

Published in final edited form as:

Curr Opin Clin Nutr Metab Care. 2011 July ; 14(4): 391–395. doi:10.1097/MCO.0b013e3283468e7e.

Nonnutritive sweeteners, energy balance and glucose homeostasis

M. Yanina Pepino and Christina Bourne

School of Medicine, Washington University in St. Louis, 660 South Euclid Avenue, Campus Box 8031, St. Louis, MO 63110

Abstract

Purpose of review—To review recent work on potential mechanisms underlying a paradoxical positive association between the consumption of nonnutritive sweeteners (NNS) and weight gain.

Recent findings—Several potential mechanism, not mutually exclusive, are hypothesized. First, by dissociating sweetness from calories, NNS could interfere with physiological responses that control homeostasis. Second, by changing the intestinal environment, NNS could affect the microbiota and in turn trigger inflammatory processes that are associated with metabolic disorders. Third, by interacting with novel sweet-taste receptors discovered in the gut, NNS could affect glucose absorptive capacity and glucose homeostasis. This last is the mechanism that has received the most attention recently. Some animal studies, but not all, found that NNS activate gut sweet taste-pathways that control incretin release and up-regulate glucose transporters. Human studies found that, at least for healthy fasted subjects, the sole interaction of NNS with sweet-taste gut receptors is insufficient to elicit incretin responses. The reasons for discrepancy between different studies is unknown but could be related to the species of mammal tested and the dose of NNS used.

Summary—Whether NNS are metabolically inactive, as previously assumed, is unclear. Further research on the potential effects of NNS on human metabolism is warranted.

Keywords

Nonnutritive sweeteners; obesity; taste receptors; incretins; glucose homeostasis

Introduction

Nonnutritive sweeteners (NNS) have existed since the end of the 19th century, when saccharin was serendipitously discovered [1]. Currently, five NNS (acesulfame potassium, aspartame, neotame, saccharin, and sucralose) are approved by the US Food and Drug Administration (FDA), and one noncaloric sugar replacement derived from a plant (rebaudioside A, stevia) is recognized as General Recommended as Safe by the FDA. Until recently, the general belief was that NNS could promote diet healthfulness by delivering a pleasant sweet taste without calories or glycemic effects. However, recent data from epidemiological studies in humans [2, 3, 4, 5*] and feeding studies in animal models [6, 7**, 8] challenge this belief suggesting that the use of NNS might dysregulate energy balance contributing to obesity and other negative health outcomes. This paper will review

Corresponding author: M. Yanina Pepino, Ph.D., Research Assistant Professor, School of Medicine, Washington University in St. Louis, 660 South Euclid Avenue, St. Louis, MO 63110, Phone : +1 314 362 8113; Fax : +1 314 362 8230, ypepino@dom.wustl.edu.

Conflict of interest: None to declare

current evidence of metabolic effects of NNS in animal models and humans and recent advances in our understanding of possible mechanisms of action underlying these effects.

Attraction to sweetness and the paradoxical association between the use of NNS and positive energy balance

Inherently, humans and most mammals are drawn to sweet tastes, whose sensation is mediated by the heterodimeric T1R1+T1R3 sweet taste receptor [9, 10, 11]. The suggested ecological value of this innate preference is that in nature, sweet tasting foods, such as fruits, or the first food of mammals, mother's milk, are associated with calories. Until few centuries ago, access to sugar was rare and luxurious, but modern technological means of refining sugars significantly increased its availability and consumption patterns.

Given that high consumption of sugar in the diet, mostly through energy-dense, nutrient-poor foods, contributes to energy intake above requirement, NNS have been recommended as a healthier alternative to satisfy human's sweet tooth [12]. However, epidemiological data reveal the consumption of NNS, mainly in diet sodas, is not necessarily linked to better health outcomes (reviewed in [8, 13, 14**]). For example, some studies, but not all [15, 16], found positive associations between the amount of NNS consumed and weight gain [2, 17] and increased incidence of metabolic syndrome [3, 4, 5*]. Several hypotheses, not mutually exclusive, could explain this seeming paradoxical association (reviewed in [14**]).

First, individuals who are already on a path of weight gain might consume NNS as a strategy to reduce calorie intake. Yet, the finding of a positive dose-response relationship between the amount of artificially sweetened beverages consumed and long-term weight gain suggests that NNS could be contributing to the risk of obesity and its metabolic consequences in its own right [2]. However, how would metabolically inert sugar-substitutes, which have very few, if any, calories, contribute to positive energy balance?

Swithers and others hypothesize that the ability of sweet taste to predict calories and evoke physiological responses that prepare the gastrointestinal tract for optimal process of ingested food, such as the cephalic response, may be degraded by the use of NNS [6, 7**, 8]. In their elegant animal model, rats are given differential experience with a sweet taste that either predicts (glucose) or does not predict (saccharine or acesulfame K) increased calories. Compared to rats that consume a diet sweetened with glucose, those consuming a diet sweetened with NNS are heavier, accumulate more fat, and respond with a weaker thermic effect of food and calorie compensation [7**]. Further supporting the hypothesis that uncoupling sweetness from calories has detrimental consequences on energy balance, recently it has been shown that rats consuming fluids sweetened with stevia, the only natural NNS, also weigh more than rats consuming fluids sweetened with glucose [8].

Another interesting potential mechanism for the paradoxical association between NNS consumption and increased body weight is the possibility that NNS alter gut microbiota. It has been shown that changes in the type of intestinal bacteria can trigger inflammatory process that promote insulin resistance, fat storage and weight gain in the host [18, 19]. In rats, 12 weeks exposure to Splenda (a NNS comprising 1% w/w sucralose with glucose (1% w/w) and maltodextrin (94% w/w) as fillers) significantly modified intestinal flora and was associated with weight gain [20].

Finally, a provocative hypothesis that emerged in the last few years, along with the discovery of sweet taste receptors in the gastrointestinal tract, is that NNS are not metabolically inert but have metabolic effects [21, 22, 23]. As will be discussed in the

following sections, NNS may affect glucose homeostasis by activating sweet taste receptors in the gut.

The discovery of sweet taste-like receptors in the gut and its role in chemosensory function

Recently, taste receptors (T1R and T2R) acting through signaling pathways similar to those found in lingual taste buds have been found in the gut of rodents and humans [21, 22, 23]. Further, data obtained from immunohistochemical studies, mouse models *in vivo* and *in vitro* and human duodenal L cells *in vitro* [21, 22], supports the hypothesis that the sweet taste receptor subunit T1R3 coupled to the taste G protein alpha-gustducin, underlie at least one of the components of sugar sensing in the gut (see [24] for a review). Studies manipulating signaling pathways involved in sweet taste transduction provide perhaps the strongest evidence suggesting the functional significance of the expression of sweet taste receptors in the intestine. Mice lacking alpha-gustducin or T1r3 show severely defective incretins response to a glucose challenge [21, 25**]. Incretins (glucagon-like peptide-1: GLP-1 and glucose-dependent insulintropic peptide: GIP), are gut hormones that are released into the blood stream and stimulate pancreatic beta-cells to secrete insulin and also intervene in the control of appetite and gut motility (reviewed in [26]). The so-called “incretin effect”, first described in the 60's refers to the fact that an oral glucose load elicits a remarkably greater insulin response than an intravenous glucose load even when both are matched to cause the same increase in blood glucose levels [27]. That taste-signaling pathways in the gut intervene in the “incretin effect” is further supported by two observations: GLP-1 release is completely blocked by sweet taste receptor antagonists in both human and murine duodenal cells [21, 22], and alpha-gustducin knockout mice have significantly disrupted glucose homeostasis both after a glucose challenge and after post-fasting feeding on chow [21].

In addition to its important function of regulating GLP-1 secretion, sweet-taste signaling pathways in the gut may play a key role in the regulation of glucose absorption from the intestinal lumen into enterocytes. Data obtained in rodents suggest that intestinal sweet taste receptors control both active glucose absorption, by modulating expression of sodium-dependent glucose transporter isoform 1 (SGLT1) [22], and passive glucose absorption, by modulating apical glucose transporter 2 (GLUT2) insertion to the intestine [23]. Unlike wild type, knockout mice lacking either alpha-gustducin or T1r3 failed to up-regulate SGLT1 intestinal expression and glucose absorptive capacity when exposed to a high carbohydrate diet (70% sucrose) [22].

Despite the strong evidence provided by alpha-gustducin and T1r3 knockout mice on the role of sweet-taste receptors in the gut, it has been recently proposed that SGLT1, not sweet taste receptors, is the intestinal glucose sensor which activation triggers incretin release [28**]. Moriya and collaborators based their hypothesis on the following three findings: 1) the co-administration of glucose with a SGLT1 inhibitor, phloridzin, in mice *in vivo* blocked glucose absorption and incretin release, 2) the administration of NNS such as sucralose or saccharin was not sufficient to elicit incretin responses, and 3) the administration of a nonmetabolizable sugar that is a SGLT1 substrate, alpha- methyl-D-glucopyranoside, triggered incretin responses which in turn were blocked by phloridzin [28**].

However, two additional observations conflict with Moriya and collaborator's hypothesis and further support the intestinal sweet taste receptor is a glucose sensor. First, the sweet sugar D-fructose, which has very low affinity for SGLT1, induces up-regulation of SGLT1 [29]. Second, recent studies in cats, a natural T1R2 knockout model, reveal that despite

relying mainly on SGLT1 for intestinal glucose transport, cats are unable to up-regulate SGLT1 in response to increase carbohydrates in their diets [30*].

Effect of NNS on glucose transport and incretin release

Studies conducted in GLP-1 secreting cells in humans (NCI-H716 L cells) and enteroendocrine cells in mouse (STC-1 and GLUTag) show that sucralose, similar to glucose, interacted with sweet taste receptors expressed in these cells and activated a cascade of events that lead to the release of GLP-1 [21, 22]. Further, like observed after intraluminal perfusion of glucose, intraluminal perfusion of NNS in anesthetized rats induced a rapid up-regulation of SGLT1 [29] and enhanced apical insertion of GLUT2 [23]. Similarly, two-week supplementation of a low carbohydrate diet with sucralose, saccharin or acesulfame-K (but not with aspartame, which does not taste sweet to mice and does not activate their sweet taste receptor) up-regulated intestinal SGLT1 expression levels to values that were similar to those measured in mice fed a high carbohydrate diet [22].

In disagreement with these findings, intragastric infusion of high concentrations of NNS did not increase plasma GLP-1 concentrations in fasted rats [31]. Likewise, the infusion of saccharin or sucralose in the upper small intestine after 18 hrs of fasting did not increase GIP or GLP-1 plasma portal concentrations in mice [28**]. In healthy humans evaluated under fasted conditions, an acute intragastric infusion of sucralose (either 0.4 mM or 4mM) did not stimulate insulin, GLP-1, or GIP release and did not slow down gastric emptying [32**]. Further, when delivered intraduodenally, sucralose did not affect postprandial blood glucose concentration, GLP-1 secretion or glucose absorption from the lumen of the small intestine in fasted healthy humans [33]. The oral administration of sucralose (2mM) [34*] or the acute intragastric infusion of aspartame, acesulfame K or sucralose [35*] to healthy human subjects in the fasted state also failed to affect GLP-1, insulin or glucose levels. These observations do not support the hypothesis that, like observed in human L-cells *in vitro* and in animal models, NNS elicit incretin responses in healthy humans. However, there is one study in young healthy adults showing that the acute consumption of NNS, namely a diet soda, immediately before glucose load significantly enhances GLP-1 secretion [36*].

Possible reasons for disagreement between studies and areas for further studies

The reason(s) for disagreement between the studies summarized in the above section is unknown but, as speculated below, it could be related to 1) the concentration of NNS used 2) the species of mammal tested and 3) the glycemic levels at the time NNS were studied.

1. The concentration of NNS at the sweet taste receptor level may affect the incretin response

At least for saccharin, and for the lingual taste bud, the relationship between concentration of the chemical compound and level of sweetness is non-linear. Saccharin elicits a sweet taste at concentrations below 6 mM but blocks the sweetness of sucrose (and of itself) at concentrations above 10 mM [37]. The data of Jang and collaborators suggests that the activity of the sweet-taste receptors in the gut might mimic the sweet taste receptors in the tongue [21]. Whereas L-cells followed a linear concentration-response curve within the 0.004mM to 5 mM sucralose range, 20 mM sucralose did not elicit a GLP-1 response. Future NNS dose-response studies evaluating incretin responses are warranted.

2. Diversity in sweet taste sensation among species may also occur at the level of the gut

Sweet-taste sensitivity varies widely among mammals [38]. For example, unlike humans, rats do not perceive aspartame, cyclamate, neotame, monellin, thaumatin or alitame as sweet [39, 40]. Although both mice and rats show a small preference for stevia extracts over water [41], they differed on their responses to sucralose. While mice avidly consume sucralose and preferred it to water [42], rats show a weak preference at best [43, 44]. The great diversity in the sensitivity of the sweet taste receptor among species (and even within strains) should be considered when designing studies that examine the effects of NNS on incretin responses.

3. NNS may only have a metabolic effect when administered in an environment of hyperglycemia

Noteworthy, to date, in most of the studies where NNS have an effect on incretin release or glucose absorptive capacity [21, 22, 23, 36*] NNS were administered in combination with food or a glucose load. Conversely, in most of the studies where NNS failed to have an effect on incretin release, NNS were administered on the fasted state [28**, 32**, 34*, 35*]. Future studies evaluating effect of NNS on incretin responses in conditions of hyperglycemia are warranted.

Conclusion

Several potential mechanisms, which are not mutually exclusive, are hypothesized to explain the paradoxical association between the consumption of NNS with few, if any, calories and weight gain observed in epidemiological studies. From a Pavlovian approach, where the dissociation of sweetness from calories would interfere with fundamental physiological responses that had evolved to control homeostasis [6, 7**, 8] to changes in the intestinal environment and thus of the microbiota [20], which could trigger inflammatory processes associated with metabolic disorders and obesity [18, 19], to interactions of NNS with novel sweet taste receptors discovered in the gut [21, 22, 23]. To date, only the last mechanism has been studied in humans. Data from humans and animal models contradict and it is not clear whether NNS by interacting with sweet taste intestinal receptors affect incretin responses *in vivo*. The five published studies conducted in humans so far [32**, 33, 34*, 35*, 36*] indicate that the sole interaction of NNS with a sweet taste gut receptor is insufficient to elicit an incretin response in healthy fasted subjects. Considering the wide variability on sweet-taste sensitivity among mammals and the unknown relationship between sweetener concentration and physiologic response, future dose-response studies that focus on potential effects of NNS on human metabolism are warranted.

Acknowledgments

This publication was made possible by Grant Number UL1 RR024992, sub award KL2RR024994 from the NIH-National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH), and NIH Roadmap for Medical Research. Its contents are solely the responsibility of the authors and do not necessarily represent the official view of NCRR or NIH

References

1. Parker KJ. Alternatives to sugar. The search for an ideal non-nutritive sweetener is almost a century old. *Nature*. 1978; 271:493–495. [PubMed: 340963]
2. Fowler SP, Williams K, Resendez RG, et al. Fueling the obesity epidemic? Artificially sweetened beverage use and long-term weight gain. *Obesity (Silver Spring)*. 2008; 16:1894–900. [PubMed: 18535548]

3. Lutsey PL, Steffen LM, Stevens J. Dietary intake and the development of the metabolic syndrome: the Atherosclerosis Risk in Communities study. *Circulation*. 2008; 117:754–761. [PubMed: 18212291]
4. Dhingra R, Sullivan L, Jacques PF, et al. Soft drink consumption and risk of developing cardiometabolic risk factors and the metabolic syndrome in middle-aged adults in the community. *Circulation*. 2007; 116:480–488. [PubMed: 17646581]
- 5*. Nettleton S, Woods B, Burrows R, Kerr A. Food allergy and food intolerance: towards a sociological agenda. *Health (London)*. 2009; 13:647–664. This is a multiethnic observational study among 6814 adults that replicates the previously reported association between the consumption of diet soda and greater risks of metabolic syndrome components and type 2 diabetes. [PubMed: 19841024]
6. Swithers SE, Davidson TL. A role for sweet taste: calorie predictive relations in energy regulation by rats. *Behav Neurosci*. 2008; 122:161–173. [PubMed: 18298259]
- 7**. Swithers SE, Baker CR, Davidson TL. General and persistent effects of high-intensity sweeteners on body weight gain and caloric compensation in rats. *Behav Neurosci*. 2009; 123:772–780. This paper not only confirms previous findings that uncoupling sweetness from calories is associated with increase body weight and fat in rats, but importantly, it shows the association previously observed was not specific to the consumption of saccharine but generalizes to a variety of nonnutritive sweeteners. [PubMed: 19634935]
8. Swithers SE, Martin AA, Davidson TL. High-intensity sweeteners and energy balance. *Physiol Behav*. 2010; 100:55–62. [PubMed: 20060008]
9. Hoon MA, Adler E, Lindemeier J, et al. Putative mammalian taste receptors: a class of taste-specific GPCRs with distinct topographic selectivity. *Cell*. 1999; 96:541–551. [PubMed: 10052456]
10. Bachmanov AA, Li X, Reed DR, et al. Positional cloning of the mouse saccharin preference (Sac) locus. *Chem Senses*. 2001; 26:925–933. [PubMed: 11555487]
11. Nelson G, Hoon MA, Chandrashekar J, et al. Mammalian sweet taste receptors. *Cell*. 2001; 106:381–390. [PubMed: 11509186]
12. Van Horn L, Johnson RK, Flickinger BD, et al. Translation and implementation of added sugars consumption recommendations: a conference report from the American Heart Association Added Sugars Conference 2010. *Circulation*. 2010; 122:2470–2490. [PubMed: 21060079]
13. Brown RJ, de Banate MA, Rother KI. Artificial sweeteners: a systematic review of metabolic effects in youth. *Int J Pediatr Obes*. 2010; 5:305–312. [PubMed: 20078374]
- 14**. Mattes RD, Popkin BM. Nonnutritive sweetener consumption in humans: effects on appetite and food intake and their putative mechanisms. *Am J Clin Nutr*. 2009; 89:1–14. This is an outstanding review of the literature on nonnutritive sweeteners and appetite. In this paper, the authors analyze mechanism by which the addition of NNS in the diet would promote energy intake. They conclude that the available evidence do not support most of the mechanisms proposed; but caution that long-term randomized control trials are required to resolve the issue. [PubMed: 19056571]
15. Ludwig DS, Peterson KE, Gortmaker SL. Relation between consumption of sugar-sweetened drinks and childhood obesity: a prospective, observational analysis. *Lancet*. 2001; 357:505–508. [PubMed: 11229668]
16. Schulze MB, Manson JE, Ludwig DS, et al. Sugar-sweetened beverages, weight gain, and incidence of type 2 diabetes in young and middle-aged women. *JAMA*. 2004; 292:927–934. [PubMed: 15328324]
17. Blum JW, Jacobsen DJ, Donnelly JE. Beverage consumption patterns in elementary school aged children across a two-year period. *J Am Coll Nutr*. 2005; 24:93–98. [PubMed: 15798075]
18. Vijay-Kumar M, Aitken JD, Carvalho FA, et al. Metabolic syndrome and altered gut microbiota in mice lacking Toll-like receptor 5. *Science*. 2010; 328:228–231. [PubMed: 20203013]
19. Backhed F, Ding H, Wang T, et al. The gut microbiota as an environmental factor that regulates fat storage. *Proc Natl Acad Sci U S A*. 2004; 101:15718–15723. [PubMed: 15505215]
20. Abou-Donia MB, El-Masry EM, Abdel-Rahman AA, et al. Splenda alters gut microflora and increases intestinal p-glycoprotein and cytochrome p-450 in male rats. *J Toxicol Environ Health A*. 2008; 71:1415–1429. [PubMed: 18800291]

21. Jang HJ, Kokrashvili Z, Theodorakis MJ, et al. Gut-expressed gustducin and taste receptors regulate secretion of glucagon-like peptide-1. *Proc Natl Acad Sci U S A*. 2007; 104:15069–15074. [PubMed: 17724330]
22. Margolskee RF, Dyer J, Kokrashvili Z, et al. T1R3 and gustducin in gut sense sugars to regulate expression of Na⁺-glucose cotransporter 1. *Proc Natl Acad Sci U S A*. 2007; 104:15075–15080. [PubMed: 17724332]
23. Mace OJ, Affleck J, Patel N, Kellett GL. Sweet taste receptors in rat small intestine stimulate glucose absorption through apical GLUT2. *J Physiol*. 2007; 582:379–392. [PubMed: 17495045]
24. Tolhurst G, Reimann F, Gribble FM. Nutritional regulation of glucagon-like peptide-1 secretion. *J Physiol*. 2009; 587:27–32. [PubMed: 19001044]
- 25*. Kokrashvili Z, Mosinger B, Margolskee RF. T1r3 and alpha-gustducin in gut regulate secretion of glucagon-like peptide-1. *Ann N Y Acad Sci*. 2009; 1170:91–94. Supporting the hypothesis that sweet taste receptors expressed in the gut are glucose sensors, this paper shows that the sweet taste receptor T1r3 is critical for the incretin effect. Mice lacking T1r3 (one of the heterodimers of the sweet taste receptor) show a severely defective GLP-1 response to a glucose challenge. [PubMed: 19686115]
26. Kim W, Egan JM. The role of incretins in glucose homeostasis and diabetes treatment. *Pharmacol Rev*. 2008; 60:470–512. [PubMed: 19074620]
27. McIntyre N, Holdsworth CD, Turner DS. New Interpretation of Oral Glucose Tolerance. *Lancet*. 1964; 2:20–21. [PubMed: 14149200]
- 28*. Moriya R, Shirakura T, Ito J, et al. Activation of sodium-glucose cotransporter 1 ameliorates hyperglycemia by mediating incretin secretion in mice. *Am J Physiol Endocrinol Metab*. 2009; 297:E1358–1365. This paper argues that sweet taste receptors in the gut are not glucose sensors. In making their case, they present findings that the presence of sweet taste in the gut is insufficient to secrete GLP-1 and that the activation of SGLT1 is required to elicit incretin responses and glucose intestinal transport. [PubMed: 19808907]
29. Stearns AT, Balakrishnan A, Rhoads DB, Tavakkolizadeh A. Rapid upregulation of sodium-glucose transporter SGLT1 in response to intestinal sweet taste stimulation. *Ann Surg*. 2010; 251:865–871. [PubMed: 20395849]
- 30*. Batchelor DJ, Al-Rammahi M, Moran AW, et al. Sodium/glucose cotransporter-1, sweet receptor, and disaccharidase expression in the intestine of the domestic dog and cat: two species of different dietary habit. *Am J Physiol Regul Integr Comp Physiol*. 2010; 300:R67–75. This paper contributes to the evidence that the sweet taste receptor in the gut is a glucose sensor by revealing that cats, which are natural T1R2 knockout models, are unable to up-regulate SGLT1 in response to increase dietary carbohydrates. [PubMed: 20980625]
31. Fujita Y, Wideman RD, Speck M, et al. Incretin release from gut is acutely enhanced by sugar but not by sweeteners in vivo. *Am J Physiol Endocrinol Metab*. 2009; 296:E473–479. This paper shows that the sole presence of NNS (in high concentrations) in the gut is not sufficient to increase GLP-1 in rats in vivo. [PubMed: 19106249]
- 32*. Ma J, Bellon M, Wishart JM, et al. Effect of the artificial sweetener, sucralose, on gastric emptying and incretin hormone release in healthy subjects. *Am J Physiol Gastrointest Liver Physiol*. 2009; 296:G735–739. This paper shows that the sole presence of NNS in the gut is insufficient to affect incretin release or gastric emptying in healthy subjects. [PubMed: 19221011]
33. Ma J, Chang J, Checklin HL, et al. Effect of the artificial sweetener, sucralose, on small intestinal glucose absorption in healthy human subjects. *Br J Nutr*. 2010; 104:803–806. [PubMed: 20420761]
- 34*. Ford HE, Peters V, Martin NM, et al. Effects of oral ingestion of sucralose on gut hormone response and appetite in healthy normal-weight subjects. *Eur J Clin Nutr*. 2011 Jan 19. [Epub ahead of print] This paper confirms previous observations in healthy humans and rats *in vivo* that the mere presence of NNS in the gut is insufficient to alter GLP-1, insulin or glucose levels.
- 35*. Steinert RE, Frey F, Topfer A, et al. Effects of carbohydrate sugars and artificial sweeteners on appetite and the secretion of gastrointestinal satiety peptides. *Br J Nutr*. 2011 Jan 24:1–9. [Epub ahead of print] This paper confirms previous observations in healthy humans and rats *in vivo* that the mere presence of NNS in the gut is insufficient to alter GLP-1, insulin or glucose levels.

- 36**. Brown RJ, Walter M, Rother KI. Ingestion of diet soda before a glucose load augments glucagon-like peptide-1 secretion. *Diabetes Care*. 2009; 32:2184–2186. This is the first paper that shows NNS interact with glucose to affect GLP-1 secretion in humans in vivo. Interestingly, despite changes in GLP-1 secretion, there were no differences on insulin and glucose levels. [PubMed: 19808921]
37. Galindo-Cuspinera V, Winnig M, Bufe B, et al. A TAS1R receptor-based explanation of sweet ‘water-taste’. *Nature*. 2006; 441:354–357. [PubMed: 16633339]
38. Li X, Glaser D, Li W, et al. Analyses of sweet receptor gene (Tas1r2) and preference for sweet stimuli in species of Carnivora. *J Hered*. 2009; 100:S90–100. [PubMed: 19366814]
39. Gordesky-Gold B, Rivers N, Ahmed OM, Breslin PA. *Drosophila melanogaster* prefers compounds perceived sweet by humans. *Chem Senses*. 2008; 33:301–309. [PubMed: 18234713]
40. Xu H, Staszewski L, Tang H, et al. Different functional roles of T1R subunits in the heteromeric taste receptors. *Proc Natl Acad Sci U S A*. 2004; 101:14258–14263. [PubMed: 15353592]
41. Sclafani A, Bahrani M, Zukerman S, Ackroff K. Stevia and saccharin preferences in rats and mice. *Chem Senses*. 2010; 35:433–443. [PubMed: 20413452]
42. Inoue M, Glendinning JJ, Theodorides ML, et al. Allelic variation of the Tas1r3 taste receptor gene selectively affects taste responses to sweeteners: evidence from 129.B6-Tas1r3 congenic mice. *Physiol Genomics*. 2007; 32:82–94. [PubMed: 17911381]
43. Sclafani A, Clare RA. Female rats show a bimodal preference response to the artificial sweetener sucralose. *Chem Senses*. 2004; 29:523–528. [PubMed: 15269124]
44. Bello NT, Hajnal A. Male rats show an indifference-avoidance response for increasing concentrations of the artificial sweetener sucralose. *Nutr Res*. 2005; 25:693–699. [PubMed: 16810335]

Key points

- The general belief that nonnutritive sweeteners promote diet healthfulness by delivering a pleasant sweet taste without calories or glycemic effects may not hold true.
- Nonnutritive sweeteners may interfere with physiological responses that control homeostasis by dissociating sweetness from calories.
- Nonnutritive sweeteners may affect glucose homeostasis by interacting with novel sweet- taste receptors discovered in the gut.
- The sole interaction of nonnutritive sweeteners with sweet- taste receptors in the gut is not enough to elicit incretin responses in healthy fasted subjects.
- Two important points to consider when designing future studies with nonnutritive sweeteners are that sweet-taste sensitivity varies widely among mammals and that the relationship between sweetener compound concentration and response may be non-linear.