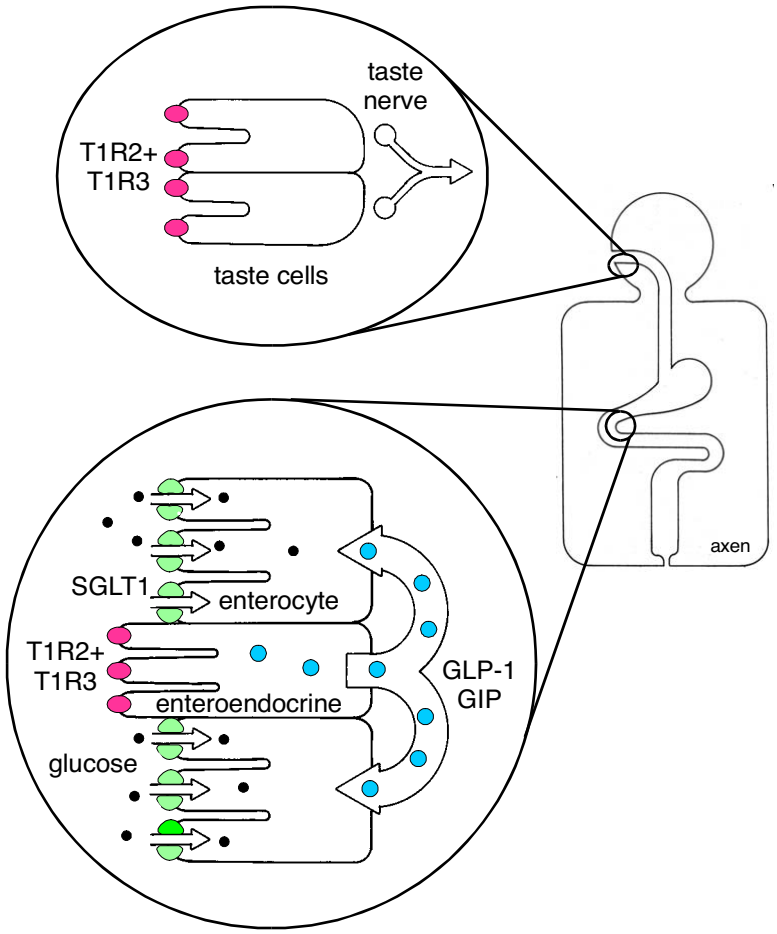

Fig. 1. T1R2+T1R3 sweet taste receptors are found in taste cells in the mouth and enteroendocrine cells in the gut. Stimulation of the T1R2+T1R3 receptors in the mouth by sugars and artificial sweeteners activates intracellular signaling elements, including α-gustducin (not shown), that trigger peripheral taste nerves and brain gustatory pathways. In the gut, stimulation of the T1R2+T1R3 receptors activates intracellular signaling elements, including α-gustducin (not shown), and causes the release of GLP-1 and GIP hormones. Among their many actions, these hormones stimulate the expression of SGLT1 in enterocytes, which, in turn, increases the absorption of glucose from the intestinal lumen.

Carbohydrates consumed in the diet are digested to sugars (glucose, fructose, and galactose) and absorbed by enterocytes in the intestines (12). Glucose is actively transported into enterocytes by the Na^+/glucose cotransporter SGLT1. (Galactose is also transported by SGLT1, whereas fructose is passively absorbed.) The expression of the SGLT1 protein, and therefore the rate of glucose absorption, is related to the amount of sugar in the gut lumen. Prior studies indicated that SGLT1 expression is regulated by a sugar sensor on the luminal membrane of gut cells, but the identity of this sensor remained unknown (3). Margolskee *et al.* (5) provide compelling evidence that the T1R2+T1R3 taste receptor is the sugar sensor that regulates SGLT1 expression via an α-gustducin signaling process. They accomplished this by comparing the effects of low- and high-sugar diets on SGLT1 expression and glucose absorption in normal mice and genetically modified knockout mice lacking either the T1R3 component of the sweet receptor (i.e., T1R3 knockout mice) or

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the α-gustducin signaling element (i.e., gustducin knockout mice). As expected, normal mice fed the high-sucrose diet displayed higher SGLT1 expression and glucose absorption than normal mice fed the low-sucrose diet. In contrast, SGLT1 expression and glucose absorption did not differ in T1R3 knockout or gustducin knockout mice fed the low- and high-sucrose diets. In another experiment, normal and knockout mice were all fed a low-carbohydrate diet, but some had plain water to drink, whereas others were given water sweetened with sucralose (the artificial sweetener in Splenda). Although sucralose itself is poorly absorbed in the intestine, it increased the expression of SGLT1 and enhanced glucose absorption in normal mice but not in T1R3 knockout or gustducin knockout mice. SGLT1 expression was also enhanced in normal mice maintained on a low-carbohydrate diet and water sweetened with saccharin or acesulfame K.

The second part of the study by Margolskee *et al.* (5) revealed that T1R2, T1R3, and gustducin are localized in intestinal endocrine cells rather than enterocytes. Enteroendocrine cells secrete a variety of gut hormones that control gut motility, nutrient absorption, and metabolism. In *in vitro* experiments using a line of murine enteroendocrine cells (GLUTag cells), Margolskee *et al.* demonstrated (*i*) that enteroendocrine cells express T1R2, T1R3, and gustducin; (*ii*) that enteroendocrine cells exposed to sucralose increase their secretion of GLP-1 and GIP, two hormones that modulate glucose transport and metabolism; and (*iii*) that the sucralose response is blocked by gumarin, an inhibitor of the T1R2+T1R3 taste receptor. Based on these results, Margolskee *et al.* proposed that glucose and other sweeteners in the gut lumen stimulate T1R2+T1R3 taste receptors on enteroendocrine cells, which provokes the release of GLP-1 and GIP, via an α-gustducin-mediated signaling process (Fig. 1). GLP-1 and GIP then have a paracrine action that promotes the expression of SGLT1 and glucose absorption. The authors speculate that a similar mechanism may facilitate glucose movement out of the enterocyte by the GLUT2 transporter. [A recent article by Mace *et al.* (13) proposed a different model in which the stimulation of T1R2+T1R3 sweet receptors enhances glucose absorption by promoting the expression of GLUT2 on the luminal membrane of intestinal cells.]

There appear to be multiple glucose sensors in the gut and other tissue.

The study by Margolskee *et al.* (5) is innovative because it simultaneously identifies the sugar sensor that regulates SGLT1 expression and a physiological function of T1R2+T1R3 sweet taste receptors in the gut. It is also provocative because it reveals a heretofore unrecognized action of artificial sweeteners in the intestinal tract. Gastrointestinal infusions of sugars suppress food intake via the release of gut hormones and vagus nerve activation (14). The role of T1R2+T1R3 receptors and the effect of artificial sweeteners in carbohydrate-induced satiety require investigation. Sugar infusions in the gut can also stimulate ingestion via a flavor conditioning process: rodents will overconsume a flavored solution that is paired with gastric infusions of sugar relative to a different flavored solution that is paired with water infusions (15). The T1R2+T1R3 receptor in the gut would appear to be a likely mediator of this effect given that it determines sugar preference at the level of the mouth. However, gastric infusions of glucose stimulate intake more than do fructose or galactose infusions in rats (16, 17) and mice (my unpublished observations). This implicates a glucose-specific sensor rather than the T1R2+T1R3 sweet receptor in the postoral stimulation of intake by sugars (see also ref. 18).

There appear to be multiple glucose sensors in the gut and other tissue (19). Recent evidence indicates that SGLT3, a protein related to SGLT1, functions as a glucose sensor rather than transporter and is implicated in glucose-stimulated release of 5-HT and the control of gastric emptying (4). The T1R2+T1R3 receptor may be unique among these sensors in its broad tuning to sugars and artificial sweeteners. Further characterization of the signaling mechanisms involved in gut taste and nutrient sensing may lead to new therapies to treat diabetes, obesity, and gut disorders.

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