GUT SWEET TASTE RECEPTORS AND HOW SWEETENERS CONTRIBUTE TO OBESITY

The gastrointestinal tract represents a sensory organ that responds to a large array of signals originating in the lumen [1]. "Molecular sensing by specific gastrointestinal cells plays a crucial role in the control of multiple fundamental functions including digestion, regulation of caloric intake, pancreatic insulin secretion, and metabolism, as well as protection from ingested harmful drugs and toxins" [2]. However, despite the fact that these fundamental properties of the gastrointestinal (GI) tract have been recognized for a considerable amount of time, "the initial molecular recognition events that sense the chemical composition of the luminal contents of the GI tract have remained elusive" [1] until recently. However, as it has been very recently understood, "the chemosensory machinery discovered in specialized neuroepithelial taste receptor cells of the lingual epithelium" appears as well "operational in enteroendocrine open cells that sense the chemical composition of the luminal content of the gut" [2]. To understand this fundamental discovery, we need to know more about taste receptors.

A novel but large family of mammalian taste receptors has been identified among rodents and humans in 2000 [3]. They consist in at least 40 different G protein-coupled receptors (GPCRs) expressed in subsets of taste receptor cells of the tongue and palate epithelia [3]. The GPCR superfamily results from the expression of about 1000 genes known to code mostly for sensory receptors involved in vision (rhodopsin sensing the photon) and above all in olfaction (hundreds of odorants having their specific GPCR) [4]. These receptors represent the largest family of transmembrane proteins and "mediate most transmembrane signal transduction" in response not only to the senses of sight, smell and taste, but also in response to hormones and neurotransmitters [5].

All the GPCRs are characterized by seven transmembrane α-helices, three extracellular loops (where the ligand binds) and three cytoplasmic loops (where the G protein binds). Heterotrimeric G proteins are composed of α-, β- and γ-subunits; they transduce external signals perceived through the heptahelical receptors to intracellular effector molecules [1]. "The G protein-mediated cascades ultimately lead to the highly refined regulation of systems such as sensory perception, cell growth, and hormonal regulation"[6].

The recently discovered taste receptors named **T2Rs** are involved in the ***bitter taste*** perception and they "are exclusively expressed in taste receptor cells that contain the G protein α-subunit gustducin, implying that they function as gustducin-linked receptors" [3]. The G protein α-subunit called gustducin or **α-gustducin** had been identified and cloned in 1992 from taste tissue, i.e. taste buds of all tongue taste papillae (circumvallate, foliate and fungiform) [7]. Gustducin "most closely resembles the transducins (the rod and cone photoreceptor G proteins), suggesting that gustducin role in taste transduction is analogous to that of transducin in light transduction" [7]. It was later on understood that **α-transducin** was also expressed in taste receptor cells [8].

After having identified in 2000 the taste receptors involved in bitter taste reception, the T2Rs, the same team reported in 2001 the characterization of mammalian ***sweet taste*** receptors, the **T1Rs** [9]. Besides, they showed that two different receptors belonging to this family, T1R2 and T1R3, "combine to function as a sweet receptor, recognizing sweet-tasting molecules as diverse as sucrose, saccharin, dulcin and acésulfame-K" [9]. The sweet receptor also binds glucose and other carbohydrates providing the sweet taste that drives our appetite for sugars.

Later on, it was recognized that T1R receptors mediate both mammalian sweet taste and ***umami taste*** [10]. The umami taste was first identified in 1909 at the Imperial University of Tokyo and it is a meaty, savory taste that drives our appetite for amino acids such as aspartate and glutamate (typically monosodium glutamate or bacon). We need amino acids, sugars and also salt, which is why ***salt taste*** recognizes sodium chloride. Oppositely, we rely on taste to reject poisons identified through the ***sour taste*** (acids and protons, appearing in damaged foods) and the ***bitter taste*** (plant alkaloids potentially harmful, certainly in excess). Below, we show how the different T1R receptors dimerize to provide the sweet taste and the umami taste receptors, both linked to G proteins [10].

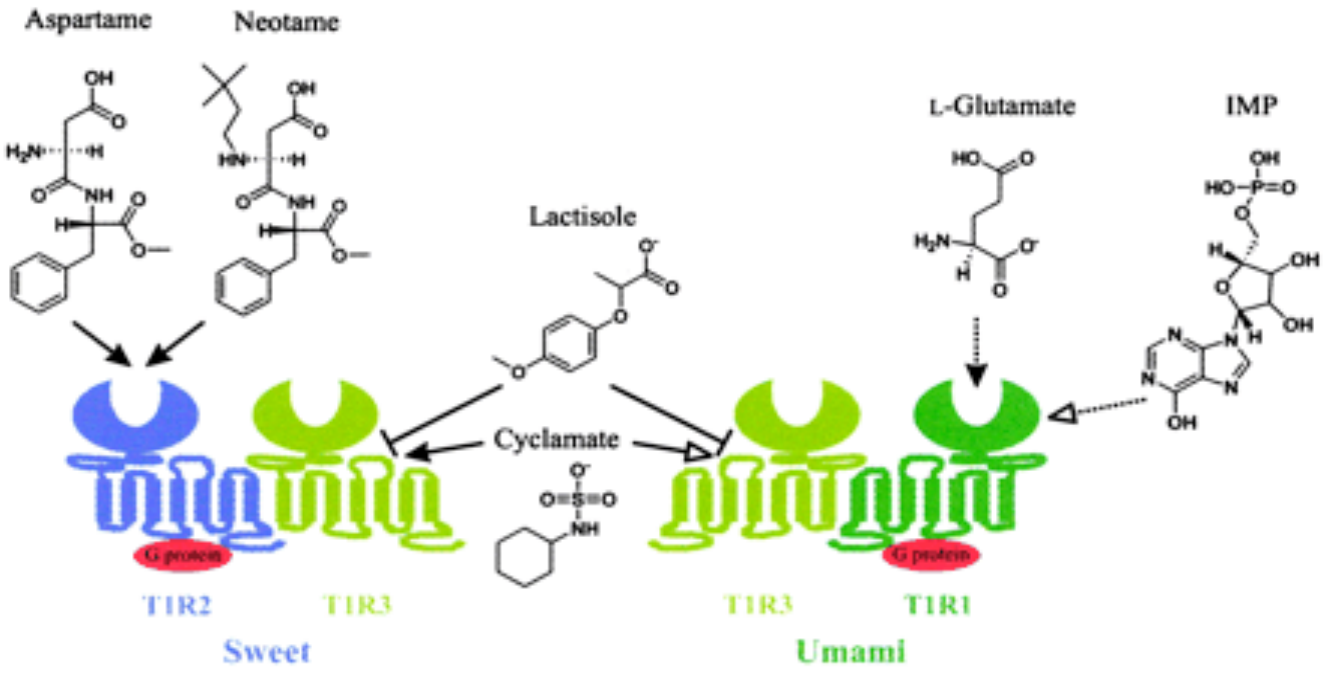


Fig. 5. A working model for the sweet and umami taste receptor structure–function relationships. Filled arrows indicate direct activation, open arrows indicate enhancement, and bar heads indicate inhibition. Xu, H., et al., *Different functional roles of T1R subunits in the heteromeric taste receptors.* Proc Natl Acad Sci U S A, 2004. **101**(39): p. 14262.

In 1996, a German team has "addressed the question of whether the epithelium of the gut might express α-gustducin, the GTP-binding α-subunit of a trimeric G protein complex that is specific for taste receptor cells of the tongue" [11]. They have shown that "α-gustducin is also expressed in the epithelium of the gut where it is associated with a specialized cell type" that was long known under the names of **brush cell** or **tuft cell** [11].

The function of this cell type, which is widespread in the digestive tract and in the respiratory tract from simple vertebrates to humans (including rodents and probably most of other mammals), has been enigmatic since [12]. However, the discovery of the presence of alpha-gustducin has provided a clue to the long-sought function of tuft cells, which appear to possess the cellular and molecular basis for chemoreception [12].

Tuft cells, which can also be called brush cells or caveolated cells (being rich in caveolae), are characterized by an extensively developed cytoplasmic tubulovesicular system and by a narrow apical pole from which emerge microvilli that are longer and thicker than those of enterocytes [13, 14]. Their close association with nerve fibers has been observed in humans and supports a receptor role for these cells [14]. Besides, microvilli display many spheres originating from the head of a polyp-like structure, suggesting a type of apocrine secretion [12].

Tuft cells have been identified in both the stomach and the gallbladder, and also in the respiratory tract of humans, besides being present in the respiratory and the gastrointestinal tract mucosa of many mammalian species [14]. Tuft cells represent scattered gut epithelial cells sharing typical cytoskeleton of gustatory receptor cells and containing alpha-gustducin in the apical brush border [15]. Though their origin and precise biological role are still under intensive debate, tuft cells express other fundamental taste-signaling proteins, such as ion-channel **TRPM5** [16], also detected in the duodenal glands together with T1R3 receptor and α-gustducin [17].

However, α-gustducin is also expressed in subsets of enteroendocrine cells, especially in the mid-jejunum [18]. "Endocrine cells within the gut epithelium from the stomach to the colon represent the largest population of hormone-producing cells in the body" [19]. They are "scattered as individual cells throughout the mucosa, comprising approximately 1% of the cells lining the intestinal lumen" [19].

"More than 30 hormone genes are currently known to be expressed in the stomach and intestines, which makes the gut the largest endocrine organ in the body" [20]. Some of those enteroendocrine cells express and release an intestinal hormone named glucagon-like peptide-1 or **GLP-1** [18]. Secreted by gut endocrine L-cells in response to glucose ingestion, GLP-1 regulates appetite, insulin secretion, and gut motility [21]. The "incretin" GLP-1 exerts important effects on pancreatic β-cells to stimulate glucose-dependent insulin secretion and increase β-cells mass [22],explaining the launch of clinically approved GLP-1 analogues such as exenatide [23].

An American team demonstrated in 2006 that "the α-subunit of the taste-specific G protein gustducin is expressed prominently in (…) enteroendocrine L-cells that express **peptide YY** [another gastrointestinal peptide involved in satiety signaling] and GLP-1 in the human colonic mucosa" [24]. In August 2007, another article published in the *PNAS* showed that "human duodenal L-cells express sweet taste receptors, taste G protein gustducin, and several other taste transduction elements"[21]. Selected as the corresponding cellular model, the human L-cell line NCI-H716 expresses sweet taste receptors and α-gustducin,, but its release of GLP-1 is promoted by sugars and by the non-caloric sweetener ***sucralose*** [21]. Thus, the modulation of GLP-1 secretion in the gut "taste cells" might have significant consequences on the metabolism, especially on meal-induced insulin secretion. Besides, providing more links, gustducin has also been found recently (article published in November 2007) in another cluster of enteroendocrine cells, i.e. the mouse stomach cells secreting **ghrelin** [25], a satiety promoting (orexigenic) peptide secreted by human stomach A-like cells only discovered in 1999 [26].

It appears that both natural sugars and artificial sweeteners are sensed by sweet taste receptors [10, 27]. Thus, sweeteners are nutritionally active and their intake may have an impact on the carbohydrate metabolism despite their lack of calories. Before considering the consequences of sweeteners intake, we must examine intestinal sugar transporters responsible for transporting the monosaccharides (glucose, galactose and fructose) from the intestinal lumen to the blood. The composition of the intestinal luminal content varies considerably with the diet. It is therefore important that the intestinal lumen "senses" and responds to any significant change by regulating its function accordingly [28]. A prototype example of this process is the modulation in the capacity of the gut to absorb monosaccharides via the intestinal luminal membrane glucose transporter **SGLT1** [28].

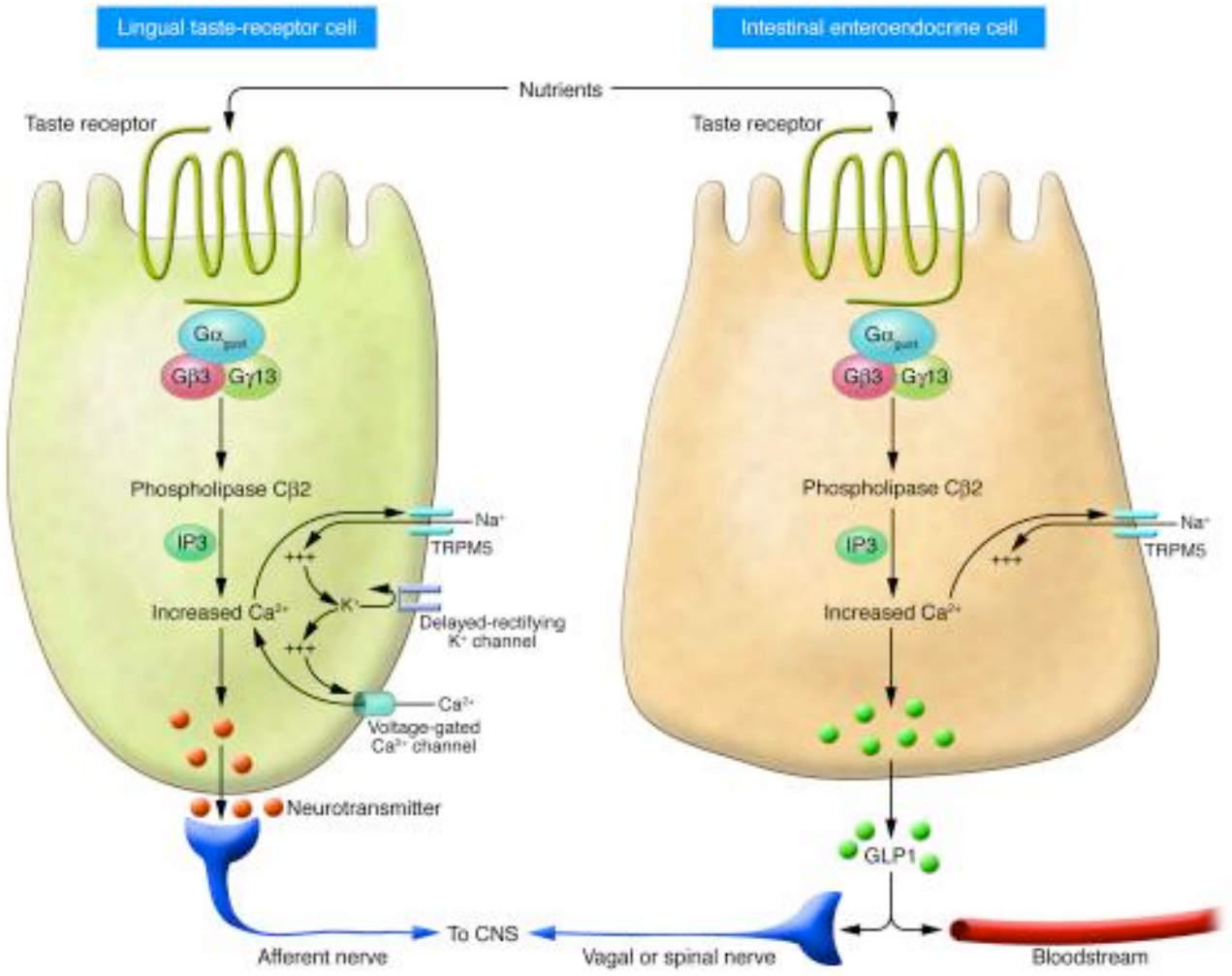
SGLT1 is located in the intestinal brush border (apical membrane) and transports ***glucose*** and ***galactose***, along with sodium (Na^+), from the intestinal lumen to the cytoplasm [29, 30]. Mutations in SGLT1 are known to cause a major defect in glucose and galactose absorption [31]. Besides, passive ***fructose*** transport from lumen to cytoplasm is mediated by the uniporter **GLUT5** present in the apical membrane [31] whereas all three monosaccharides - glucose, galactose and fructose - are passively transported from the cytoplasm to the blood capillaries by two uniporters **GLUT2** and **GLUT5** located in the basolateral membrane of enterocytes [30, 31].

"Sugar consumption and subsequent sugar metabolism are known to regulate the expression of genes involved in intestinal sugar absorption and delivery"[32]. Therefore, it is logical to consider that sugar-sensing receptors in membranes facing the intestinal lumen can also modulate intestinal sugar absorption [32]. "In cultured enterocytes, both apical and basolateral fructose could increase the expression of GLUT5", whereas "basolateral sugar administration could stimulate the expression of GLUT2"[32]. In 2003, a team from the University of Liverpool used sheep intestine as a model to show that luminal monosaccharides, both metabolisable and non metabolisable, regulate the expression of the sodium-dependent glucose transporter isoform 1 (SGLT1) [33]. "Introduction of D-glucose and some D-glucose analogues into ruminant sheep intestine resulted in > 50-fold enhancement of SGLT1 expression" [33]. Finally, the authors concluded that luminal glucose is sensed by a glucose sensor - distinct from SGLT1 - located on the luminal membrane of the gut epithelium and linked to a G protein-coupled receptor, resulting ultimately in the modulation of intestinal monosaccharide absorption [28].

"Although expression of SGLT1 is regulated by luminal monosaccharides, the luminal glucose sensor mediating this process was unknown"[34]. The English team has now demonstrated, as explained in another article published in August 2007 (*PNAS*), that "the sweet taste receptor subunit T1R3 and the taste G protein gustducin, expressed in enteroendocrine cells, underlie intestinal sugar sensing" and regulate the expression of SGLT1 [34]. Indeed, dietary sugars as well as artificial sweeteners increase SGLT1 expression together with glucose absorptive capacity in wild-type mice, but not in knockout mice lacking T1R3 or α-gustducin [34].

In an extensive interview realized by Health Orbit on the 21st of August 2007, the leading author declared that: "*Surprisingly we also found that the receptor was able to detect artificial sweeteners in foods and drinks resulting in increased capacity of the intestine to absorb dietary sugars, which would explain why these sweeteners are unsuccessful at helping people lose weight*". Interestingly, Professor Soraya SHIRAZI-BEECHEY belongs to the University of Liverpool Faculty of Veterinary Science and she will research how to activate the receptor through dietary supplements, before and during horse races, in order to increase intestinal absorption of glucose among horses, as they need high levels of glucose to sustain them in long races.

In 2005, it was also shown that "the expression, at mRNA and protein levels, of members of the TR1 sweet taste receptors, and the α-subunit of the G-protein gustducin" occur in the small intestine and [in] the enteroendocrine cell line STC-1" [28], which endogenously expresses and secretes **cholecystokinin** (**CCK**), one additional gut peptide involved in satiety signaling. "An interesting, unanswered question is whether the umami receptor, which mediates protein taste sensation in the tongue, contributes to enteroendocrine cell protein detection" [35].



"Several types of enteroendocrine cell throughout the gut express components of nutrient-sensing and signal-transduction systems that were previously thought to be selective to taste-bud cells. These include apical G protein-coupled receptors for sweet and bitter chemicals, [and] the unusual G protein isoform gustducin" [35].

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