International Journal of Obesity Supplements (2019) 9:1–9
https://doi.org/10.1038/s41367-019-0012-6

REVIEW ARTICLE

Check for updates

Taste and the Gastrointestinal tract: from physiology to potential therapeutic target for obesity

Giovanni Sarnelli[1] · Giuseppe Annunziata[2] · Silvia Magno[3] · Claudia Oriolo[4] · Silvia Savastano[5] · Annamaria Colao[5] · on behalf of the Obesity Programs of nutrition, Education, Research and Assessment (OPERA) group

Published online: 12 April 2019

Abstract

Flavor is the combination of gustatory, olfactory and trigeminal sensations, representing the three main sensory pathways that allow detecting environmental chemical substances. Taste, in particular, is a complex chemosensory path that allows identification of substances present in ingested foods and beverages. In this manuscript, we propose a conceptual roadmap from aspects related to the evolution and the physiological role of taste, up to the current knowledge about its implication in the modulation of a healthy state, or obesity. More specifically, we focused on the role of stimulation of taste receptors in releasing gut hormones (also known as enterohormones), and their effects on the regulation of food intake, by inducing satiety, either by locally acting (in the gastrointestinal tract), or centrally (in the brain). Recent evidence demonstrated that some enterohormones are able to modulate gastrointestinal motility, thus affecting an orexigenic responses in the central nervous system. In keeping with this, we discuss the ability of the gustatory system to be a final checkpoint control for food intake regulation, and we speculate about taste perception manipulation in the management of obesity.

The ancestral role of taste sensing: from evolutionary to current implications

To understand the ancestral role of taste perception we have to go back into the past, looking at the *Drosophila Melanogaster*, the common fruit fly, which represents the perfect example to help us to understand sensory processing from detection to behavior. Indeed, through the gustatory receptor neurons (GRNs) located on the proboscis labellum, internal mouthparts, legs, and wings, *Drosophila* detects, like mammals, just a few different taste modalities and uses this information for feeding decisions, suggesting that strategies for taste coding could share similarities across organisms.

Humans can perceive a large number of chemical substances, but five main taste qualities can be distinguished: acid, sweet, bitter, salty and umami. Recently, a dedicated neurosensory pathway connected to CO_2 has also been discovered, supporting the hypothesis of a distinct taste for carbonation, that may also influence the perception of other tastes [1, 2].

Acid perception allows the organism to avoid the consumption of degraded or harmful substances due to the presence of high concentrations of hydrogenions (H^+). Indeed, a process of edibility alteration is very common in spoiled foods, a process which results in the production of substances potentially harmful to the body. These alteration phenomena, nowadays, are less frequent than in the past, with the industrial processes and the use of preservatives

Members of Obesity Programs of nutrition, Education, Research and Assessment (OPERA) group are listed in Acknowledgements.

✉ Giovanni Sarnelli
giovanni.sarnelli@unina.it

[1] Department of Clinical Medicine and Surgery, Division of Gastroenterology, University of Naples Federico II, Naples, Italy

[2] Department of Pharmacy, University of Naples Federico II, Naples, Italy

[3] Obesity Center at the Endocrinology Unit, Department of Clinical and Experimental Medicine, Pisa, Italy

[4] Endocrinology Unit, Medical Department of Care Continuity and Disability, University of Bologna, Bologna, Italy

[5] Dipartimento di Medicina Clinica e Chirurgia, Unit of Endocrinology, Federico II University Medical School of Naples, Napoli, Italy

involved in food production, even if these processes are unable to completely protect food from this degradation process. Therefore, the perception of acid arises as a defense system that protects us from the introduction of potentially altered and harmful foods, even if, nowadays, the sour taste is appreciated in certain gustatory contexts: the use of wine vinegar to season certain foods or the consumption of certain fermented dairy products confirm this food choice. This behavior is an important aspect of taste related to learning and hedonistic evaluation [3].The bitter taste also developed as a defense system for humans. It allows the discrimination of foods that are potentially harmful to our body [4]. The thiocyanate chemical group, for example, is responsible for bitter taste and it is present in many toxic compounds arising from plants, mainly belonging to the family of the *Brassicaceae* [5]. The rejection of bitter foods, thus, has an ancestral origin: it is perceived, indeed, as a potential danger to health. The perception of sweet taste plays a fundamental role in human nutrition because it is associated with the presence of energetic substances in food and beverages. Carbohydrate rich foods mostly have a high-energy content and are the primary source of energy, being essential for both cell metabolism and energy homeostasis. The positive hedonic value and the high sensory quality, associated with behavioral acceptance, are closely interlinked factors. These factors demonstrate how, most likely, the perception of sweet taste evolved to recognize basic and fundamental metabolic energy sources [3]. The salty taste is sensed by detection of the sodium cation. The most common ingredient to stimulate this taste, indeed, is sodium chloride. However, salty taste is also stimulated by other salts, in particular by other cations, such as potassium or lithium, which can also induce a perceptible bitterness and may be toxic to human metabolism. The development of this perception in humans is connected to the necessity to introduce a certain quantity of ions in the body for the maintenance of the hydro-electrolytic balance. The ability to perceive salt is, therefore, fundamental for homeostasis of electrolytes, since it allows to recognize foods that contain minerals [3]. Umami is a Japanese term that means “tasty” or “delicious”. This taste allows us to recognize certain amino acids, such as free glutamate, used as flavor enhancers and particularly present in foods rich in proteins such as meats and aged cheeses. Recently, both behavioral and physiological experiments have demonstrated the independence of the umami taste; specific receptors for the amino acid, glutamate have been indeed identified, and it has been clarified that they have mechanisms of reception different and independent from other taste receptors [3]. From an evolutionary point of view, it can be argued that the gustatory systems developed in order to promote the survival and the adaptation of individuals and species. Nowadays, however, taste has largely lost this function and evolutionary meaning, but it remains one of the most important factors in determining the palatability of foods, influencing the nutritional habits of individuals.

Several studies showed that the ability to respond to taste can substantially vary depending on demographic variables such as gender [6], ethnicity [7] and age [8]; the perception of taste, indeed, is greater in the newborn and in children, and decreases progressively in adults and especially in the elderly [8]. Nicklaus et al. [9] disclosed that the taste experiences of the newborn during weaning are able to influence and determine their food choices as adults. In particular, it is interesting to note how gustatory perception is modified in different individuals, according to the type of taste. This phenomenon influences eating behavior and nutrient intake differently. These findings are attributable to the presence of candidate genes as responsible for genotypic and phenotypic differences in gustatory perception. The polymorphisms of genes that code for gustatory receptors can also explain some of the alterations observed in the perception of fundamental flavors [9].Within this framework, several studies focused on the relationship between the ability to perceive the bitter taste of the thiocyanates Phenylthiocarbamide (PTC) and Propylthiouracil (PTU)and food habits and preferences. These studies showed that it is possible to distinguish three categories of individuals: (i) “Non Taster”, people who perceive very little or no bitter taste; (ii) “Medium Tasters”, able to perceive it and (iii) “Super Tasters”, extremely sensitive to bitter and with a very high perception for this taste [10]. Super-tasters avoid certain foods, including certain types of vegetables, fats and spicy foods compared to people unable to perceive PTC/PTU (non-tasters) [11, 12]. About 75% of the Caucasian population was sensitive and able to perceive PTC and PTU, while 25% were classified as non-tasters [13]. Similarly, there is evidence that the variation in the perception of sweet taste is correlated with the preferences and intake of vegetables [11], and others established that substances perceived as sweet can induce a cephalic phase and certain reflexes of the hormonal response able to influence appetite and nutritional habits [14]. Thus, individuals with abnormal taste reactivity appear to modify the intake of certain foods according to the altered perception of different tastes, resulting in greater susceptibility to perturbing metabolic homeostasis. This genetic variability influences particularly the choice of food and eating behavior with repercussions on the state of health, in particular on the risk of developing certain diet-related diseases, such as obesity [15]. Recently, researchers suggested that sensitivity to sweet [16, 17] and salty [18] tastes is closely related to Body Mass Index (BMI). In particular, individuals with a lower taste capacity had a greater BMI than those with more sensitivity to these tastes [19]. Similarly, Bartoshuk and colleagues suggested that, among the population of people with obesity, the

Table 1 Structure and function of taste receptors

Taste	Categories	Receptor
Sweet	G protein-coupled receptors (GPCRs)	T1R1-T1R2
Umami	G protein-coupled receptors (GPCRs)	T1R1-T1R3
Bitter	G protein-coupled receptors (GPCRs)	T2R
Salty	Ionchannels	Epithelialsodiumchannel (ENaC)
Sour	Ionchannels	Acid sensing ion channel (ASIC)

perception of sweet taste and fats present in foods may be reduced, with a decisive preference and an active search for very sweet and fat foods [20, 21]. Additionally, the perception of bitter taste was also associated with BMI and visceral adiposity, which increased in non-tasters compared to medium and super-taster individuals [17, 22, 23].

Taste receptors in the gastrointestinal tract and enterohormones

Tastes are detected by specific receptors, as summarized in Table 1. In particular, salty and sour sensory perceptions are transduced by ion channels. Bitter, sweet, and umami are transduced by two distinct families of G protein-coupled receptors (GPCRs): Taste Receptor family Type 1 (TAS1R or T1R) and Taste Receptor family Type 2 (TAS2R or T2R). Heterodimerization-based isoforms of T1Rs are involved in perception of umami and sweet tastes; in particular, the T1R1-T1R3 isoform is involved in detection of umami taste, whereas the T1R2-T1R3 isoform detects sweet taste [24]. On the other hand, bitter substances are detected by T2Rs, of which about 30 different isoforms have been identified [24, 25].

In general, when tastants bind to either receptor, they activate a transduction cascade through the associated G protein, more specifically the α-gustducin, which is recognized to be a marker for detection of chemosensory cells. The stimulation of taste receptors (TASRs) causes the activation of phospholipase C-beta 2 (PLCβ2), with consequent release of the second messenger inositol 1,4,5-trisphosphate (IP3), which triggers the IP3-Receptor type 3 (IP3R3), resulting in increased intracellular calcium concentrations ($[Ca^{2+}]i$). This increase in $[Ca^{2+}]i$, in turn, stimulates both a transient receptor potential (TRP) channels activation to depolarize the cell, and stimulate hormone release [26, 27].

Currently it is well-known that taste cells are widespread not only in the oral cavity, but even in other tissues, including the gastrointestinal (GI) tract. TASRs, indeed, were firstly reported in the gut of rodents in 1996 by Höfer and co-workers, who described the presence of α-gustducin in brush border cells [28]. Subsequently Wu and colleagues demonstrated the expression of multiple T2Rs in intestinal Secretin Tumor Cell (STC-1) line [29], suggesting a strong relationship between taste cells in the GI tract and hormone response. In the GI tract, indeed, several groups of cells, also called enteroendocrine cells (EECs), are able to secrete various enterohormones, and they approximately represent 1% of all epithelial cells [24, 30]. In response to changes in GI lumen composition, EECs secrete a series of hormones, including 'gastrin' (secreted by G cells), 'ghrelin' (secreted by P or X/A cells), 'somatostatin' (secreted by D cells), 'cholecystokinin (CCK)' (secreted by I cells), 'serotonin' (secreted by enterochromaffin cells), 'glucose-dependent insulinotropic peptide (GIP)' (secreted by K cells), 'glucagon-like peptides (GLPs)', and 'peptide tyrosine-tyrosine (PYY)' (secreted by L cells) [24]. These hormones, released in response to TASRs stimulation, play an important role in the control of several functions, such as regulation of food intake, digestion or rejection of food and hormone secretion [31]. Particularly, they can act locally, with a paracrine action on other cells and/or on nerve terminations (vagal afferents), or reach the bloodstream. Vagal afferents terminate close to EECs and contain receptors for CCK (CCK1R), GLP-1 (GLP-1 R) and PYY. This local action is involved in eliciting adequate GI motor responses to assimilate nutrients and/or eliminate waste or harmful products. In addition, they are able to transmit signals to inform the brain [32–34], as described below.

According to the epithelial localization, EECs can be divided into two populations: the *open-type cells* have microvilli that allow them to sense the content in the lumen, representing the trigger to hormone release; in contrast, the *closed-type cells* do not reach the epithelial surface and can only receive information from the lumen through neural pathways or signals from the blood stream. Hass and coworkers, however, suggested that the *closed-type cells* can also receive information from another type of cells, named brush cells [35] that are a group of solitary chemosensory cells without intracellular secretory vesicles, typical of the EECs. These cells possess a single apical tuft of rigid gustatory microvilli and express signaling proteins like α-gustducin, α-transducin and TRPM5cation channel [36].

TASRs are expressed in all the functional areas of the intestine. The small intestine consists of three different parts (the duodenum, jejunum and ileum) and it is the main site of digestion and absorption in the GI tract. The duodenum is the site where preparation for absorption begins, and it receives bile and pancreatic juice through the pancreatic duct. The jejunum is the middle section of the small intestine and the main site where products of digestion are absorbed into the bloodstream. The main function of the ileum is the absorption of vitamin B12, bile salts (predominantly linked to dietary fat in micelles), and products

of digestion that were not absorbed by the jejunum. In the duodenum, the arrival of carbohydrates, fats, hydrolyzed proteins and other substances stimulate the release of the CCK from I-cells. CCK exerts a marked satiating effect, acting by slowing gastric emptying [33]. I-cells also express lipid sensors (G-protein coupled receptor (GPR)-120 and free fatty acid (FFA) receptor (FFAR)-1) and receptors for amino acids and peptides (calcium sensing receptor-(CaSR)), umami and bitter taste. Immunolocalization studies confirmed that I-cells do not express the sweet taste receptor-specific subunit, T1R2 [37]. T1Rs are also expressed on L-cells, detecting sweet compounds and responding by stimulation of GLP-1 release. In addition, immunohistochemistry studies conducted on human ileal tissues showed that bitter TASRs were also expressed on L-cells, suggesting that TASRs stimulation by bitter substances could have a role in glucose and insulin metabolism [27, 38], as also reported in a recent narrative review [39]. Interestingly, L-cells and subtypes also express FFA receptors (GPR119-GPR120, FFAR1) and amino acids receptor (GPRC6A). Immunofluorescence experiments demonstrated that K-cells and subtypes express FFA receptors (GPR119-GPR120, FFAR1) but not taste receptors [24]. In the colon, PYY-producing L-cells express FFA receptors (FFAR2 and FFAR3). *In vitro* studies demonstrated that T2Rsare also expressed on epithelial cells. Probably, this expression is consistent with a role of T2R in defensive mechanisms against potentially harmful substances, but their role has not been completely clarified [40]. However, T2Rs seem to induce secretion of anion and water to flush out potentially dangerous substances from the colon. On the other hand, there is no evidence of T1Rs in the colon [27, 41].

Interestingly, the stomach also expresses TASRs. Recent immunofluorescence studies indicated that X/A cells are positive for gustatory G-proteins, α-gustducin and α-transducin and express (i) sweet and umami subunit T1R3 (ii) T2Rs and (iii) GPR120 [42]. In particular, X/A cells release ghrelin in response to activation by the appropriate ligand. Accordingly, when the stomach receives sweet compounds or glutamate-rich food, the ghrelin blood levels increase, resulting in stimulating further food intake [24, 26]. Moreover, the distal stomach (antrum) also contains EECs, which are important regulators of gastric secretion and motility. These cells express receptors for protein breakdown products (such as, GPR92, GPRC6A andCaSR) [27].

Taste receptors stimulation, GI physiology and the brain

In recent years, the interest of scientific research towards the study of possible implications of TASRs located in extra-oral sites has grown. Indeed, the knowledge of the co-localization of TASRs in EECs, which are involved in the release of enterohormones [43], led to consider the possibility that TASRs stimulation may be a useful therapeutic target for the management of several diseases, including type 2 diabetes mellitus (T2DM) and obesity. In particular, the TASRs-mediated increased release of enterohormones is of great interest considering the strong effect of these hormones in regulating peripheral mechanisms of satiety, mainly by slowing gastric emptying and reducing food intake, contributing to obesity therapy [33]. Specifically, the major actors involved in this complex relationship between taste sensing and hormone response are GLP-1, CCK and PYY, which exert an orexigenic effects, and ghrelin, one of the main orexigenic hormones [33]. Ghrelin is a 28-amino acid peptide hormone secreted by endocrine cells of the gastric fundus, which exerts an orexigenic activity, contributing to the induction of hunger [33]. On the other hand, ghrelin is also able to inhibit the reduction of feeding induced by leptin, suggesting a competitive relationship between these two hormones [44]. Interestingly, ghrelin is also involved in increasing the hedonic response to food [45], inducing contractions in the intestinal tract [46] and accelerating the gastric emptying [47]. GLP-1 is a peptide-derived hormone released by intestinal L cells and degraded in a few minutes by Dipeptidyl Peptidase (DPP)-4, found mainly in the plasma [33]. Although the main action of GLP-1 is the enhancement of glucose-dependent insulin secretion [48], this hormone is also strongly involved in promoting satiety by slowing gastric emptying [49, 50]. CCK is a 58-amino acids peptide hormone that also exerts a marked satiating effect, by acting mainly in delaying gastric emptying [33].

As described above, several TASRs are expressed in the EECs of the GI tract, and their stimulation is associated with the release of many enterohormones. T1Rs stimulation increases the release of GIP and GLP-1 [51–53]. In particular, studies conducted in vitro using endocrine cell lines [52], ex vivo using intestinal tissue [54] and *in vivo* on α-gustducin and/or T1R3 knockout mice [37, 55, 56] demonstrated significant increases in GLP-1and GIP levels. Particularly, studies provided evidence that this increase in enterohormones release directly depends on both α-gustducin and T1R3 stimulation [52, 57–59]. Most interestingly, these studies indicated that enterohormones levels were significantly reduced after treatment with T1R inhibitors, such as lactisole [57, 58], gurmarin [52] or 3-deoxyglucosone, that is able to reduce the expression of T1Rs subunit and down-regulate T1R signaling pathways [60].

Evidence also supported the role of the sweet TASRs (T1R2-T1R3) in the glucose-stimulated GLP-1 secretion (GSGS) from the small intestine. Sweet taste receptor agonists (such as, glucose, fructose and sucralose) stimulate

GSGS from mice and human EECs. GSGS, in turn, is significantly impaired in T1R3-knockout rodents [51, 56, 61]. The activation of sweet TASRs by sugars or sweeteners in the upper parts of the GI tract also drives the insertion of the sodium–glucose cotransporter 1 (SGLT1) and glucose transporter 2 (GLUT2) in apical membrane of enterocytes; further supporting this finding there is the evidence that their expression and/or the translocation is down-regulated in $T1R3^{-/-}$ and α-$gustducin^{-/-}$ knockout mice [52].

Interestingly, not only T1Rs in the intestine, but also those expressed in the stomach are strongly involved in an orexigenic hormones release [62, 63]. Studies in healthy subjects aimed to investigate the role of T1R on enterohormones release. In particular, intragastric infusion of glucose or mixed liquid meal was performed, and GLP-1, PYY [62, 63] and CCK [62] levels were monitored. In addition, lactisole was used as a probe over the physiological role of T1Rs; the authors found increased levels of all monitored enterohormones after intragastric administration of glucose or liquid meal. In contrast, lactisole caused a significant reduction in GLP-1 and PYY [62, 63], but not in CCK levels [62], suggesting that CCK release is not mediated by T1Rs stimulation in stomach.

Furthermore, T1Rs are able to detect not only sweeteners, but also other nutrients, such as amino acids [64]. Daly et al. conducted an *ex vivo* study on intestinal tissue from mouse showing that certain amino acids, including Phenylalanine, Leucine and Glutamine, are able to induce CCK release by stimulating T1R1-T1R3 [54], suggesting a role of this class of TASRs in detecting these nutrients from food.

Evidence showed that the intestinal T2R activation is strongly involved in the regulation of satiety. The administration of bitter compounds was shown to delay gastric emptying in mice [42, 65, 66] and humans [66], resulting in reduced energy intake [67]. These effects were further explained by the inhibition of bitter compounds of the gastric accommodation reflex [66], a pathophysiological mechanism that has been shown to be significantly associated with early satiation and reduced food intake [68, 69]. However, several studies provided the evidence that increased satiety can be mediated by endocrine mechanisms, too. In particular, the stimulation of T2R is able to evoke a hormonal response, in which various hormones are involved, including ghrelin, GLP-1 and CCK. Janssen and colleagues (2011) provided interesting evidence about the effects of bitter compounds-mediated stimulation of T2R on ghrelin levels and gastric emptying. A mixture of T2R-agonists bitter compounds (Denatonium benzoate, PTC, PTU, quinine and salicin) was intra-gastrically administrated to mice, and ghrelin levels and food intake were monitored. In treated mice, plasma levels of ghrelin were significantly increased, suggesting the role of T2R stimulation in the release of this hormone. In addition, while food intake was increased during the first 30 min, a prolonged and significant reduction was observed during the 4 h following the administration of the bitter compounds, likely associated with delayed gastric emptying [42].

Several in vitro studies investigated the effects of bitter compounds on GLP-1 release in relation to the stimulation of T2R. The activity of several bitter substances (such as PTC, Denatonium benzoate, 1,10-phenanthroline and Berberine) was tested on different GLP-1-expressingcell lines, showing an increased release of this hormone through T2R activation [48, 70–73]. Similarly, T2R stimulation by steroid glycosides was demonstrated to increase the release of CCK on HuTu-80 cells [74]. Interestingly, a study conducted on EECs and intestine tissues from mice provided evidence that the expression of the T2R gene is regulated by sterol regulatory element-binding protein-2, which is also able to enhance the subsequent release of CCK [75].Overall, these findings have also been confirmed by *in vivo* animal-based studies, mainly conducted on diabetic or leptin receptor deficient mice [43, 48, 71], and humans. Andreozzi and co-workers (2015) showed that the administration of quinine (a potent T2Rs agonist) in acid-resistant capsule significantly increased CCK levels within 60 and 90 min after ingestion, resulting in reduced food intake [67].

Recently, a marked relationship between taste sensing and the brain was established. Neuroimaging studies using positron emission tomography and functional magnetic resonance imaging, indeed, provided evidence about the capacity of brain in processing external chemical stimuli, such as food. In particular, Prinster and co-workers showed that the right insular cortex is involved in taste discrimination, hypothesizing that the Primary Taste Cortex is involved in a particular response to the tastes, allowing the discrimination between safe nutrients and harmful substances [76]. Additionally, electrophysiological studies showed the capacity of brain neurons to respond to several tastants [77], suggesting the presence of TASRs in the brain. Singh and colleagues, demonstrated the presence of functional T2R (isoforms T2R4, T2R10 and T2R38) in brain cells, by using Reverse Transcriptase-Polymerase Chain Reaction analysis and immunohistochemistry experiments [78]. Moreover, neuroimaging studies showed that peripheral TASRs stimulation is able to activate specific cortical fields in the primary gustatory cortex [79].In this context, the expression “food for thought” does not just assume the mere meaning of a metaphor, but support the idea that food constituents may affect brain molecular pathways, likely by acting on taste receptors.

Further supporting this concept is evidence showing the action of gastrointestinal hormones on specific receptors located in the brain, paving the way to a CNS-regulation of food intake. Ghrelin, CCK and PYY seem to be the main

actors in this complex relationship between gut and brain. Indeed, in the arcuate nucleus (ARC), pro-opiomelanocortin (POMC)/cocaine-amphetamine regulated transcript (CART) and agouti-related protein (AGRP)/ neuropeptide Y (NPY) neurons have been found to express gastrointestinal hormones receptors. This subset of neurons, through the transmission of specific signals to neurons of the paraventricular nucleus (PVN), are involved in the reduction and the increase of food intake, respectively.

Leptin receptors (LepR) are also expressed in both AGRP/NPY and POMC/CART neurons [80], and CCK has been demonstrated to interact with these receptors. More specifically, CCK is able to stimulate and inhibit POMC/CART and AGRP/NPY, respectively; similarly, PYY interacts with a specific receptor on AGRP/NPY neuron, inhibiting its activity. Both CCK and PYY, thus, exerting central an orexigenic activities. On the other hand, ghrelin stimulates AGRP/NPY, through an interaction with a specific receptor on this neuron, resulting in exerting an orexigenic activity [81].

Conclusion and future perspectives: taste modulation, GI physiology and food intake

A number of studies investigated the role of TASRs in regulating several physiological functions, including hormones release, regulation of GI motility and stimulation of certain brain areas. TASRs stimulation induces the release of enterohormones, whose effects are able to control food intake, by acting in the periphery on gastrointestinal motility, and, at a central level inducing an orexigenic responses, respectively. These effects have been claimed as useful therapeutic targets for the management of obesity, paving the way to consider the pharmacological modulation of taste receptors, as a promising and novel therapeutic strategy for the control of food intake.

Although there is evidence showing the effects of sweet taste receptors (T1R) in increasing enterohormones release, greatest interest is focused about the effects of TASRs stimulation by bitter substances (T2R). Food science researchers, indeed, are currently investigating specific functional foods or nutraceutical compound sable to enhance enterohormones release by modulating TASR activity. In this sense, the availability of T2R stimulating natural, or food-derived bitter compounds appears promising, also because these will avoid the use of other bioactive components with higher energy content, or artificial sweeteners as T1R agonists. An alternative approach may be to stimulate sweet sensing TASRs by using natural and non-caloric sweeteners, or to deceive taste perception by taste altering substances, with miraculin being one of the most interesting molecules. Miraculin is a taste-modifying protein from *Synsepalum dulcificum*, a fruit plant originating from Africa [82, 83], that has the ability to transform acid tasting foods into sweet ones. Several studies demonstrated the ability of miraculin to stimulate T1R2-T1R3, however, miraculin seems to be active in stimulating T1Rs only at acidic pH, whereas when pH is neutral, it changes into an antagonist of T1Rs [82].

The formulation of functional foods with the addition of bitter substances has also been claimed as a potential strategy to modulate food intake through the stimulation of taste receptors. In order to mask the bitter taste, that could compromise the palatability of products and could generate adverse reactions, it has been thought to microencapsulate bitter substances and to add them to the food matrix. In addition, these food-engineered products would allow to by-passing the acidity of the gastric content that may partly alter their chemical structure and function. Recently, a functional dessert containing microencapsulated bitter compounds from Gentiana lutea was developed. The authors found that consumption of this pudding was able to increase the postprandial GLP-1 levels and to significantly reduce food intake [84], without any bitter taste perception.

In conclusion, there is increasing evidence showing the role of taste receptors stimulation in releasing enterohormones, and their effects on the regulation of food intake, by inducing satiety, either by acting locally (in the gastrointestinal tract), or centrally (in the brain). In this context the modulation of taste receptors activity, by drugs or specifically designed functional food, appears as an innovative strategy for the control of food intake and, most importantly for the prevention and management of obesity.

Acknowledgements Obesity Programs of nutrition, Education, Research and Assessment (OPERA) group members served as collaborators and approved the final version of the manuscript: Annamaria Colao, Antonio Aversa, Barbara Altieri, Luigi Angrisani, Giuseppe Annunziata, Rocco Barazzoni, Luigi Barrea, Giuseppe Bellastella, Bernadette Biondi, Elena Cantone, Brunella Capaldo, Sara Cassarano, Rosario Cuomo, Luigi Di Luigi, Andrea Di Nisio, Carla Di Somma, Ludovico Docimo, Katherine Esposito, Carlo Foresta, Pietro Forestieri, Alessandra Gambineri, Francesco Garifalos, Cristiano Giardiello, Carla Giordano, Francesco Giorgino, Dario Giugliano, Daniela Laudisio, Davide Lauro, Andrea Lenzi, Silvia Magno, Paolo Macchia, MariaIda Maiorino, Emilio Manno, Chiara Marocco, Paolo Marzullo, Chiara Mele, Davide Menafra, Silvia Migliaccio, Marcello Monda, Filomena Morisco, Fabrizio Muratori, Giovanna Muscogiuri, Mario Musella, Gerardo Nardone, Claudia Oriolo, Uberto Pagotto, Pasquale Perrone Filardi, Luigi Piazza, Rosario Pivonello,Barbara Polese, Paolo Pozzilli, Giulia Puliani, Stefano Radellini, Gabriele Riccardi, Domenico Salvatore, Ferruccio Santini, Giovanni Sarnelli, Lorenzo Scappaticcio, Silvia Savastano,Bruno Trimarco, Dario Tuccinardi,Paola Vairano, Nunzia Verde, Roberto Vettor.

Funding Information: This article is published as part of a supplement funded by Endocrinology Unit, Department of Clinical Medicine and Surgery, University Federico II, Naples, Italy.

Author contributions Giovanni Sarnelli and Giuseppe Annunziata contributed equally to this work.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Publisher's note: Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. Chandrashekar J, Yarmolinsky D, von Buchholtz L, Oka Y, Sly W, Ryba NJ, et al. The taste of carbonation. Science. 2009; 326:443–5.
2. Di Salle F, Cantone E, Savarese MF, Aragri A, Prinster A, Nicolai E, et al. Effect of carbonation on brain processing of sweet stimuli in humans. Gastroenterology. 2013;145:537–9.
3. Yamamoto K, Ishimaru Y. Oral and extra-oral taste perception. Semin Cell Dev Biol. 2013;24:240–6.
4. Lu P, Zhang CH, Lifshitz LM, ZhuGe R. Extraoral bitter taste receptors in health and disease. J Gen Physiol. 2017;149:181–97.
5. Han H, Kwon H. Estimated dietary intake of thiocyanate from Brassicaceae family in Korean diet. J Toxicol Environ Health A. 2009;72:1380–7.
6. Haase L, Green E, Murphy C. Males and females show differential brain activation to taste when hungry and sated in gustatory and reward areas. Appetite. 2011;57:421–34.
7. Nahab F, Le A, Judd S, Frankel MR, Ard J, Newby PK, et al. 2011. Racial and geographic differences in fish consumption: the REGARDS study. Neurology. 2011;76:154–8.
8. Heft MW, Robinson ME. Age differences in orofacial sensory thresholds. J Dent Res. 2010;89:1102–5.
9. Nicklaus S, Boggio V, Chabanet C, Issanchou S. A prospective study of food variety seeking in childhood, adolescence and early adult life. Appetite. 2005;44:289–97.
10. Guo SW, Reed DR. The genetics of phenylthiocarbamide perception. Ann Hum Biol. 2001;28:111–42.
11. Dinehart ME, Hayes JE, Bartoshuk LM, Lanier SL, Duffy VB. Bitter taste markers explain variability in vegetable sweetness, bitterness, and intake. PhysiolBehav. 2006;87:304–13.
12. Tepper BJ, Williams TZ, Burgess JR, Antalis CJ, Mattes RD. Genetic variation in bitter taste and plasma markers of anti-oxidant status in college women. Int J Food SciNutr. 2009;60(Suppl2): 35–45.
13. Bartoshuk LM, Duffy VB, Miller IJ. PTC/PROP tasting: anatomy, psychophysics, and sex effects. Physiol Behav. 1994;56:1165–71.
14. Teff KL. Cephalic phase pancreatic polypeptide responses to liquid and solid stimuli in humans. Physiol Behav. 2010;99: 317–23.
15. Garcia-Bailo B, Toguri C, Eny KM, El-Sohemy A. Genetic variation in taste and its influence on food selection. OMICS. 2009;13:69–80.
16. Salbe AD, DelParigi A, Pratley RE, Drewnowski A, Tataranni PA. Taste preferences and body weight changes in an obesity-prone population. Am J ClinNutr. 2004;79:372–8.
17. Tepper BJ, Koelliker Y, Zhao L, Ullrich NV, Lanzara C, d'Adamo P, et al. Variation in the bitter-taste receptor gene TAS2R38, and adiposity in a genetically isolated population in Southern Italy. Obesity. 2008;16:2289–95.
18. Skrandies W, Zschieschang R. Olfactory and gustatory functions and its relation to body weight. Physiol Behav. 2015;142:1–4.
19. Eny KM, Wolever TM, Corey PN, El-Sohemy A. Genetic variation in TAS1R2 (Ile191Val) is associated with consumption of sugars in overweight and obese individuals in 2 distinct populations. Am J ClinNutr. 2010;92:1501–10.
20. Bartoshuk LM, Duffy VB, Hayes JE, Moskowitz HR, Snyder DJ. Psychophysics of sweet and fat perception in obesity: problems, solutions and new perspectives. Philos Trans R SocLond B Biol Sci. 2006;361:1137–48.
21. Bartoshuk LM, Catalanotto F, Hoffman H, Logan H, Snyder DJ. Taste damage (otitis media, tonsillectomy and head and neck cancer), oral sensations and BMI. PhysiolBehav. 2012;107: 516–26.
22. Tepper BJ, Ullrich NV. Influence of genetic taste sensitivity to 6-n-propylthiouracil (PROP), dietary restraint and disinhibition on body mass index in middle-aged women. PhysiolBehav. 2002;75:305–12.
23. Goldstein GL, Daun H, Tepper BJ. Adiposity in middle-age women is associated with genetic taste blindness to 6-n-propylthiouracil. Obes Res. 2005;13:1017–23.
24. Furness JB, Rivera LR, Cho HJ, Bravo DM, Callaghan B. The gut as a sensory organ. Nat Rev GastroenterolHepatol. 2013;10: 729–40.
25. Adler E, Hoon MA, Mueller KL, Chandrashekar J, Ryba NJ, Zuker CS. A novel family of mammalian taste receptors. Cell. 2000;100:693–702.
26. Finger TE, Kinnamon SC. Taste isn't just for taste buds anymore. F1000 Biol Rep. 2011;3:20.
27. Depoortere I. Taste receptors of the gut: emerging roles in health and disease. Recent advances in basic science. Gut. 2014;63: 179–90.
28. Höfer D, Püschel B, Drenckhahn D. Taste receptor-like cells in the rat gut identified by expression of alpha-gustducin. Proc Natl Acad Sci USA. 1996;93:6631–4.
29. Wu SV, Rozengurt N, Yang M, Young SH, Sinnett-Smith J, Rozengurt E. Expression of bitter taste receptors of the T2R family in the gastrointestinal tract and enteroendocrine STC-1 cells. Proc Natl Acad Sci USA. 2002;99:2392–7.
30. Gerbe F, Legraverend C, Jay P. The intestinal epithelium tuft cells: specification and function. Cell Mol Life Sci. 2012;69: 2907–17.
31. Janssen S, Depoortere I. Nutrient sensing in the gut: new roads to therapeutics? Trends Endocrinol Metab. 2013;24:92–100.
32. Lee AA, Owyang C. Sugar, sweet taste receptors, and brain responses. Nutrients. 2017; 9: pii: E653.
33. Steinert RE, Feinle-Bisset C, Asarian L, Horowitz M, Beglinger C, Geary N. Ghrelin, CCK, GLP-1, and PYY(3-36): secretory controls and physiological roles in eating and glycemia in health, obesity, and after RYGB. Physiol Rev. 2017;97:411–63.
34. Steensels S, Depoortere I. Chemoreceptors in the gut. Annu Rev Physiol. 2018;80:117–41.
35. Hass N, Schwarzenbacher K, Breer H. A cluster of gustducin-expressing cells in the mouse stomach associated with two distinct populations of enteroendocrine cells. Histochem Cell Biol. 2007;128:457–71.
36. Ekstrand B, Young JF, Rasmussen MK. Taste receptors in the gut - a new target for health promoting properties in diet. Food Res Int. 2017;100:1–8.
37. Daly K, Al-Rammahi M, Arora DK, Moran AW, Proudman CJ, Ninomiya Y, et al. Expression of sweet receptor components in equine small intestine: relevance to intestinal glucose transport. Am J Physiol Regul Integr Comp Physiol. 2012;303:R199–208.
38. Dotson CD, Zhang L, Xu H, Shin YK, Vigues S, Ott SH, et al. Bitter taste receptors influence glucose homeostasis. PLoS ONE. 2008;3:e3974.
39. Barrea L, Annunziata G, Muscogiuri G, Arnone A, Tenore GC, Colao A et al. Could hop-derived bitter compounds improve

glucose homeostasis by stimulating the secretion of GLP-1? Crit Rev Food Sci Nutr. 2017; https://doi.org/10.1080/10408398.2017.1378168.
40. Prandi S, Bromke M, Hübner S, Voigt A, Boehm U, Meyerhof W, et al. A subset of mouse colonic goblet cells expresses the bitter taste receptor Tas2r131. PLoS ONE. 2013;8:e82820.
41. Kaji I, Karaki S, Fukami Y, Terasaki M, Kuwahara A. Secretory effects of a luminal bitter tastant and expressions of bitter taste receptors, T2Rs, in the human and rat large intestine. Am J Physiol Gastrointest Liver Physiol. 2009;296:G971–981.
42. Janssen S, Laermans J, Verhulst P, Thijs T, Tack J, Depoortere I. Bitter taste receptors and α-gustducin regulate the secretion of ghrelin with functional effects on food intake and gastric emptying. Proc Natl Acad Sci USA. 2011;108:2094–9.
43. Li J, Xu J, Hou R, Jin X, Wang J, Yang N, et al. Qing-Hua Granule induces GLP-1 secretion via bitter taste receptor in db/db mice. Biomed Pharmacother. 2017;89:10–17.
44. Nakazato M, Murakami N, Date Y, Kojima M, Matsuo H, Kangawa K, et al. A role for ghrelin in the central regulation of feeding. Nature. 2001;409:194–8.
45. Malik S, McGlone F, Bedrossian D, Dagher A. Ghrelin modulates brain activity in areas that control appetitive behavior. Cell Metab. 2008;7:400–9.
46. Tack J, Depoortere I, Bisschops R, Delporte C, Coulie B, Meulemans A, et al. Influence of ghrelin on interdigestive gastrointestinal motility in humans. Gut. 2006;55:327–33.
47. Tack J, Depoortere I, Bisschops R, Verbeke K, Janssens J, Peeters T. Influence of ghrelin on gastric emptying and meal-related symptoms in idiopathic gastroparesis. Aliment Pharmacol Ther. 2005;22:847–53.
48. Pham H, Hui H, Morvaridi S, Cai J, Zhang S, Tan J, et al. A bitter pill for type 2 diabetes? The activation of bitter taste receptor TAS2R38 can stimulate GLP-1 release from enteroendocrine L-cells. Biochem Biophys Res Commun. 2016;475:295–300.
49. Steinert RE, Beglinger C, Langhans W. Intestinal GLP-1 and satiation: from man to rodents and back. Int J Obes. 2016;40:198–205.
50. Zanchi D, Depoorter A, Egloff L, Haller S, Mählmann L, Lang UE, et al. The impact of gut hormones on the neural circuit of appetite and satiety: a systematic review. Neurosci Biobehav Rev. 2017;80:457–75.
51. Jang HJ, Kokrashvili Z, Theodorakis MJ, Carlson OD, Kim BJ, Zhou J, et al. Gut-expressed gustducin and taste receptors regulate secretion of glucagon-like peptide-1. Proc Natl Acad Sci USA. 2007;104:15069–74.
52. Margolskee RF, Dyer J, Kokrashvili Z, Salmon KS, Ilegems E, Daly K, et al. T1R3 and gustducin in gut sense sugars to regulate expression of Na + -glucose cotransporter 1. Proc Natl Acad Sci USA. 2007;104:15075–80.
53. 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.
54. Daly K, Al-Rammahi M, Moran A, Marcello M, Ninomiya Y, Shirazi-Beechey SP. Sensing of amino acids by the gutexpressed taste receptor T1R1–T1R3 stimulates CCK secretion. Am J Physiol Gastrointest Liver Physiol. 2013;304:G271–G282.
55. Kokrashvili Z, Mosinger B, Margolskee RF. Taste signaling elements expressed in gut enteroendocrine cells regulate nutrient-responsive secretion of gut hormones. Am J ClinNutr. 2009;90:822S–825S.
56. Geraedts MC, Takahashi T, Vigues S, Markwardt ML, Nkobena A, Cockerham RE, et al. Transformation of postingestive glucose responses after deletion of sweet taste receptor subunits or gastric bypass surgery. Am J Physiol Endocrinol Metab. 2012;303:E464–474.
57. Xu H, Staszewski L, Tang H, Adler E, Zoller M, Li X. Different functional roles of T1R subunits in the heteromeric taste receptors. Proc Natl Acad Sci USA. 2004;101:14258–63.
58. Galindo-Cuspinera V, Winnig M, Bufe B, Meyerhof W, Breslin PA. A TAS1R receptor-based explanation of sweet 'water-taste'. Nature. 2006;441:354–7.
59. Ohtsu Y, Nakagawa Y, Nagasawa M, Takeda S, Arakawa H, Kojima I. Diverse signaling systems activated by the sweet taste receptor in human GLP-1-secreting cells. Mol Cell Endocrinol. 2014;394:70–79.
60. Wang F, Song X, Zhou L, Liang G, Huang F, Jiang G et al. The downregulation of sweet taste receptor signaling in enteroendocrine L-cells mediates 3-deoxyglucosone-induced attenuation of high glucose-stimulated GLP-1 secretion. Arch Physiol Biochem. 2017; https://doi.org/10.1080/13813455.2017.1419366.
61. Murovets VO, Bachmanov AA, Zolotarev VA. Impaired glucose metabolism in mice lacking the Tas1r3 taste receptor gene. PLoS ONE. 2015;10:e0130997.
62. Gerspach AC, Steinert RE, Schönenberger L, Graber-Maier A, Beglinger C. The role of the gut sweet taste receptor in regulating GLP-1, PYY, and CCK release in humans. Am J Physiol Endocrinol Metab. 2011;301:E317–325.
63. Steinert RE, Gerspach AC, Gutmann H, Asarian L, Drewe J, Beglinger C. The functional involvement of gut-expressed sweet taste receptors in glucose-stimulated secretion of glucagon-like peptide-1 (GLP-1) and peptide YY (PYY). Clin Nutr. 2011;30:524–32.
64. Shirazi-Beechey SP, Daly K, Al-Rammahi M, Moran AW, Bravo D. Role of nutrient-sensing taste 1 receptor (T1R) family members in gastrointestinal chemosensing. Br J Nutr. 2014;111(Suppl1):S8–15.
65. Glendinning JI, Yiin YM, Ackroff K, Sclafani A. Intragastric infusion of denatonium conditions flavor aversions and delays gastric emptying in rodents. Physiol Behav. 2008;93:757–65.
66. Avau B, Rotondo A, Thijs T, Andrews CN, Janssen P, Tack J, et al. Targeting extra-oral bitter taste receptors modulates gastrointestinal motility with effects on satiation. Sci Rep. 2015;5:15985.
67. Andreozzi P, Sarnelli G, Pesce M, Zito FP, Alessandro AD, Verlezza V, et al. The bitter taste receptor agonist quinine reduces calorie intake and increases the postprandial release of cholecystokinin in healthy subjects. J Neurogastroenterol Motil. 2015;21:511–9.
68. Tack J, Piessevaux H, Coulie B, Caenepeel P, Janssens J. Role of impaired gastric accommodation to a meal in functional dyspepsia. Gastroenterology. 1998;115:1346–52.
69. Tack J, Caenepeel P, Piessevaux H, Cuomo R, Janssens J. Assessment of meal induced gastric accommodation by a satiety drinking test in health and in severe functional dyspepsia. Gut. 2003;52:1271–7.
70. Rozengurt N, Wu SV, Chen MC, Huang C, Sternini C, Rozengurt E. Colocalization of the alpha-subunit of gustducin with PYY and GLP-1 in L cells of human colon. Am J Physiol Gastrointest Liver Physiol. 2006;291:G792–802.
71. Kim KS, Egan JM, Jang HJ. Denatonium induces secretion of glucagon-like peptide-1 through activation of bitter taste receptor pathways. Diabetologia. 2014;57:2117–25.
72. Park J, Kim KS, Kim KH, Lee IS, Jeong HS, Kim Y, et al. GLP-1 secretion is stimulated by 1,10-phenanthroline via colocalized T2R5 signal transduction in human enteroendocrine L cell. Biochem Biophys Res Commun. 2015;468:306–11.
73. Yu Y, Hao G, Zhang Q, Hua W, Wang M, Zhou W, et al. Berberine induces GLP-1 secretion through activation of bitter taste receptor pathways. Biochem Pharmacol. 2015;97:173–7.
74. Le Nevé B, Foltz M, Daniel H, Gouka R. The steroid glycoside H.g.-12 from Hoodia gordonii activates the human bitter receptor TAS2R14 and induces CCK release from HuTu-80 cells. Am J Physiol Gastrointest Liver Physiol. 2010;299:G1368–1375.

75. Jeon TI, Zhu B, Larson JL, Osborne TF. SREBP-2 regulates gut peptide secretion through intestinal bitter taste receptor signaling in mice. J Clin Invest. 2008;118:3693–3700.
76. Prinster A, Cantone E, Verlezza V, Magliulo M, Sarnelli G, Iengo M, et al. Cortical representation of different taste modalities on the gustatory cortex: a pilot study. PLoS ONE. 2017;12:e0190164.
77. Roitman MF, Wheeler RA, Carelli RM. Nucleus accumbens neurons are innately tuned for rewarding and aversive taste stimuli, encode their predictors, and are linked to motor output. Neuron. 2005;45:587–97.
78. Singh N, Vrontakis M, Parkinson F, Chelikani P. Functional bitter taste receptors are expressed in brain cells. Biochem Biophys Res Commun. 2011;406:146–51.
79. Chen X, Gabitto M, Peng Y, Ryba NJ, Zuker CS. A gustotopic map of taste qualities in the mammalian brain. Science. 2011;333:1262–6.
80. Baskin DG, Breininger JF, Schwartz MW. Leptin receptor mRNA identifies a subpopulation of neuropeptide Y neurons activated by fasting in rat hypothalamus. Diabetes. 1999;48:828–33.
81. Stocker CJ, Cawthorne MA. The influence of leptin on early life programming of obesity. Trends Biotechnol. 2008;26:545–51.
82. Misaka T. Molecular mechanisms of the action of miraculin, a taste-modifying protein. Semin Cell Dev Biol. 2013;24:222–5.
83. Swamy KB, Hadi SA, Sekaran M, Pichika MR. The clinical effects of Synsepalumdulcificum: a review. J Med Food. 2014;17:1165–9.
84. Mennella I, Fogliano V, Ferracane R, Arlorio M, Pattarino F, Vitaglione P. Microencapsulated bitter compounds (from Gentianalutea) reduce daily Energy intakes in humans. Br J Nutr. 2016; https://doi.org/10.1017/S0007114516003858.