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T1R3: how to indulge the gut's sweet tooth

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MORE THAN 300 YEARS HAVE PASSED since Lorenzo Bellini's (1643–1704) poetic description of the taste papillae in his work *Gustus Organum* (1665; see http://books.google.com/books/about/Gustus_organum.html?id=Uo6RE1CdjUwC):

"Many papillae are evident, I might say, innumerable, and the appearance is so elegant that they catch the view and thoughts of the observer, and control him for a long time and not without enjoyment . . ." (3).

However, only at the beginning of the 20th Century were the chemoreceptive areas of the human tongue for the qualities of sweet, sour, salty, and bitter tastes established (9), closely followed by the description of the distinctive quality of umami taste (12). Another hundred years passed before the actual sweet taste receptor was identified as a heterodimer of T1R2 and T1R3 proteins, members of the T1R G protein-coupled family of receptors (18), thereby establishing the missing link between the luminal sweet nutrients (e.g., glucose) and the already known second messengers within the taste cell, e.g., gustducin (17, 26), adenylyl cylase, and cyclic AMP (25), as well as phospholipase Cβ2 and calcium (23, 27).

Even before the description of the specific sweet taste receptor T1R2/T1R3, the major signaling components of the taste cascade were identified in the intestinal tract, first in the rat intestine (10). Only four years after identification of the T1R2/T1R3 sweet receptor on the taste cell, the expression of T1R2 and T1R3 was verified in an intestinal cell line (STC-1, a pluripotential enteroendocrine cell line) as well as directly in the mouse small intestine (5). In 2007, Jang et al. (13) first established the link between the sweet taste transduction elements and secretion of the hormone glucagon-like peptide-1 (GLP-1) from the enteroendocrine L cell, proposing that glucose-associated GLP-1 secretion is mediated by the sweet taste receptor (for recent review see Ref. 24).

The intestinal hormone GLP-1 is secreted by enteroendocrine L cells in response to numerous stimuli, particularly following direct stimulation with nutrients, e.g., carbohydrates or fat (11, 14). The biological actions of GLP-1 include increased insulin secretion and decreased glucagon release from the pancreatic islets; furthermore, GLP-1 delays gastric emptying and reduces appetite (2). As a result of these potent antidiabetic and anorectic properties, GLP-1 analogs and GLP-1 degradation inhibitors have been successfully introduced to the clinic and are considered safe for treatment of type 2 diabetes, particularly in morbidly obese patients (4). More recently, the cardioprotective properties of GLP-1 and its degradation products were described, particularly in patients with ischemic heart failure (19), suggesting possible future developments for GLP-1-based therapies. Understandably, these results increased focus on mechanisms underlying GLP-1 secretion from the intestinal L cell as a potential novel approach in the therapy of type 2 diabetes.

While the increased GLP-1 secretion following stimulation with glucose was well established in vivo (6) and in vitro (21), the mechanisms underlying increased secretion were less clear. As an alternative approach to intestinal sweet taste receptors, the glucose-dependent closure of the K_{ATP} channel and the activation of sodium-glucose cotransporter (SGLT1) were considered important mediators of glucose-induced GLP-1 secretion, particularly due to the low expression levels of the taste transduction elements and a missing effect of artificial sweeteners in primary mouse L cells (22). Some other working groups also reported that artificial sweeteners do not stimulate GLP-1 secretion release in rodents and humans, questioning the role of the sweet taste receptor pathway in glucose-stimulated GLP-1 secretion (7, 15, 16). To address this controversy (for reviews see Refs. 20 and 24), further studies in mice lacking T1R2 and T1R3 were urgently needed to verify the role of the T1R2/T1R3 sweet taste receptor pathway in glucose-stimulated GLP-1 secretion.

Excitingly, the study by Geraedts et al. (17a) in a recent issue of this Journal addresses just this quite intriguing question of the biological relevance of T1R2 and T1R3 molecules in glucose-associated GLP-1 secretion in mice. The authors used established models of T1R2 and T1R3 knockout mice; additionally, some of the results of the study were reevaluated in rats with Roux-Y gastric bypass (RYGB), an established model for surgical treatment of morbidly obese patients. Interestingly, the T1R3 but not the T1R2 knockout mice showed an impaired response to an intestinal glucose load, particularly, decreased insulin levels and increased glucose levels, as shown by an oral glucose tolerance test. Furthermore, intestinal explants from the small intestine of T1R3 knockout mice failed to secrete GLP-1 following stimulation with glucose, fructose, and sucrose, suggesting a key role of T1R3 for GLP-1 secretion. The addition of glibenclamide, a potent inhibitor of K_{ATP} channels, did not affect GLP-1 secretion from the small intestine. However, unexpectedly, the T1R3 knockout animals showed increased GLP-1 secretion from large intestinal explants; moreover, glibenclamide significantly potentiated the GLP-1 secretion from the colonic explants, suggesting a role of K_{ATP} channels in GLP-1 secretion from the large, but not the small, intestine. To address these surprising findings, the authors further evaluated the changes in intestinal luminal content, detecting a significantly increased carbohydrate load in the large intestine of the T1R3 knockout animals. As a supportive model, the authors used RYGB rats; excitingly, the RYGB rat intestinal explants showed a comparable increase in colonic GLP-1 secretion. As expected, the RYGB rats also showed increased intestinal carbohydrate load, suggestive of a common mechanism.

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Collectively, this study indicates that the T1R3, but not the T1R2 receptor, is required for glucose-dependent GLP-1 secretion in mice. The role of the sweet taste transduction system in the intestine thus appears to be strengthened by these findings. However, the carbohydrate-associated shift in GLP-1 secretion is speculative, and the actual mechanisms underlying the glucose-sensing apparatus, particularly in the colon, remain unknown. Furthermore, the appearance of two different types of GLP-1 secretion modes (small and large intestine) is unexpected and requires further investigation. Ultimately, this study raises the question of structurally different L cells in the large and small intestine, as also suggested by a recent publication by Habib et al. (8). The phenotype of the enteroendocrine cells seems not to be constant but distinct, depending on the localization of the cell in the gut (1). More studies in native L cells and further differentiation of available L cell lines are required to understand the mechanisms underlying these quite intriguing findings.

Taken together, Geraedts et al. clearly establish a key role for the T1R3 receptor in glucose-associated GLP-1 secretion, therein extending our understanding of the versatility of the enteroendocrine L cell and ultimately providing alternative approaches for future therapy of morbid obesity and type 2 diabetes mellitus.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: R.I. and L.M.L. drafted manuscript; R.I. and L.M.L. edited and revised manuscript; R.I. and L.M.L. approved final version of manuscript.

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