FOCUS

Our innate attraction to sweet-tasting foods, which served our ancestors in the tropical forests, has since become a public health concern

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Type 1 Taste Receptors in Taste and Metabolism

by Matthew Kochem

Key insights

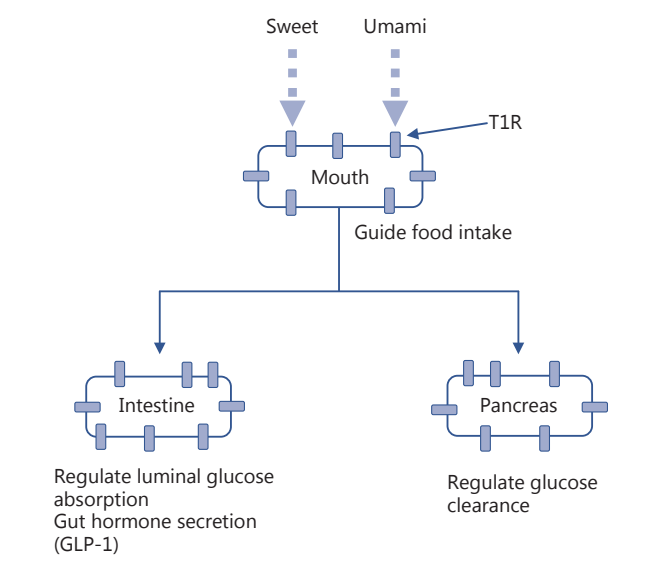
Type 1 taste receptors (T1Rs) transduce sweet and savory tastes. Not only expressed on the tongue and mouth, T1Rs are also found in other metabolically active tissues throughout the body, such as the intestine and pancreas. These receptors convey the presence of sugars and amino acids, guiding food intake and regulating the metabolic response to foods.

Current knowledge

The consumption of a carbohydrate-rich meal causes a dramatic change in blood glucose levels. It is important to control large glucose fluctuations, since excessive amounts of glucose contribute to protein glycosylation and blood vessel damage. T1Rs may play a role in the post-oral absorption and metabolism of nutrients such as glucose. In the intestine and pancreas, T1Rs act as sensors that stimulate glucose absorption in the intestinal lumen and promote its clearance from the blood. Activation of T1Rs in the intestine is thought to stimulate the secretion of incretins (such as the hormone GLP-1) that in turn upregulate glucose transporter expression and potentiate glucose-stimulated insulin secretion.

Practical implications

GLP-1 is an incretin hormone that plays a central role in glucose-stimulated insulin secretion in the pancreas. GLP-1 is an attractive candidate for the treatment of type 2 diabetes mellitus (T2DM). GLP-1 receptor mimetic drugs such as liraglutide and exenatide are currently used for the treatment of T2DM. The emerging role of T1Rs in glucose regulation has also raised interest in the metabolic effects of sweeteners in the diet. However, it is still unclear whether T1Rs affect insulin secretion, glucose clearance, or both. Because these receptors facilitate nutrient consumption and absorption, T1R inhibition may in fact be beneficial in obesogenic environments. In vivo studies suggest that the absence of T1R may be beneficial in an obesogenic environment: T1R knockout mice were less likely to become obese when fed a high-fat diet. Although more research is needed, inhibition of T1Rs may therefore present an alternative strategy for the prevention of diabetes.



T1Rs play many roles in guiding food intake, absorption, and metabolism.

Recommended reading

Knop FK, et al.: Reduced incretin effect in type 2 diabetes cause or consequence of the diabetic state? Diabetes 2007;56:1951–1959.

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Type 1 Taste Receptors in Taste and Metabolism

Matthew Kochem

Rutgers University Department of Nutritional Sciences, New Brunswick, NJ, USA

Key Messages

- Type 1 taste receptors (T1Rs) guide the consumption of sweet and savory foods.
- T1Rs are expressed in non-oral tissues, where they are thought to stimulate absorptive and hormonal responses to ingested foods.
- Mice lacking T1Rs are partially protected against diet-induced obesity and hyperinsulinemia.
- Further research is needed to determine the effects of T1R activity on human health.

Keywords

Taste receptor · T1R · Sweet · Savory · Umami · Taste · Perception · Glycemia · Insulin · Obesity

Abstract

Our sense of taste allows us to evaluate the nutritive value of foods prior to ingesting them. Sweet taste signals the presence of sugars, and savory taste signals the presence of amino acids. The ability to identify these macronutrients in foods was likely crucial for the survival of our species when nourishing food sources were sparse. In modern, industrialized settings, taste perception continues to play an important role in human health as we attempt to prevent and treat conditions stemming from overnutrition. Recent research has revealed that type 1 taste receptors (T1Rs), which are largely responsible for sweet and umami taste, may also influence the absorption and metabolism of the foods we eat. Preliminary research shows that T1Rs contribute to intestinal glucose absorption, blood sugar and insulin regulation, and the body's responses to excessive energy intake. In light of these findings, T1Rs have come to be understood as nutrient sensors, among other roles, that facilitate the selection, digestion, and metabolism of foods.

Introduction

Type 1 taste receptors (T1Rs) in the mouth signal the presence of saccharides and amino acids [1, 2]. The ability to detect these nutrients underlies a critical set of psychological and physiological processes that ensure human survival. T1Rs are largely responsible for the conscious perception of the appetitive sweet and umami tastes, which guide food intake [3]. Taste receptors may also regulate metabolic processes which promote efficient digestion and assimilation of the foods we eat.

Taste perception allows us to evaluate the chemical makeup of foods in order to determine whether they contain nutrients and/or toxins. Savory (umami) taste perception, primarily stimulated by glutamate and ribonucleotides, guides the consumption of protein sources.

KARGER

E-Mail karger@karger.com
www.karger.com/anm

Matthew Kochem, PhD
1016 Howell Mill Road, Apt. 2410
Atlanta, GA 30318 (USA)
E-Mail kochem@scarletmail.rutgers.ed

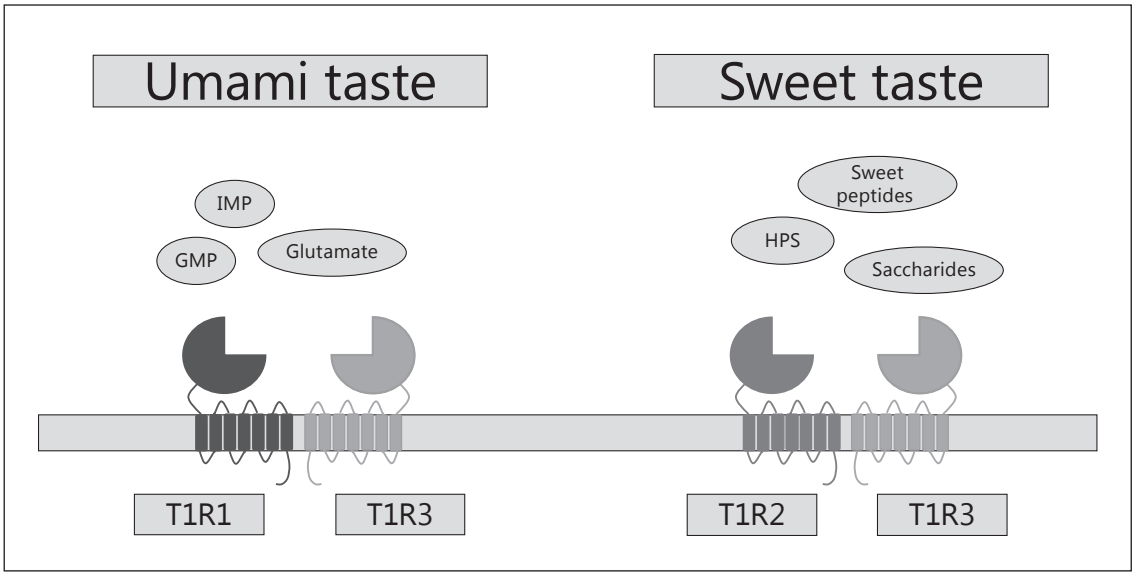

Fig. 1. Type 1 taste receptor (T1R) subunits form heterodimers to bind sweet and umami compounds. IMP, inosine monophosphate; GMP, guanosine monophosphate; HPS, high-potency sweeteners.

This helps to ensure the consumption of essential amino acids, which cannot be synthesized by the body and must be obtained in the diet. Similarly, sweet taste perception guides the intake of carbohydrate, a critical energy source for the brain and other tissues. Considering the energy demands of growth, it is unsurprising that infants and children are innately and strongly attracted to sweet-tasting compounds [4].

Taste receptors are also implicated in the regulation of nutrient metabolism. Recent research shows that taste receptors are expressed not only in the oral cavity, but in metabolically active tissues throughout the body [5–13]. The majority of this work has focused on the roles of intestinal and pancreatic T1Rs in glucose metabolism. Data from in vitro and animal studies suggest that taste receptors in the intestine and pancreas facilitate glucose absorption and disposal [5, 14, 15]. Animals lacking T1Rs display dramatically altered responses to food ingestion and respond differently to obesogenic diets.

Because they participate in a host of processes involved in the consumption and metabolism of foods, taste receptors may play a key part in our understanding of nutrition-related diseases. This review will discuss the basic functions of T1Rs, the importance of sweet and savory taste, and the striking effects of taste receptors on metabolism and long-term health.

T1R Structure and Signaling

The umami and sweet taste receptors are heteromeric, G-protein-coupled receptors (Fig. 1). T1R1-T1R3 is activated by glutamate and aspartate, as well as certain 5′-ribonucleotides, such as inosine and guanosine [1, 16]. T1R2-T1R3 is activated by a diverse set of stimuli including carbohydrates (mono- and disaccharides), sugar alcohols, sweet peptides and proteins, and other small molecule sweeteners [16]. In rodents, T1r3 ablation drastically reduces neural and behavior responses to umami and sweet stimuli [3]. Interestingly, sweet and umami taste are not entirely abolished in these animals, suggesting additional sensors for these stimuli. The residual responses to monosodium glutamate may be transduced by mGluRs [17, 18], and residual sweet responses may be transduced by components of the sodium potassium pump (Na+/K+-ATPase), sodium-glucose linked transporter 1 (SGLT1), and glucose transporters (GLUTs) in taste cells [19].

T1Rs are expressed on taste cells, which are arranged in groups called taste buds. Taste buds are distributed in distinct loci throughout the oral cavity, each of which is innervated by branches of the 7th, 9th, and 10th cranial nerves [20]. Taste buds are found on the fungiform papillae on the anterior tongue, the foliate and circumvallate papillae on the posterior tongue, and the smooth epithelia of the soft palate and the pharynx [20]. An often cited

but inaccurate belief is that specific regions of the oral cavity are solely responsible for specific taste modalities [21]. Although certain regions of the oral cavity are particularly responsive to certain taste qualities, all taste modalities can be elicited in all regions. Sweet and umami taste transduction begins when taste stimuli enter the taste bud pore and bind T1Rs on taste cells, which are electrically active, specialized, epithelial cells. Taste receptor binding can activate GTP-binding proteins, which begin the intracellular signaling cascade leading to taste cell depolarization and neurotransmitter (e.g., ATP, serotonin) release [22]. The signal is then carried to the brain by depolarized primary afferent taste neurons. The brain represents taste from unique patterns of activity across large networks of neurons, connecting opercular, insular, and orbito-frontal cortices, among other regions [20].

T1Rs Guide Food Selection

Taste is a highly adaptive chemical sense. We use our sense of taste when foraging to identify the chemical makeup of a potential food source in order to assess its nutrient content. Appetitive taste stimuli reinforce the consumption of needed nutrients. Aversive stimuli, on the other hand, discourage the consumption of potential toxins or harmful microbes.

Umami taste guides the consumption of foods rich in free amino acids, which are essential for survival. Monosodium glutamate, a primary elicitor of umami taste, enhances the palatability of foods [23]. Umami taste is hypothesized to have evolved to guide the ingestion of foods rich in free amino acids, including certain vegetables and meats, as well as fermented, aged, or cooked foods [24]. Similarly, salty tastes identify sodium and other ions which serve a host of physiological functions, including the maintenance of membrane potentials and regulation of blood volume. Sweet taste identifies sugar-rich foods. The ability to identify sweet foodstuffs containing sugars may have been critical for the survival of human ancestors [25]. Given that all species of living apes other than humans are largely frugivorous, the diets of human ancestors were likely comprised predominantly of fruits. If so, sweet taste perception would be key for the identification of nourishing foods. Sour taste indicates the presence of acid, which is aversive at high levels and appetitive at low levels, especially when mixed with sugar (such as in fruit) [25]. Bitter taste, which is aversive at high intensities and can induce nausea, is adaptive because it deters us from consuming large quantities of toxins [26].

The critical link between taste perception and food ingestion is highlighted in patients with taste disorders. Taste sensitivity can be partially lost (hypogeusia) or entirely lost (ageusia) due to various causes at the cellular and organ level stemming from aging, disease states, and medical therapies [27]. Taste is also lost in patients receiving radiotherapy (head and neck areas). Loss of taste sensitivity is associated with unintentional weight loss and reduced quality of life [28, 29]. Taste and flavor enhancement have been successfully employed as a means of increasing food intake and improving health status in elderly patients [30].

Sweet taste is a particularly important topic with regards to human health. Our innate attraction to sweet-tasting foods, which served our ancestors in the tropical forests, has since become a public health concern. Carbohydrate-rich foods are no longer scarce, thanks to advances in agriculture and technology. The amount of food energy available per capita has increased to the point that the major nutritional challenge for humans of industrialized nations has shifted from undernutrition to overnutrition [31]. The prevalence of conditions related to overnutrition such as obesity, type 2 diabetes mellitus, and fatty liver disease increased dramatically in the latter half of the 20th century [32]. The epidemic of nutrition-related diseases has been attributed to a long list of factors, but one of the most often cited causes is the overconsumption of added-sugar foods, including sugar-sweetened beverages [33]. High-potency sweeteners (HPS), which bind and activate T1Rs to stimulate sweet taste, present a low- or no-calorie alternative to sugar consumption. Although some observational studies have shown that "diet" beverage consumption is not associated with weight loss [34, 35], several clinical studies have found that they can be effective tools for achieving weight loss [36, 37]. As will be discussed below, the recent discovery of taste receptors in metabolically active tissues has generated intense interest in the potential health impacts of HPS.

The recent discovery of taste receptors in metabolically active tissues has generated intense interest in the potential health impacts of HPS

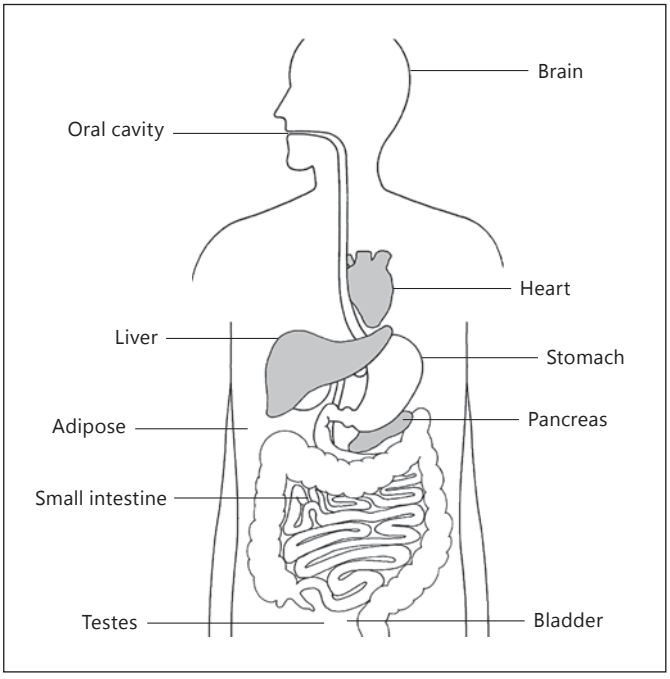

Fig. 2. Type 1 taste receptors are expressed throughout the body.

Taste Perception Primes Regulatory Physiology

Consuming a carbohydrate-rich meal causes a dramatic change in blood glucose [38]. It is important to defend against such changes because excessive amounts of glucose in the blood can damage blood vessels, glycosylate proteins, and promote the pathogenesis of chronic disease [39, 40]. As Ivan Pavlov demonstrated, associated food cues or the perception of food in the oral cavity can trigger digestive responses [41]. These responses are entirely independent of food ingestion, as evidenced by the fact that Pavlov observed them in fistulated animals and with very small stimulus volumes. They are absent, however, in vagotomized animals. Pavlov termed these phenomena "psychic reflexes" because they are neurally mediated. Currently, these effects are called cephalic phase responses. Cephalic phase insulin response (CPIR) exerts powerful effects on our bodies' responses to food ingestion. CPIR is a small, transient increase in plasma insulin that occurs before exogenous glucose appears in the blood [42]. The effects of CPIR can be observed by infusing glucose intravenously with and without sham feeding. When glucose infusion is paired with sham feeding (which stimulates CPIR), the resulting plasma glucose AUC is approximately 30% lower than the glucose AUC without sham feeding [43, 44]. Considering that the magnitude of CPIR is relatively small, its effects on postprandial glucose are striking.

In humans and animals, saccharides elicit CPIR [45–47]. Although this might suggest that CPIR is mediated by T1Rs, the sensory mechanisms underlying CPIR are unclear. HPS do not reliably elicit cephalic phase responses, which suggests that CPIR may be mediated by T1R-independent carbohydrate detection in the oral cavity [48–50]. More recently, it was shown that oral stimulation with glucose stimulates CPIR in T1R knockout animals [46]. And fructose, which does not bind SGLT1, fails to stimulate CPIR. These findings support the hypothesis that SGLT1 may be responsible for non-T1R-mediated taste responses [19].

T1Rs May Facilitate Glucose Absorption

In addition to their roles in conscious taste perception, T1Rs may help guide post-oral absorption and metabolism of nutrients. Within the last decade, taste receptors have been identified in the intestine [5], stomach [11], liver [6], pancreas [6], adipocytes [7], skeletal muscle [8], heart [10], brain [9], testes [12], and bladder [13] (Fig. 2). Recent research has largely focused on the functions of T1Rs in the intestine and pancreas. In these tissues, it is thought that T1Rs serve as sensors that stimulate luminal glucose absorption as well as blood glucose clearance. Because blood glucose dysregulation is a hallmark of diabetes mellitus and its comorbidities, the role of T1Rs in glucose metabolism is a subject of growing interest.

In the intestine, T1Rs have been shown to activate processes involved in luminal glucose absorption, including glucose transporter expression and gut hormone secretion [5]. To briefly review the mechanisms of glucose absorption, glucose is taken up in the lumen by SGLT1. SGLT1 is an active transporter that uses the sodium gradient to move glucose across the apical membrane of the enterocyte. Glucose is transported out of the enterocyte and into the circulation through glucose transporter 2 (GLUT2) via facilitated diffusion. When luminal glucose concentration is high, GLUT2 translocates to the apical membrane to enhance glucose absorption [51]. SGLT1 expression also increases in response to carbohydrate feeding [52].

It is thought that T1Rs in the intestine act as sensors to detect glucose levels and coordinate absorptive responses. This hypothesis is based upon several lines of evidence from studies in animal models. T1R3 knockout mice show blunted SGLT1 expression and glucose absorption in response to sugar ingestion relative to wild-type mice

[5]. And intestinal perfusion with HPS (which bind and activate T1R2-T1R3) upregulates apical translocation of GLUT2 and glucose absorption [14]. Further, the addition of HPS to a low-carbohydrate diet increases luminal SGLT1 expression, and this effect is dependent on T1R3 expression [5]. T1Rs are also implicated in the secretion of incretin hormones in the gut, which potentiate glucose-stimulated insulin secretion. T1Rs are expressed on the surface of enteroendocrine L-cells, which secrete GLP-1 when exposed to HPS [53, 54]. This effect is blocked by lactisole, a T1R3 antagonist [54]. T1R3 ablation abolishes the GLP-1 response to glucose in the intestine [53].

Based upon these findings, it is hypothesized that T1R activation in L-cells stimulates the secretion of incretins, like GLP-1, which upregulate glucose transporter expression elsewhere in the lumen via paracrine signaling and ultimately increase glucose absorption [5]. This hypothesis is supported by a study in humans showing that elevated duodenal T1R2 expression is associated with increased glucose absorption [55]. However, several clinical studies have shown that HPS consumption (which theoretically stimulates luminal T1Rs) does not acutely enhance glucose absorption [56, 57]. Further clinical trials are needed to determine whether T1Rs influence glucose absorption in humans.

T1Rs May Promote Plasma Glucose Clearance

The finding that T1R activation in the intestine stimulates GLP-1 secretion is particularly striking because it implies a role for T1Rs in insulin secretion and blood glucose clearance. GLP-1 is an incretin hormone, which potentiates glucose-stimulated insulin secretion in the pancreas. The "incretin effect" describes the phenomenon whereby a fixed amount of glucose elicits a greater insulin response when administered orally relative to intravenous administration [58]. As a consequence of the enhanced insulin response, the incretin effect improves glucose clearance and results in lower postprandial glucose responses. The incretin effect is due primarily to GLP-1 and gastric inhibitory peptide (GIP) [59]. In addition to promoting acute insulin responses, the incretin hormones also promote beta cell proliferation [60]. The incretin effect is impaired in type 2 diabetes mellitus (T2DM) [61]. In T2DM, GIP sensitivity is impaired [62]. GLP-1 sensitivity remains intact, but its abundance is reduced [62]. Because GLP-1 remains effective in T2DM, it is a particularly attractive candidate for pharmaceutical therapies. GLP-1 receptor mimetic drugs such as liraglutide and exenatide are effective diabetes treatments [63]. The incretin hormones are degraded by dipeptidyl peptidase-IV (DPP-IV). Presently, DPP-IV inhibitors are also prescribed to control glycemia in diabetics [64].

The notion that T1Rs play a role in glucose clearance is further supported by studies showing that T1Rs are expressed in pancreatic beta cells in humans and mice [6, 65]. Murine beta cells secrete insulin when exposed to HPS, and this effect is blocked by sweet taste inhibitors [65, 66]. Furthermore, when glucose is administered via intraperitoneal injection (which bypasses oral and intestinal taste receptors), T1R3 knockout mice display drastically reduced insulin responses and heightened plasma glucose compared to wild types [15]. Thus, in these animals, pancreatic T1Rs influence insulin response and glucose tolerance independent of preabsorptive responses. The observation that T1R knockout animals are glucose intolerant underlines the potential importance of T1Rs in glucose clearance. In sum, it is hypothesized that T1Rs in the oral cavity inform food selection, intestinal T1Rs facilitate glucose absorption, and pancreatic T1Rs stimulate glucose clearance into cells (Fig. 3).

It remains unclear, however, whether T1Rs influence insulin secretion or glucose clearance in humans. Several clinical studies have examined whether HPS ingestion (which presumably activates extra-oral taste receptors) elicits changes in blood sugar and insulin. HPS consumption in the absence of glucose has been consistently shown to have no effect on GLP-1, insulin, and glucose [67–69]. However, when consumed prior to or in combination with a glucose load, HPS elicit striking, albeit mixed, effects in some studies. To date, only 9 studies have examined the effect of an HPS on measures of glucose tolerance [56, 57, 70–76] (Table 1). Only 1 study has shown a significant increase in plasma insulin responses, and interestingly there were no effects on GLP-1 or blood sugar outcomes [70]. In contrast, a later study showed that HPS enhanced GLP-1, reduced blood sugar, and had no effect on insulin responses [73]. Three studies have shown significant enhancement of GLP-1 responses with no effects on blood sugar or insulin [56, 71, 72]. Three studies showed no effects on any outcomes [57, 74–76]. These discrepancies remain to be explained but may be due to differences in patient populations, HPS products used, HPS doses, and method of delivery (pre-load vs. concomitant consumption with sugar). HPS vary widely in terms of chemical structure, potency, maximal activity, and metabolism. For instance, whereas aspartame does not enter the circulation because it is degraded to its amino acid constituents in the alimentary tract, acesulfame potassi-

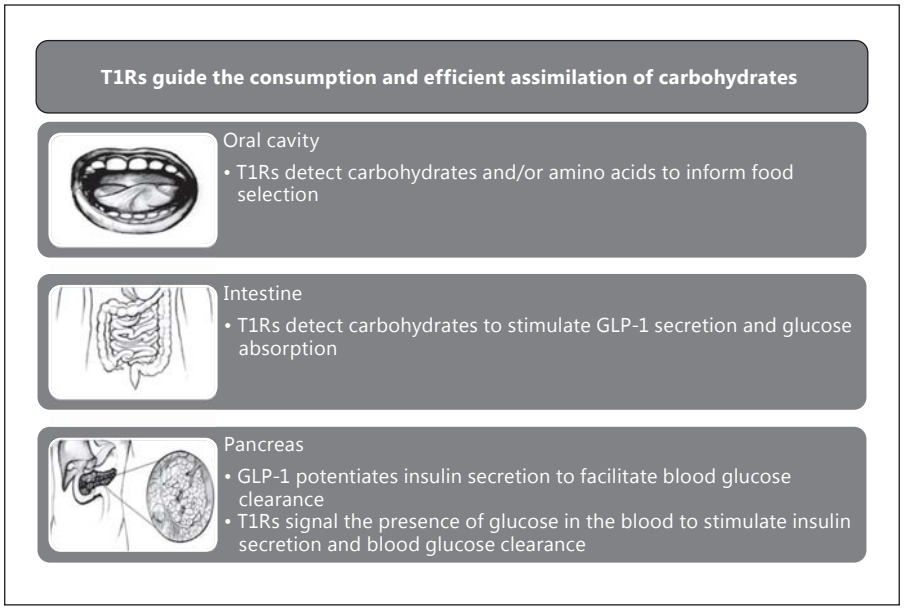

Fig. 3. Type 1 taste receptors (T1Rs) are hypothesized to guide the ingestion of foods and stimulate absorptive responses.

um is absorbed in the intestine and excreted entirely in urine. It is also likely that oral ingestion of small doses of HPS may be an ineffective means of studying pancreatic T1R activation, given that most HPS are poorly absorbed and the pancreas is exposed to little dietary HPS.

T1Rs in Modern Diets

As described above, T1R knockout animals show drastic impairments in glucose tolerance and hormone secretion relative to wild types when fed standard chow diets [15]. In this context, the absence of T1R function represents a substantial metabolic disadvantage. The picture changes, however, when these animals are fed obesogenic diets. In a study of carbohydrate-induced obesity, wild-type mice became obese when their diets were supplemented with a 34% sucrose solution, but T1R3 knockouts did not [77]. The effect was independent of caloric intake, which suggests that the effect was due to differences in carbohydrate utilization between strains. However, when diets were supplemented with more palatable solutions containing lipid, both wild types and knockouts became obese. In a study of animals fed high-fat (Western) diets, T1R2 and T1R3 knockouts had smaller adipocytes and reduced adiposity relative to wild types [78]. In a similar study, T1R2 knockout animals had reduced fat mass, reduced liver triglyceride accumulation, and increased lean mass relative to wild types [79]. In addition, T1R2 knockouts were protected against diet-induced hyperinsulinemia. T1R2 knockouts were hyperphagic relative to controls and showed increased carbohydrate oxidation, which provides further evidence that the effects were driven by differences in carbohydrate utilization.

These studies show that in obesogenic environments, the absence of T1R function confers metabolic benefits. On the surface, this contradicts the notion that T1Rs were important to the survival of our species. There are clear differences, however, between the lifestyles of ancestral and modern humans. It was likely imperative for human ancestors to identify a potential food source before ingesting it, lest they face the consequences of starvation or toxin ingestion. It would have also been adaptive for early humans to efficiently absorb nutrients and store fat in the event that food availability became limited in the future. In modern times, however, nourishing food sources abound and humans face challenges stemming from overnutrition. A reduction in efficiency might now impart a benefit, as illustrated by the use of acarbose (a drug which inhibits carbohydrate digestion) to treat diabetes.

More work is needed to determine the mechanisms through which T1R ablation protects against diet-induced metabolic dysfunction. Because T1Rs are knocked out whole-body in these animals, it is unclear whether the observed effects are due to their activity in the gut, pancreas, adipose, or elsewhere. Reduced T1R activity in the pancreas may explain the observed protection against hyperinsulinemia, which in turn may reduce liver fat accumulation and adipocyte hypertrophy [79]. T1Rs are also

Table 1. Clinical trials examining the effects of HPS on OGTT outcomes yield inconsistent results

First author [Ref.], year	Subjects	Design	Effects of HPS on GLP-1, insulin, and glucose
Brown [71], 2009	Healthy (n = 22)	Subjects consumed 240 mL stimuli prior to OGTT; crossover design; stimuli: – cola sweetened with 68 mg sucralose + 41 mg acesulfame potassium – carbonated water	Diet cola increased GLP-1 response to OGTT relative to water No effect on glucose or insulin
Brown [76], 2011	Healthy (n = 8)	Subjects consumed 355 mL stimuli; crossover design; stimuli: – water – water + 50 g sucrose – water + 6 g sucralose – water + 50 g sucrose + 6 g Splenda	No effect of HPS on glucose or insulin responses
Brown [72], 2012	Healthy (n = 25) T1DM (n = 9) T2DM (n = 10)	Subjects consumed 240 mL stimuli prior to OGTT; crossover design; stimuli: – diet soda containing 26 mg acesulfame potassium + 46 mg sucralose – carbonated water	Diet soda increased GLP-1 response to OGTT relative to water (only in T1DM and healthy subjects) No effect on glucose
Pepino [70], 2013	Morbidly obese (n = 17)	Subjects consumed 60 mL stimuli prior to OGTT; crossover design; stimuli: – water + 48 mg sucralose – water	Sucralose increased glucose and insulin responses to OGTT No effect on GLP-1
Wu [75], 2013	Healthy (n = 10)	Subjects consumed 240 mL stimuli prior to OGTT; crossover design; stimuli: – water – water + 52 mg sucralose – water + 200 mg acesulfame potassium – water + 46 mg sucralose + 26 mg acesulfame potassium	No effect of HPS on glucose or insulin responses
Bryant [74], 2014	Healthy (n = 10)	Subjects consumed 250 mL stimuli; crossover design; stimuli: – water + 45 g glucose – water + 45 g glucose + 150 mg aspartame – water + 45 g glucose + 20 mg saccharin – water + 45 g glucose + 85 mg acesulfame potassium	No effect of HPS on glucose response
Temizkan [73], 2015	Healthy (n = 8) T2DM (n = 8)	Subjects consumed 200 mL stimuli prior to OGTT; crossover design; stimuli: – water – water + 72 mg aspartame – water + 24 mg sucralose	Sucralose increased GLP-1 and decreased glucose responses to OGTT No effect on insulin
Sylvetsky [56], 2016	Arm 1: healthy (n = 30) Arm 2: healthy (n = 31)	Conducted in 2 arms; subjects consumed 355 mL stimuli prior to OGTT; crossover design; stimuli: *Arm 1* – water – water + 68 mg sucralose – water + 170 mg sucralose – water + 250 mg sucralose *Arm 2* – carbonated water – diet soda containing 68 mg sucralose + 41 mg acesulfame potassium – diet soda containing 18 mg sucralose + 18 mg acesulfame potassium + 57 mg aspartame – carbonated water + 68 mg sucralose + 41 mg acesulfame potassium	*Arm 1* No effect of HPS on GLP-1, glucose, or insulin *Arm 2* Diet soda containing 68 mg sucralose + 41 mg acesulfame potassium increased GLP-1 response relative to water No effect on glucose or insulin
Karimian Azari [57], 2017	Healthy (n = 10)	Subjects consumed stimuli prior to OGTT; crossover design; stimuli: – water – water + 300 ppm saccharin – water + 500 ppm lactisole (T1R3 inverse agonist) – water + 300 ppm saccharin + 500 ppm lactisole	No effect of saccharin on GLP-1, glucose, or insulin Lactisole increased insulin response to OGTT

HPS, high-potency sweetener; OGTT, oral glucose tolerance test; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

expressed in adipocytes [7], and it is possible that their ablation may alter lipid metabolism. The effects of T1R ablation on lipid metabolism are particularly intriguing because clofibric acid, a blood-lipid-lowering prescription drug, inhibits T1R3 in vitro and blocks sweet and umami taste in vivo [80–82]. Moreover, the physiological effects of T1R ablation appear to overlap with the physiological effects of clofibric acid treatment. Both reduce ectopic lipid accumulation [79, 83] and improve insulinemia [79, 84]. Clofibric acid is thought to exert its effects through PPAR alpha activation [85], but its effects on extra-oral T1Rs have not been examined in vivo. Further clinical studies with clofibric acid or other T1R inhibitors such as lactisole may be helpful in clarifying the contribution of T1Rs to metabolic outcomes.

Conclusion

T1Rs facilitate the identification and assimilation of nutrients. T1Rs are important receptors in the transduction of sweet and umami tastes, which help to ensure the consumption of sugars and amino acids. Recently, T1Rs have been identified in metabolically active tissues throughout the body. Preliminary work indicates that they promote absorptive and hormonal responses to food ingestion. T1Rs were highly adaptive for human ancestors who needed to quickly evaluate the nutritive value of foods and efficiently store fuel. However, in modern, obesogenic environments, overstimulation of these responses may not be beneficial to long-term health. To that point, studies in knockout animals suggest that T1R inactivation may protect against diet-induced conditions such as obesity, hyperinsulinemia, and liver steatosis. Further research is needed to clarify the functions of T1Rs in humans and to determine whether their activation or inhibition can be leveraged to influence metabolic outcomes.

Disclosure Statement

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