Non-Nutritive Sweeteners and their Role in the Gastrointestinal Tract

Rebecca J. Brown and Kristina I. Rother
National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, Maryland 20892-1645

Context: Non-nutritive sweeteners can bind to sweet-taste receptors present not only in the oral cavity, but also on enteroendocrine and pancreatic islet cells. Thus, these sweeteners may have biological activity by eliciting or inhibiting hormone secretion. Because consumption of non-nutritive sweeteners is common in the United States, understanding the physiological effects of these substances is of interest and importance.

Evidence Acquisition: A PubMed (1960–2012) search was performed to identify articles examining the effects of non-nutritive sweeteners on gastrointestinal physiology and hormone secretion.

Evidence Synthesis: The majority of in vitro studies showed that non-nutritive sweeteners can elicit secretion of gut hormones such as glucagon-like peptide 1 and glucose-dependent insulinotropic peptide in enteroendocrine or islet cells. In rodents, non-nutritive sweeteners increased the rate of intestinal glucose absorption, but did not alter gut hormone secretion in the absence of glucose. Most studies in humans have not detected effects of non-nutritive sweeteners on gut hormones or glucose absorption. Of eight human studies, one showed increased glucose-stimulated glucagon-like peptide 1 secretion after diet soda consumption, and one showed decreased glucagon secretion after stevia ingestion.

Conclusions: In humans, few studies have examined the hormonal effects of non-nutritive sweeteners, and inconsistent results have been reported, with the majority not recapitulating in vitro data. Further research is needed to determine whether non-nutritive sweeteners have physiologically significant biological activity in humans. (J Clin Endocrinol Metab 97: 2597–2605, 2012)

Non-nutritive sweetener consumption, largely in the form of diet soda, has been associated in epidemiological studies with numerous adverse metabolic outcomes, including weight gain, the metabolic syndrome, and diabetes (1–7). In contrast, a small number of randomized, controlled trials involving these sweeteners have generally shown neutral to mildly beneficial metabolic outcomes with non-nutritive sweetener use, such as weight stability or decreased weight regain after dieting (8–10). Certainly, epidemiological studies cannot demonstrate causality, and one likely explanation for the observed correlation between weight gain and non-nutritive sweetener use is that people at risk of weight gain may choose to consume these sweeteners in an effort to reduce caloric sugar consumption. Another potential explanation for the epidemiological association between non-nutritive sweetener use and weight gain, largely supported by rodent data (11), is that training people to associate the sensation of “sweetness” with foods or drinks that are low in calories may cause them to overeat when presented with high-calorie, sugar-sweetened versions of these foods and beverages.

Although non-nutritive sweeteners have generally been considered metabolically inert, recent data suggest that these sweeteners may have physiological effects that alter appetite and/or glucose metabolism. Much of the research discussed in this review was predicated by the discovery of the structure of the sweet-taste receptor in 2001, followed
shortly by the demonstration that sweet-taste receptors, in addition to being located on taste buds in the oropharynx, are found in enteroendocrine cells of the gastrointestinal tract (12, 13) and other tissues, such as the pancreas (14).

**Taste Perception**

To understand the role of non-nutritive sweeteners in physiology, it is critical to understand taste perception. This has been thoroughly reviewed by others (15, 16), and is briefly summarized here. The tongue contains three varieties of taste papillae—the fungiform, foliate, and circumvallate—each of which contains one to hundreds of taste buds. The classic representation of the tongue as having regions specialized for differing tastes has been largely debunked, with the observation that all of the five major tastes [sweet, bitter, salty, sour, and umami (the taste of “savory,” exemplified by monosodium glutamate and aspartate)] can be sensed in all regions of the tongue. Sweet, bitter, and umami tastes are sensed via G protein-coupled taste receptors located on taste receptor cells within taste buds and elsewhere in the oropharynx. Each individual cell expresses a single receptor type (either sweet, bitter, or umami), and thus is specialized to perceive a single taste (17). These cells project to neurons in the brain, permitting conscious awareness of taste. The sweet, bitter, and umami receptors are heterodimeric receptors, with the combination of subunits conveying their flavor specificity. The umami taste receptor has a T1R1 and a T1R3 subunit, whereas the sweet-taste receptor has a T1R2 and a T1R3 subunit (15). The bitter taste receptor family contains numerous binary combinations (~25 in humans) of type 2 receptors. Because bitter tastants are often toxins, the substantial heterogeneity of bitter receptors is likely due to the evolutionary advantages of being able to detect a broad range of potentially toxic substances (18). Sour taste is sensed via ion channels. The taste of sodium salts is sensed at least in part via amiloride-sensitive sodium channels (19), but the sensory mechanisms for other salts have not been identified.

The sweet-taste receptor can bind to chemicals of widely varying structures, including the caloric sugars (e.g. sucrose, glucose, and fructose), sweet proteins such as thaumatin and monellin, and non-nutritive sweeteners. Non-nutritive sweeteners are also known as “artificial sweeteners” or “low-calorie sweeteners,” because some (such as aspartame) have measurable caloric value, albeit negligible at the concentrations used. Chemical and sensory properties of the six Food and Drug Administration (FDA)-approved non-nutritive sweeteners (with sucrose for comparison) are shown in Table 1. The sweeteners are:

- Acesulfame-K, aspartame, neotame, saccharin, stevia, and sucralose. Stevia is a botanically derived sweetener from the *Stevia rebaudiana* plant and consists of related chemicals called steviol glycosides; only the sweetest of these, rebu dioxide A, is shown in Table 1. Typical concentrations of sweeteners in carbonated beverages are also listed; these are frequently lower than anticipated based on sweetness equivalence because many beverages contain more than one non-nutritive sweetener. The metabolic fate of non-nutritive sweeteners varies from presumed excretion in a nonmetabolized manner (acesulfame-K, saccharin, sucralose) to intestinal breakdown into the sweetener’s components (e.g. aspartame becomes aspartic acid, phenylalanine, and methanol) or deesterification (neotame) (20).

Given the chemical heterogeneity of these compounds, it is not surprising that not all bind to the same ligand binding domain of the sweet-taste receptor (21, 22). However, all non-nutritive sweeteners have the ability to activate the oropharyngeal sweet-taste receptors, thereby generating a signal that ultimately results in the conscious perception of sweetness. Upon ligand binding to the receptor, associated G proteins, such as α-gustducin, are activated, resulting in increased phospholipase Cβ2, which increases production of the second messengers inositol trisphosphate and diacylglycerol. This in turn leads to activation of the taste-transduction channel, TRPM5 (transient receptor potential cation channel subfamily M member 5, also known as long transient receptor potential channel 5), resulting in increased intracellular calcium and neurotransmitter release (16). There are important species differences in the perception of sweet compounds. For example, the non-nutritive sweetener aspartame does not stimulate sweet-taste receptors in the mouse, and thus mice do not exhibit behavioral responses to aspartame (17).

**Not Just in the Mouth?**

After the discovery of the structure of the sweet-taste receptor (17) and its G protein, gustducin (23), immunohistochemical techniques were used to identify sites of tissue expression of these proteins outside of the oral cavity. It was quickly learned that sweet-taste receptors were located in other regions of the gastrointestinal tract—most notably, in enteroendocrine L cells (24, 25) and K cells (26). Enterendocrine cells are specialized cells of the gastrointestinal tract that secrete a variety of hormones. They are sparse, comprising less than 1% of epithelial cells within the intestine. In addition to the gastrointestinal mucosa, sweet-taste receptors have also been identified in pancreatic β-cells (14), in the biliary tract (27), and in the...
### TABLE 1. Chemical properties of FDA-approved non-nutritive sweeteners

<table>
<thead>
<tr>
<th>Chemical name</th>
<th>Structure</th>
<th>Sweetness (compared to 5% sucrose)</th>
<th>Sweetness recognition threshold (mmol/L)</th>
<th>Concentration at half maximal sweetness response (mmol/L)</th>
<th>Mean concentration in carbonated soft drinks (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sucrose</td>
<td><img src="image" alt="Sucrose structure" /></td>
<td>1x</td>
<td>16.6</td>
<td>Not determined</td>
<td>329</td>
</tr>
<tr>
<td>Acesulfame-Potassium</td>
<td><img src="image" alt="Acesulfame-Potassium structure" /></td>
<td>140x</td>
<td>0.161</td>
<td>2.34</td>
<td>0.44</td>
</tr>
<tr>
<td>Aspartame</td>
<td><img src="image" alt="Aspartame structure" /></td>
<td>200x</td>
<td>0.0449</td>
<td>1.90</td>
<td>0.16</td>
</tr>
<tr>
<td>Neotame</td>
<td><img src="image" alt="Neotame structure" /></td>
<td>11,000x</td>
<td>0.00114</td>
<td>Not tested</td>
<td>Not tested</td>
</tr>
<tr>
<td>Rebaudioside A</td>
<td><img src="image" alt="Rebaudioside A structure" /></td>
<td>250x</td>
<td>0.013</td>
<td>0.21</td>
<td>Not tested</td>
</tr>
<tr>
<td>Saccharin</td>
<td><img src="image" alt="Saccharin structure" /></td>
<td>450x</td>
<td>0.0497</td>
<td>0.52</td>
<td>0.15</td>
</tr>
<tr>
<td>Sucralose</td>
<td><img src="image" alt="Sucralose structure" /></td>
<td>600x</td>
<td>0.00877</td>
<td>0.28</td>
<td>0.14</td>
</tr>
</tbody>
</table>

Sweetness data were obtained from psychophysical testing in human volunteers (58, 59). The sweetness recognition threshold is the lowest concentration at which subjects identified the solution as sweet. For the non-nutritive sweeteners, subjects’ perception of sweetness reached a maximum asymptotically. Thus, the concentration range from sweetness recognition to half maximal sweetness provides a sense of the biological response range of sweet-taste receptors to individual sweeteners. Sucrose was not tested at high enough concentrations to determine maximal sweetness. Mean concentrations of sweeteners in carbonated soft drinks were obtained from a sample of 19 beverages from Belgium (60).
lungs (28). It is important to note, however, that conscious perception of sweetness is conveyed only after activation of oral sweet-taste receptors; sweet-taste receptors in the gastrointestinal tract and other tissues do not convey taste.

The functional importance of sweet-taste receptors on enterendocrine cells was recently investigated in two publications from the Beglinger group (25, 29) using the sweet-taste inhibitor, lactisole. Lactisole [sodium 2-(4-methoxyphenoxo) propionate] inhibits sweet and umami taste perception in primates by binding to the transmembrane domain of the T1R3 receptor (30). In human psychophysical studies, lactisole decreased sweetness perception for 12 of 15 sweet compounds tested, including both caloric and non-nutritive sweeteners (31). The Beglinger group studies demonstrated that, in healthy humans, the addition of lactisole to an intragastric infusion of glucose decreased secretion of glucagon-like peptide 1 (GLP-1) and peptide YY (PYY) (both made by L cells) by 24 to 47% and 15 to 27%, respectively. In contrast, cholecystokinin secretion (from I cells, which are not known to express sweet-taste receptors) was unaffected by lactisole. These data support the idea that ligand binding to sweet-taste receptors on L cells is partially responsible for L-cell hormone secretion; there are undoubtedly sweet-taste receptor-independent mechanisms as well.

**Non-Nutritive Sweeteners and Hormone Secretion**

Given that both non-nutritive and caloric sweeteners bind to oral sweet-taste receptors, resulting in the conscious sensation of sweetness, it is logical to hypothesize that non-nutritive sweeteners could bind to sweet-taste receptors on enterendocrine cells, likewise causing signal transduction and downstream actions such as hormone secretion. This possibility has been explored in multiple systems, from cell lines to rodents to humans, with inconsistent results (Table 2–4).

*Jang* et al. (32) showed that the non-nutritive sweetener sucralose (the active ingredient in Splenda) stimulated GLP-1 secretion from a human L-cell line (NCI-H716 cells) in a dose-dependent fashion. This GLP-1 secretion could be blocked by the sweet-taste inhibitor lactisole, implying that sucralose was acting via sweet-taste receptors. Similar results were published by Margolskee *et al.* (24), showing that sucralose stimulated both GLP-1 and glucose-dependent insulinotropic peptide (GIP) secretion from a murine enterendocrine cell line (GLUTag cells); this effect was likewise blocked by the sweet-taste inhibitor, gurmarin, implying that the effect was sweet-taste receptor mediated. These results were not confirmed in two other studies, however, in which sucralose and another sweetener, acesulfame-K, failed to increase GLP-1 in cultured mouse intestine (33), or GIP secretion in isolated mouse K cells (34). The concentrations of non-nutritive sweeteners used in these *in vitro* studies (Table 2) were generally in the upper half of, or well above, the expected dynamic response range of the sweet-taste receptor, and discrepant results among the studies cannot be easily explained on the basis of the sweetener concentrations used.

The majority of *in vivo* data have failed to confirm effects of non-nutritive sweeteners on hormone secretion observed *in vitro*. Fujita *et al.* (26) found that gastric gavage (thus bypassing lingual taste receptors) of four different non-nutritive sweeteners (acesulfame-K, stevia, d-tryptophan, and sucralose) failed to increase GLP-1 or GIP secretion in rats. It is notable that in this experiment, the doses of sweetener given (1 g/kg) were 1000-fold in excess of the concentrations typically found in commercial products such as diet sodas. Four similar experiments in healthy humans showed no effect of oral sucralose (35, 36) or intragastric sucralose, aspartame, or acesulfame-K on GLP-1, PYY, ghrelin, or GIP secretion (37, 38). Taken together, these data support the notion that non-nutritive

---

**TABLE 2.** Effects of non-nutritive sweeteners on gut hormones and glucose absorption: *in vitro* effects

<table>
<thead>
<tr>
<th>Sweetener</th>
<th>Concentration</th>
<th>Model system</th>
<th>Biological effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acesulfame-K</td>
<td>2 mM (33)</td>
<td>Cultured mouse intestine</td>
<td>No effect on GLP-1</td>
</tr>
<tr>
<td></td>
<td>50 mM (14)</td>
<td>MIN6 cells</td>
<td>Increased glucose-stimulated insulin secretion</td>
</tr>
<tr>
<td>Saccharin</td>
<td>50 mM (14)</td>
<td>MIN6 cells</td>
<td>Increased glucose-stimulated insulin secretion</td>
</tr>
<tr>
<td>Sucralose</td>
<td>0.2, 1, 5, 20 mM (32)</td>
<td>NCI-H716 cells</td>
<td>GLP-1 secretion at 1 and 5 mM but not at 0.2 or 20 mM GIP and GLP-1 secretion</td>
</tr>
<tr>
<td></td>
<td>50 mM (24)</td>
<td>GLUTag cells</td>
<td>No effect on GIP</td>
</tr>
<tr>
<td></td>
<td>1 mM (34)</td>
<td>Isolated mouse K-cells</td>
<td>No effect on GLP-1 at 1 mM. Increased GLP-1 at 20 mM only in colon (not small bowel)</td>
</tr>
<tr>
<td></td>
<td>1 and 20 mM (33)</td>
<td>Cultured mouse intestine</td>
<td>Increased glucose-stimulated insulin secretion</td>
</tr>
<tr>
<td></td>
<td>50 mM (14)</td>
<td>MIN6 cells</td>
<td>Increased glucose-stimulated insulin secretion</td>
</tr>
<tr>
<td></td>
<td>10 and 50 mM (14)</td>
<td>Isolated mouse islets</td>
<td>Increased glucose-stimulated insulin secretion</td>
</tr>
<tr>
<td></td>
<td>2.5 mM (43)</td>
<td>Isolated rat islets</td>
<td>Increased glucose-stimulated insulin secretion</td>
</tr>
</tbody>
</table>

Measurable biological effects are italicized. NCI-H716 is a human L cell line; GLUTag is a mouse enterendocrine cell line; MIN6 is a mouse insulinoma (β-cell) line.
sweeteners in isolation are not a sufficient stimulus to cause gut hormone secretion in vivo.

Our group examined this question using a slightly different design, testing whether non-nutritive sweeteners in a commercially available diet soda could change gut hormone secretion in combination with caloric sugars (39). Healthy adolescents and young adults drank either caffeine-free Diet Rite cola or carbonated water, followed 10 min later by an oral glucose load in a randomized, crossover design. We found that the plasma GLP-1 area under the curve after glucose ingestion was 34% higher after diet soda compared with carbonated water ($P = 0.029$). This finding was replicated in patients with type 1 diabetes, in whom the GLP-1 area under the curve was 43% higher in the diet soda condition, but not in those with type 2 diabetes (40). These data imply that diet soda (presumably via the non-nutritive sweeteners) enhances glucose-stimulated GLP-1 secretion, although it is not clear from the experiment whether this effect was mediated via sweet-taste receptors on enteroendocrine cells, lingual sweet-taste receptors, or another mechanism altogether. In addition, the clinical significance of this finding is not clear because insulin levels were not statistically different between the two conditions, and other GLP-1 effects, such as satiety and gastric emptying, were not measured. It is noteworthy that these findings were not confirmed by another study, which found no difference in plasma GLP-1 during intraduodenal infusion of 4 mM sucralose vs. saline in combination with glucose (41). Data from Gerspach et al. (29) support the idea that sweet-taste sensing is less important for GLP-1 secretion after intraduodenal vs. intragastric delivery of glucose, potentially accounting for the differing results in the two studies. Wu et al. (42) studied the effects of sucralose before a solid meal (powdered potatoes with 20 g glucose and egg yolk) and reported no effect on GIP or GLP-1 secretion; however, there was no unsweetened control.

Pancreatic β-cells, although located outside the intestinal epithelium, may be considered enteroendocrine cells. In 2009, Nakagawa et al. (14) identified sweet-taste receptors in MIN6 cells (a mouse insulinoma cell line frequently used to study β-cell function) and in mouse islets.

### Table 3. Effects of non-nutritive sweeteners on gut hormones and glucose absorption: in vivo effects on animals

<table>
<thead>
<tr>
<th>Sweetener</th>
<th>Dose</th>
<th>Model system</th>
<th>Biological effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acesulfame-K</td>
<td>10 mg in drinking water × 2 wk (24)</td>
<td>Mouse</td>
<td>Increased SGLT-1 expression</td>
</tr>
<tr>
<td></td>
<td>1 g/kg (26)</td>
<td>Rat</td>
<td>No effect on GIP or GLP-1</td>
</tr>
<tr>
<td>Aspartame</td>
<td>1 mM in drinking water × 2 wk (24)</td>
<td>Mouse</td>
<td>No effect on SGLT-1 expression</td>
</tr>
<tr>
<td>D-tryptophan</td>
<td>50 mg/kg (26)</td>
<td>Rat</td>
<td>No effect on GIP or GLP-1</td>
</tr>
<tr>
<td>Saccharin</td>
<td>20 mM × 2 wk (24)</td>
<td>Mouse</td>
<td>Increased SGLT-1 expression</td>
</tr>
<tr>
<td>Stevia</td>
<td>1 g/kg (26)</td>
<td>Rat</td>
<td>No effect on GIP or GLP-1</td>
</tr>
<tr>
<td></td>
<td>0.03 g/kg/d (46)</td>
<td>Rat (T2D)</td>
<td>Reduced glucose, insulin, and glucagon</td>
</tr>
<tr>
<td>Sucralose</td>
<td>2 mM in drinking water × 2 wk (24)</td>
<td>Mouse</td>
<td>Increased SGLT-1 expression</td>
</tr>
<tr>
<td></td>
<td>1 mM intestinal infusion (51)</td>
<td>Rat</td>
<td>No effect on GIP or GLP-1</td>
</tr>
</tbody>
</table>

Measurable biological effects are italicized. T2D, type 2 diabetes.

### Table 4. Effects of non-nutritive sweeteners on gut hormones and glucose absorption: in vivo effects on humans

<table>
<thead>
<tr>
<th>Sweetener</th>
<th>Dose</th>
<th>Subjects</th>
<th>Biological effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acesulfame-K</td>
<td>220 mg (25)</td>
<td>Healthy</td>
<td>No effect on PYY or GLP-1</td>
</tr>
<tr>
<td>Acesulfame-K +</td>
<td>26 mg acesulfame-K +</td>
<td>T1D, T2D</td>
<td>Increased glucose-stimulated GLP-1 in healthy and T1D, but not T2D. No effect on insulin, glucose, GIP, or PYY</td>
</tr>
<tr>
<td>in diet cola</td>
<td>46 mg sucralose (39, 40)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspartame</td>
<td>169 mg (25)</td>
<td>Healthy</td>
<td>No effect on PYY or GLP-1</td>
</tr>
<tr>
<td>Stevia</td>
<td>1 g (47)</td>
<td>T2D</td>
<td>Decreased glucagon and blood glucose.</td>
</tr>
<tr>
<td>Sucralose</td>
<td>41.5 mg (35)</td>
<td>Healthy</td>
<td>No effect on PYY or GLP-1</td>
</tr>
<tr>
<td></td>
<td>62 mg (25)</td>
<td>Healthy</td>
<td>No effect on PYY or GLP-1</td>
</tr>
<tr>
<td></td>
<td>80 and 800 mg (37)</td>
<td>Healthy</td>
<td>No effect on GIP or GLP-1</td>
</tr>
<tr>
<td></td>
<td>960 mg (41)</td>
<td>Healthy</td>
<td>No effect on glucose-stimulated GLP-1 or glucose absorption rate</td>
</tr>
<tr>
<td></td>
<td>85 mg (36)</td>
<td>Healthy</td>
<td>No effect on ghrelin, glucagon, insulin, or glucose</td>
</tr>
<tr>
<td></td>
<td>60 mg (42)</td>
<td>Healthy</td>
<td>No effect on mixed-meal stimulated GLP-1, GIP</td>
</tr>
</tbody>
</table>

Measurable biological effects are italicized. NCI-H716 is a human L cell line; GLUTag is a mouse enteroendocrine cell line; MIN6 is a mouse insulinoma (β-cell) line. T1D, Type 1 diabetes; T2D, type 2 diabetes.
In MIN6 cells, the non-nutritive sweeteners sucralose, saccharin, and acesulfame-K stimulated insulin secretion in the presence of glucose at low concentration (3 mM), and sucralose augmented glucose-stimulated insulin secretion across a range of glucose concentrations, from 3 to 25 mM. Consistent with known intracellular signaling mechanisms in lingual taste cells, sucralose increased intracellular Ca\(^{2+}\), and this effect was blocked by the sweet-antagonist gurmarin, implying that it was mediated via sweet-taste receptors. In isolated mouse islets, sucralose enhanced glucose-stimulated insulin secretion at low glucose concentrations (2.8 mM), but not at high glucose concentrations (20 mM). Although non-nutritive sweetener concentrations within islets in vivo have not been measured, the 10 to 50 mM concentrations used in these experiments are likely to be an order of magnitude above what might be found in humans, thus bringing into question the biological relevance of these results. However, in rat islets, 2.5 mM saccharin, a concentration that might conceivably be achieved by high levels of consumption in humans, was shown to increase basal insulin secretion (43). The effects on islet hormone secretion of the plant-derived sweetener, stevia, and its sweetest component molecule, rebaudioside A, have been extensively studied by the Hermansen group. Their work suggests that this class of compounds enhances glucose-stimulated insulin secretion via inhibition of ATP-sensitive K-channels (44, 45) and lowers blood glucose in both rodents (46) and humans (47) with type 2 diabetes primarily by suppressing glucagon release.

**Non-Nutritive Sweeteners and Intestinal Glucose Absorption**

Dietary glucose is absorbed across the enterocytes of the intestinal wall via the active Na\(^+/\)glucose cotransporter (SGLT-1) on the apical (luminal) membrane and the passive glucose transporter 2 (GLUT2) on the basolateral membrane of the enterocyte (Fig. 1A). In order for intestinal transport to adapt to dietary glucose concentrations, there must be a glucose sensing mechanism present in the gastrointestinal tract; the sweet-taste receptor is one such sensor (13, 24). Glucose binding to sweet-taste receptors on intestinal enteroendocrine cells causes secretion of GLP-1 and GLP-2 release. GLP-2 may cause up-regulation of SGLT-1 via enteric neurons. GLP-1 may act in a paracrine manner on nearby enterocytes to up-regulate apical GLUT2. Non-nutritive sweeteners can also bind to enteroendocrine sweet-taste receptors, causing GLP-1 release (in vitro) and increased intestinal glucose uptake (in rodents).
(glucose-galactose malabsorption) have severe carbohydrate malabsorption, emphasizing the functional importance of this glucose transporter (50).

Margolskee et al. (24) studied the role of non-nutritive sweeteners in the regulation of intestinal glucose absorption in mice, demonstrating that sucralose, acesulfame-K, and saccharin (but not aspartame, which is not sensed as sweet by rodents) up-regulated SGLT-1. This up-regulation resulted in a 1.9-fold increase in SGLT-1-mediated glucose transport measured in vitro. In 2007, Mace et al. (51) showed that these sweeteners could double the in vivo rate of intestinal glucose absorption in rats by increasing GLUT2 insertion into the apical membrane of enterocytes.

The effect of non-nutritive sweeteners on glucose absorption in humans was examined by Ma et al. (41). In healthy adults, they found no difference in intestinal glucose absorption during intraduodenal infusion of 4 mM sucralose vs. saline in combination with glucose. In this study, the rate of intestinal glucose absorption was measured by adding a non-metabolizable glucose analog, 3-O-methyl glucose (3OMG), to the intestinal perfusate. 3OMG is absorbed across enterocytes identically to glucose and is subsequently excreted by the kidney over 48 h (52). Serum levels of 3OMG over 2–3 h after ingestion can thus be used as a proxy for the rate of intestinal glucose absorption. Because this is an indirect measure, however, it may be less sensitive than direct measures of intestinal glucose absorption used in rodent studies. At the current time, there is insufficient evidence to support an effect of non-nutritive sweeteners on intestinal glucose absorption in healthy humans.

Non-Nutritive Sweetener Effects on the Microbiome

Connections between nutrition, gut microbial communities, and specific aspects of our health, such as the function of the immune system and the development of obesity, are under intense investigation (53, 54). A bidirectional influence of nutritional components such as non-nutritive sweeteners on the gut microbiome and vice versa is highly likely. For example, rodent studies have shown that germ-free animals up-regulate their sweet-taste receptors and glucose transporters in the proximal small intestine and preferentially consume nutritive compared with non-nutritive sweeteners (55). Abou-Donia et al. (56) suggested that sucralose may alter the microbiome of rats and furthermore reported that sucralose up-regulated intestinal enzymes important for drug metabolism. To date, there are no published studies in humans examining these questions.

Conclusions

The identification of sweet-taste receptors in enteroendocrine cells, both in the intestinal epithelium and the pancreas, has led to important insights into the mechanisms underlying glucose sensing, glucose transport, and hormone secretion. Non-nutritive sweeteners have allowed researchers to distinguish effects that are mediated via sweet-taste receptors (that bind to non-nutritive sweeteners) from effects mediated by other glucose sensors and transporters, such as SGLT-1. Given the epidemiological data associating non-nutritive sweetener use with weight gain and diabetes, it is intriguing to speculate that intestinal sweet-taste receptors might provide a mechanistic link. Egan and Margolskee (57) proposed that non-nutritive sweeteners binding to intestinal sweet-taste receptors would lead to increased GLP-1 secretion, which in turn would increase insulin secretion and lower blood glucose, and thus increase appetite and induce weight gain. Corkey (43) raised a similar provocative hypothesis in the 2011 Banting Lecture, speculating that non-nutritive sweeteners and other food additives might induce pancreatic β-cell hypersecretion, leading to hepatic insulin resistance and increased fat accumulation, both key components of obesity and type 2 diabetes.

Although most in vitro data support the idea that non-nutritive sweeteners can increase hormone secretion by enteroendocrine cells or pancreatic β-cells, the available in vivo data have generally not supported this. In both rodents and humans, non-nutritive sweeteners in the absence of metabolizable sugars have not altered hormone secretion in vivo. When given in combination with metabolizable sugars, non-nutritive sweeteners increased intestinal glucose absorption in rodents, but not humans. One human study showed that non-nutritive sweeteners may increase GLP-1 when given in combination with metabolizable sugars, but this finding needs to be replicated. To date, solid evidence for a clinically relevant role of non-nutritive sweeteners on gut hormones or glucose metabolism in humans remains to be established. Ongoing and future clinical studies will hopefully soon provide answers to the highly relevant questions about the effects of non-nutritive sweeteners on gut hormones, glucose metabolism, and ultimately human weight regulation.

Acknowledgments

We thank Allison Sylvetsky for critical review of the manuscript.

Address all correspondence and requests for reprints to: Rebecca J. Brown, M.D., Building 10, Room 7C-432A, 9000 Rockville Pike, Bethesda, Maryland 20892-1645. E-mail: brownrebecca@mail.nih.gov.
This work was supported by the intramural research program of the National Institute of Diabetes and Digestive and Kidney Diseases.

Disclosure Summary: The authors have no conflicts of interest.

References


12. Montmayeur JP, Matsunami H 2002 Receptors for bitter and sweet taste receptors of the T1R family in the intestinal tract and taste receptors regulate secretion of glucagon-like peptide-1 (GLP-1) and peptide YY (PYY). Clin Nutr 30:524–532


31. Steinert RE, Frey F, Topfer A, Drewe J, Beimler C 2011 Effects of carbohydrate sugars and artificial sweeteners on appetite and the


57. Egan JM, Margolskee RF 2008 Taste cells of the gut and gastrointestinal chemosensation. Mol Interv 8:78–81

