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T1R Sweet Taste Receptors: From Gustation to Systemic Physiology and Therapeutic Potential for Better Bitter Blocker Research

1. Introduction: The Dual Role of T1R Sweet Taste Receptors – From Gustation to Systemic Chemosensation

The sense of taste, or gustation, serves as a critical sentinel at the gateway of the digestive system, guiding food choices essential for survival and physiological maintenance.[1] Traditionally, taste perception is categorized into five distinct qualities: sweet, sour, salty, bitter, and umami. These sensations provide vital information about the chemical composition of ingested substances, with sweet, umami, and salty tastes typically signaling nutritive content (carbohydrates, amino acids, and sodium, respectively), while bitter and sour tastes often warn against potential toxins or acidity.[1] The molecular underpinnings of these taste modalities have been progressively elucidated, with a significant advancement being the discovery of the Taste Receptor type 1 (T1R) family of G protein-coupled receptors (GPCRs), which are responsible for detecting sweet and umami stimuli.[1]

Initially, the function of these T1R receptors was thought to be exclusively confined to taste receptor cells (TRCs) within the oral cavity. However, a paradigm shift occurred with the accumulation of evidence demonstrating that T1R receptors and their associated signaling components are not restricted to the tongue. Instead, they exhibit a surprisingly widespread distribution in numerous non-gustatory tissues throughout the body, including the gastrointestinal tract, pancreas, brain, and even the musculoskeletal system.[1] This discovery has fundamentally transformed the understanding of these receptors, expanding their role from mere mediators of conscious taste perception to integral "nutrient sensors" that participate in monitoring global glucose and amino acid status and orchestrating a wide array of systemic

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physiological responses.[1] The initial discovery of these extra-oral taste receptors was described as "baffling," but it is now understood that they function as local chemoreceptors, even if not linked to conscious taste perception.[5]

The broad expression of T1R receptors across diverse organ systems points towards a deeply conserved evolutionary strategy for nutrient detection that extends far beyond the conscious appreciation of taste. This implies a fundamental biological imperative, enabling organisms not only to select appropriate food sources but also to physiologically prepare for and manage nutrient processing at multiple systemic levels. The conservation of T1Rs among vertebrates underscores their critical role.[2] Thus, the function of these receptors is not merely about experiencing palatability; it is intrinsically linked to the optimization of physiological processes essential for energy acquisition, utilization, and overall homeostasis.

Furthermore, the existence of these extra-oral "taste" receptors necessitates a re-evaluation of the traditional concept of taste as a sensation localized solely to the oral cavity. It suggests, instead, that the chemosensation of nutrients is a distributed physiological function. The oral component provides conscious perception, hedonic assessment, and initial guidance for food intake.[3] Concurrently, the extra-oral components, utilizing similar molecular machinery, mediate unconscious, direct physiological regulation in response to the presence of nutrients in various internal environments.[3] This integrated chemosensory system allows for a holistic bodily response to nutrient ingestion, coordinating digestive, metabolic, and endocrine functions.

This report aims to provide a comprehensive review of the T1R sweet taste receptors, tracing their journey from their established role in gustatory signal transduction to their multifaceted functions in systemic physiology. It will explore their molecular architecture, ligand interactions, and signaling mechanisms, followed by an examination of their extra-oral distribution and the profound impact of their activation on digestive processes, endocrine signaling, neural pathways, metabolic regulation,

and overall homeostasis, including the implications for various organ systems such as the musculoskeletal system.[8]

2. Molecular Architecture and Gustatory Function of T1R Sweet Taste Receptors

The ability to perceive sweet taste is a fundamental sensory experience that guides nutrient intake. This perception is primarily initiated by a specific molecular complex, the T1R2/T1R3 heterodimeric receptor, located within specialized cells of the oral cavity.

2.1. The T1R2/T1R3 Heterodimer: Structure, Ligands, and Species Variability

Sweet taste is predominantly mediated by a heterodimeric receptor composed of two distinct protein subunits: Taste 1 Receptor Member 2 (T1R2) and Taste 1 Receptor Member 3 (T1R3).[2] T1R3 serves as an obligate partner, dimerizing with T1R2 to form the sweet taste receptor and with T1R1 to form the umami (savory L-amino acid) taste receptor.[7] This shared reliance on T1R3 for detecting two distinct, yet calorically significant, taste modalities positions it as a central molecular hub for sensing key macronutrients. The expression levels and functional state of T1R3 could, therefore, represent critical regulatory points that influence an organism's overall capacity to sense and respond to carbohydrates and amino acids, both in the oral cavity and systemically. Any modulation of T1R3 availability or function could potentially shift the balance of sweet versus umami sensing or alter the detection thresholds for these nutrients.

Structurally, T1R proteins belong to Class C of the G protein-coupled receptor (GPCR) superfamily. They are characterized by a large extracellular N-terminal domain, which includes a Venus flytrap module (VFTM) or bilobed domain, connected via a cysteine-rich domain to the canonical seven transmembrane helices typical of GPCRs.[2] The VFTM is the primary binding site for most sweet-tasting molecules,

undergoing conformational changes upon ligand binding to initiate downstream signaling.[6]

The T1R2/T1R3 receptor is remarkable for its ability to recognize a chemically diverse array of compounds perceived as sweet. These include natural sugars such as sucrose and glucose, certain D-amino acids, some sweet-tasting proteins (e.g., monellin, thaumatin), and a wide variety of artificial or non-nutritive sweeteners (NNS) like saccharin, sucralose, and aspartame.[2] This broad ligand specificity allows for the detection of energy-rich carbohydrates as well as compounds that mimic their taste.

Significant species-specific differences exist in sweet taste perception, which are attributable to variations in the T1R gene sequences. For instance, many rodents, unlike humans, do not exhibit a preference for the artificial sweetener aspartame, and their T1R2/T1R3 receptor does not bind this compound effectively.[2] In humans, the genes encoding the T1R subunits, *TAS1R1*, *TAS1R2*, and *TAS1R3*, are clustered on the short arm of chromosome 1 (1p36).[2] The existence of genetic polymorphisms within these *TAS1R* genes in the human population [5], coupled with the observed species variability, strongly suggests that individual genetic differences likely contribute to variations in sweet taste perception, preferences, and potentially, systemic metabolic responses to sweeteners. Such individual "taste worlds" could have significant implications for dietary choices, susceptibility to diet-related diseases, and the efficacy of personalized nutrition strategies.

While the T1R2/T1R3 heterodimer is the principal sweet taste receptor, some evidence suggests that T1R3 may also function independently as a homodimer (T1R3/T1R3) to detect high concentrations of sucrose.[2] This potential alternative mechanism could be particularly relevant for sensing caloric overload from highly sweetened foods.

Table 1: Characteristics of T1R Receptor Subunits and Heterodimers

Receptor Subunit/Complex	Primary Taste Modality/Function	Key Ligands	Key G-protein Association(s) (Oral)
T1R1	Component of Umami Receptor	-	(Forms heterodimer)
T1R2	Component of Sweet Receptor	-	(Forms heterodimer)
T1R3	Obligate component of Sweet and Umami Receptors; Potential high-concentration sugar sensor	-	(Forms heterodimers/homodimer)
T1R1/T1R3	Umami	L-amino acids (e.g., L-glutamate, L-aspartate)	α-gustducin, Transducin
T1R2/T1R3	Sweet	Natural sugars (glucose, sucrose, fructose), artificial sweeteners, sweet proteins	α-gustducin, Gα14
T1R3/T1R3 (potential)	High-concentration Sweet (speculative)	High concentrations of sucrose	Likely α-gustducin

Sources: [1]

2.2. Localization and Signal Transduction in Oral Taste Buds

The initial stage of gustatory processing occurs within taste buds, which are specialized sensory organs located predominantly on the papillae of the tongue, but also found on the palate and other areas of the oral cavity.[3] Each taste bud is a cluster of 50-100 elongated taste receptor cells (TRCs), which can be broadly classified into different types based on their morphology and function. Sweet, bitter, and umami stimuli are primarily detected by Type II TRCs (also known as receptor cells).[2] Within these Type II cells, T1R3 is typically co-expressed with either T1R1 (for umami taste) or T1R2 (for sweet taste), although some taste cells in mammals may express only T1R3.[2]

The binding of a sweet ligand to the T1R2/T1R3 heterodimer on the apical membrane of a Type II TRC initiates a well-defined intracellular signal transduction cascade [1]:

1. **Receptor Activation and G Protein Coupling:** Upon ligand binding, the T1R2/T1R3 receptor undergoes a conformational change, leading to the activation of an associated heterotrimeric G protein. The primary G protein implicated in sweet taste transduction is gustducin, specifically its α-subunit (α-gustducin). However, other G proteins, such as Gα14, have also been found co-expressed with T1R3 in some taste cells, suggesting potential for alternative or modulatory signaling pathways.[6]
2. **Effector Enzyme Activation:** The activated G protein (either the dissociated α-gustducin subunit or the βγ complex, Gβ3Gγ13) stimulates the membrane-bound enzyme Phospholipase C β2 (PLCβ2).
3. **Second Messenger Generation:** PLCβ2 catalyzes the hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP$_2$), a membrane phospholipid, into two intracellular second messengers: inositol 1,4,5-trisphosphate (IP$_3$) and diacylglycerol (DAG).
4. **Intracellular Calcium Release:** IP$_3$ diffuses through the cytoplasm and binds to IP$_3$ receptors (specifically the type 3 isoform, IP$_3$R3) located on the membrane of the endoplasmic reticulum, which serves as an intracellular calcium store. This binding triggers the release of Ca^{2+} from the endoplasmic reticulum into the cytosol, leading to a transient increase in intracellular

Ca^{2+} concentration.

5. **TRPM5 Channel Activation:** The elevation in cytosolic Ca^{2+} activates a non-selective cation channel called Transient Receptor Potential cation channel subfamily M member 5 (TRPM5).
6. **Cell Depolarization and Neurotransmitter Release:** The opening of TRPM5 channels allows an influx of Na^{+} ions, leading to depolarization of the TRC membrane. This depolarization, if sufficient, generates action potentials and ultimately triggers the release of adenosine triphosphate (ATP) from the Type II cell. ATP acts as the primary neurotransmitter for sweet, bitter, and umami tastes.[6]
7. **Neural Transmission:** The released ATP activates P2X2/P2X3 purinergic receptors on the afferent nerve fibers of cranial nerves VII (facial), IX (glossopharyngeal), and X (vagus), which innervate the taste buds.[12] These nerves then transmit the taste signal to the gustatory processing centers in the brainstem and ultimately to the gustatory cortex for conscious perception of sweetness.

While this T1R2/T1R3-α-gustducin-PLCβ2-IP$_3$-Ca$^{2+}–TRPM5–ATPpathwayisconsideredcanonicalforsweettaste,theco–expressionofothersignalingmolecules,suchasG\alpha$14, and the potential for T1R3 homodimers to sense high sugar concentrations [2], suggest that sweet taste transduction may possess a greater degree of complexity and nuance than a single, linear pathway. This inherent complexity could allow for differential signaling or modulation based on the specific type or concentration of the sweetener, or the prevailing physiological state of the organism. For example, Gα14 might mediate responses to particular classes of sweeteners or modulate the gain of the primary α-gustducin pathway. Similarly, T1R3 homodimers could represent a distinct sensing mechanism tailored for conditions of caloric excess. Such intricacies could provide the gustatory system with a sophisticated capacity for fine-tuning responses to a diverse world of sweet stimuli.

3. Extra-Oral T1R Sweet Taste Receptors: A Widespread Network for Systemic Nutrient Sensing

The discovery that T1R sweet taste receptors and their associated signaling machinery are not confined to the oral cavity has revolutionized our understanding of nutrient sensing. These receptors form an extensive extra-oral network, enabling various organs and tissues to directly detect the presence of sugars and other sweet-tasting compounds, thereby initiating localized and systemic physiological responses independent of conscious taste perception.

3.1. Distribution in the Gastrointestinal (GI) Tract

The GI tract is a prominent site for extra-oral T1R expression. Accumulating evidence demonstrates the presence of T1R2 and T1R3 subunits, along with signaling molecules like α-gustducin, in various segments, including the stomach, duodenum, jejunum, ileum, and colon.[3] These receptors are primarily concentrated on enteroendocrine cells (EECs), which are specialized chemosensory cells scattered throughout the gut epithelium. EECs collectively constitute the largest endocrine organ in the body and play a crucial role in gut-brain communication by releasing hormones in response to luminal stimuli.[3]

Specific EEC populations expressing T1Rs include:

- **L-cells:** Found predominantly in the distal small intestine (ileum) and colon, L-cells express T1R2/T1R3 and function as glucose sensors. Activation of these receptors by sugars or NNS triggers the release of glucagon-like peptide-1 (GLP-1).[3]
- **K-cells:** Located mainly in the proximal small intestine (duodenum and jejunum), K-cells secrete glucose-dependent insulinotropic peptide (GIP) in response to glucose. While GIP secretion is SGLT1-dependent, the precise involvement of T1R receptors in K-cell activation is an area of ongoing investigation.[3]
- **Enterochromaffin (EC) cells:** Distributed throughout the GI tract, EC cells

express T1Rs and release serotonin (5-hydroxytryptamine, 5-HT) in response to sweet stimuli like sucralose.[3]

- **Stomach:** In the stomach, T1R3 and α-gustducin have been identified in ghrelin-secreting cells, suggesting a potential role for sweet sensing in the regulation of this orexigenic hormone.[6]

Beyond EECs, T1R components may also be present on enterocytes (absorptive intestinal cells) and brush cells, further indicating their involvement in direct nutrient handling and local signaling.[6]

3.2. Presence in the Pancreas

The endocrine pancreas, particularly the insulin-secreting β-cells within the islets of Langerhans, is another critical site for extra-oral T1R expression. Functional T1R2, T1R3, and α-gustducin have been identified on the surface of pancreatic β-cells in both rodents and humans.[1] This localization suggests a direct mechanism by which the pancreas can "taste" or sense sweet compounds, including sugars and NNS, and modulate insulin secretion independently of changes in blood glucose levels that occur via nutrient metabolism. The T1R2 subunit, for example, has been shown to be essential for fructose-induced insulin release.[11]

3.3. Presence in the Central Nervous System (CNS)

T1R sweet taste receptors are also expressed within the CNS, indicating a role in direct central nutrient sensing. T1R2 and T1R3 have been identified in key hypothalamic areas, such as the arcuate nucleus (ARC) and paraventricular nucleus (PVN), regions critically involved in the regulation of appetite, energy expenditure, and glucose homeostasis.[1] These hypothalamic T1Rs are thought to function as nutrient sensors, contributing to the brain's ability to monitor energy status and coordinate appropriate metabolic and behavioral responses.[3] Expression has also been noted in other brain regions like the hippocampus, Cornu ammonis fields, and dentate gyrus neurons,

though their functions in these areas are less well understood.[6]

3.4. Presence in Other Key Tissues

The distribution of T1R receptors extends to a remarkable variety of other tissues, highlighting their diverse physiological roles:

- **Musculoskeletal System:** Emerging research has identified T1R1, T1R2, and T1R3 expression in skeletal muscle and bone. In skeletal muscle, these receptors, particularly T1R3, are implicated in nutrient status detection, myogenesis, and potentially in the context of sarcopenia.[1] In bone, T1R2 and T1R3 appear to regulate postnatal bone mass and remodeling, potentially by influencing the differentiation balance between osteoblasts and adipocytes within the bone marrow microenvironment, which has implications for conditions like osteoporosis.[1]
- **Adipose Tissue:** Adipocytes express functional T1R2 and T1R3 receptors. These receptors are proposed to play a role in regulating adipogenesis (fat cell formation) and lipolysis (fat breakdown), thereby directly linking sweet sensing to fat storage and metabolism.[1]
- **Respiratory System/Airway:** T1R2/T1R3 receptors are expressed in the nasal epithelium and other parts of the airway. Here, they are not involved in taste perception but contribute to innate immune responses, acting as chemoreceptors for bacterial products or other irritants.[3]
- **Other Tissues:** Expression of T1R subunits, predominantly T1R3, has also been reported in the liver, kidney, testes, heart, bladder, and various immune cells (e.g., lymphocytes).[1] While the precise functions in many of these locations are still under active investigation, these findings suggest potential roles in processes as diverse as renal function, male fertility (T1R3 in spermatozoa), cardiac function, bladder contractility, and immune modulation.

The widespread distribution of T1Rs throughout the body implies the existence of a highly coordinated and integrated network where different organs and tissues can

independently sense the availability of key nutrients, particularly sugars (via T1R2/T1R3) and amino acids (via T1R1/T1R3). This decentralized yet interconnected system allows for robust and context-dependent physiological responses to nutrient intake and fluctuations in internal energy status, contributing to the maintenance of overall energy homeostasis. The frequent and sometimes prominent expression of T1R3 in diverse tissues, even in contexts where "sweet taste" per se is not the primary perceived function (e.g., testes, heart), also suggests that T1R3 may possess pleiotropic roles extending beyond the simple detection of dietary sugars for caloric purposes. It might be involved in sensing other endogenous or exogenous ligands or participate in cellular processes unrelated to direct nutrient metabolism, such as tissue development, cell differentiation, or immune surveillance.

This extensive extra-oral presence of T1R2/T1R3 also carries important implications for the use of NNS. Compounds designed to activate oral sweet receptors for taste modification will inevitably interact with these same receptors in numerous other physiological systems. This raises critical questions about the potential for unintended "off-target" effects and the long-term systemic consequences of chronic NNS consumption, as these substances could elicit physiological responses in the gut, pancreas, brain, and adipose tissue, among others, without an accompanying caloric load.

Table 2: Summary of Extra-Oral T1R2/T1R3 Receptor Locations and Established/Proposed Functions

Tissue/Organ System	Specific Cell Types (if known)	T1R Subunits Expressed	Key Established/Proposed Physiological Roles	Key Supporting Source(s)

Gastrointestinal Tract				
Stomach	Ghrelin-secreting EECs, Brush cells	T1R3, α-gustducin	Potential regulation of ghrelin secretion	6
Duodenum, Jejunum (Proximal Small Intestine)	L-cells, K-cells, EC cells, Enterocytes	T1R2, T1R3, α-gustducin	GLP-1 & GIP secretion, Serotonin release, Glucose absorption (SGLT1, GLUT2 regulation), Nutrient sensing	3
Ileum (Distal Small Intestine), Colon	L-cells, EECs	T1R2, T1R3, α-gustducin	GLP-1 secretion, Nutrient sensing, Potential motility regulation	3
Pancreas	β-cells (Islets of Langerhans)	T1R2, T1R3, α-gustducin	Direct stimulation/potentiation of insulin secretion (non-metabolic pathway), Fructose-induced insulin release	1
Central Nervous				

System				
Hypothalamus (ARC, PVN)	Neurons	T1R2, T1R3	Glucose sensing, Regulation of appetite, energy balance, and glucose homeostasis	3
Hippocampus, Other areas	Neurons	T1R2, T1R3	Learning, Memory (proposed)	6
Musculoskeletal System				
Skeletal Muscle	Myocytes, Muscle stem cells	T1R1, T1R3	Nutrient status detection (MTORC1, autophagy), Myogenesis regulation, Implicated in sarcopenia	1
Bone	Osteoblasts, Osteoclasts, Bone marrow stromal cells	T1R2, T1R3	Regulation of postnatal bone mass and remodeling, Osteoblast/adipocyte differentiation, Implicated in	1

			osteoporosis	
Adipose Tissue	Adipocytes	T1R2, T1R3	Regulation of adipogenesis and lipolysis, Energy storage modulation	1
Respiratory System	Nasal epithelial cells, Airway epithelial cells	T1R2, T1R3	Innate immune responses, Chemosensation of bacterial products/irritants	3
Other Tissues				
Heart	Cardiomyocytes	T1R3	Putative nutrient sensing, Function largely unknown	1
Liver	Hepatocytes (likely)	T1R3	Function largely unknown, potential metabolic sensing	4
Kidney	Renal tubular cells (likely)	T1R3	Function largely unknown, potential role in solute handling	4

Testes	Spermatozoa, Leydig cells, Sertoli cells (human/mouse)	T1R3, α-gustducin	Male fertility, Spermatogenesis (T1R3 blockade linked to sterility in mice)	3
Bladder	Urothelial cells	T1R2, T1R3	Modulation of bladder contraction	6
Immune System	Lymphocytes, Thymus	T1R3	Potential role in immune modulation, Function largely unknown	6

ARC: Arcuate Nucleus; PVN: Paraventricular Nucleus; EECs: Enteroendocrine cells. This table summarizes key findings and proposed roles; functions in many extra-oral tissues are still under active investigation.

4. Systemic Physiological Impact of T1R Receptor Activation

The activation of T1R sweet taste receptors, both within the oral cavity and in their diverse extra-oral locations, initiates a complex cascade of physiological responses that extend far beyond simple taste perception. These receptors are integral components of a sophisticated chemosensory system that profoundly influences digestive processes, endocrine balance, neural regulation, and the function of various other organ systems, thereby contributing to overall metabolic homeostasis.

4.1. Regulation of Digestive Processes and Nutrient Homeostasis

The gastrointestinal tract, richly endowed with T1R receptors, serves as a primary site

where sweet sensing translates into direct physiological actions crucial for nutrient processing and energy balance.

Gut-Level Nutrient Sensing and Hormone Release:
Luminal sugars and NNS activate T1R2/T1R3 receptors on EECs, triggering the secretion of several key gut hormones. Most notably, this includes the incretin hormones glucagon-like peptide-1 (GLP-1) from L-cells and glucose-dependent insulinotropic peptide (GIP) from K-cells.3 These hormones play pivotal roles in postprandial glucose regulation by potentiating insulin secretion from pancreatic β-cells in a glucose-dependent manner, slowing gastric emptying, and promoting satiety.21 For instance, studies have shown that T1R3 and the glucose transporter SGLT1 interact within L-cells to optimize GLP-1 production.3 Activation of T1Rs on enterochromaffin (EC) cells also stimulates the release of serotonin (5-HT), a neurotransmitter and hormone that influences gut motility, secretion, and visceral sensation.3 Furthermore, T1R3 expression in ghrelin-secreting cells of the stomach suggests a potential role for sweet sensing in modulating the release of this hunger-stimulating hormone, although this requires further investigation.6
Glucose Absorption and Transporter Regulation:
Beyond hormonal signaling, gut T1R activation directly influences the capacity of the intestine to absorb dietary sugars. Stimulation of these receptors by sugars or NNS leads to an upregulation in the expression and/or apical membrane trafficking of key glucose transporters, such as the sodium-glucose cotransporter 1 (SGLT1) and the facilitated glucose transporter 2 (GLUT2), in enterocytes.3 This enhancement of glucose transport machinery optimizes the uptake of dietary carbohydrates. The mechanisms involved can be indirect, via the action of released incretins like GLP-1 and GIP 4, or more direct, involving T1R signaling within enterocytes that activates Protein Kinase C βII (PKCβII), which in turn promotes GLUT2 insertion into the apical membrane.14 Studies involving T1R2 knockout mice have demonstrated that T1R2 signaling in the upper intestine is crucial for potentiating glucose absorption, an effect mediated by GLUT2 trafficking and dependent on the secretion of glucagon-like peptide-2 (GLP-2) and subsequent activation of enteric neurons.25 Conversely, genetic knockout of T1R3 or α-gustducin has been shown to impair this diet-induced upregulation of glucose transporters.4
Influence on Gut Motility and Energy Intake Regulation:
The gut hormones released in response to T1R activation, such as GLP-1 and peptide YY

(PYY), exert significant effects on gastrointestinal motility. They typically inhibit gastric emptying and slow intestinal transit, a phenomenon often referred to as the "ileal brake".3 This slowing of nutrient passage through the gut contributes to feelings of fullness and satiety, thereby helping to limit meal size and overall energy intake. While direct effects of T1R2/T1R3 activation on gut smooth muscle are less clearly defined, the hormonally mediated pathway is well-established. For comparison, activation of the umami receptor T1R1/T1R3 in the colon has been shown to directly elicit peristaltic reflexes 29, indicating that T1R family members can indeed directly influence motility patterns. The collective impact of these gut-level T1R activities is a sophisticated regulation of nutrient digestion, absorption, and transit, all coordinated with central appetite control mechanisms via the gut-brain axis.12

4.2. Endocrine Responses and Metabolic Control

The influence of T1R activation extends to systemic endocrine regulation, most notably through anticipatory responses triggered by oral taste and direct effects on pancreatic hormone secretion.

Cephalic Phase Responses (CPRs): Oral Sweet Taste and Pre-absorptive Hormone Release:
The sensory experience of sweet taste in the mouth, even before nutrients are absorbed, can trigger what are known as cephalic phase responses (CPRs). These include an early rise in insulin secretion (Cephalic Phase Insulin Release - CPIR) and, as more recent evidence suggests, GLP-1 release.30 These anticipatory hormonal surges are thought to prepare the body for the impending arrival of glucose and other nutrients, potentially improving subsequent glucose tolerance and metabolic handling.30 CPRs are primarily mediated by neural pathways, with the vagus nerve playing a critical role in transmitting signals from oral taste receptors to the pancreas and gut.30 One hypothesis posits that oral glucose-driven GLP-1 release from enteroendocrine cells might act as an early incretin signal that mediates the insulin CPR neurally through a vago-vagal reflex.30 The ability of NNS to consistently elicit robust CPRs, particularly CPIR, remains a subject of debate, with some studies showing effects while others find none, especially with chronic exposure.31 This discrepancy may relate to the lack of caloric reinforcement with NNS, potentially weakening the learned association over time.
Direct Effects on Pancreatic β-cell Function:
Beyond neurally mediated CPRs, T1R2/T1R3 receptors located directly on pancreatic β-cells

provide another layer of metabolic control. Activation of these pancreatic sweet taste receptors by various sweeteners, including NNS (e.g., sucralose, saccharin) and certain sugars like fructose, can directly stimulate insulin secretion or potentiate glucose-stimulated insulin secretion (GSIS).1 This represents a non-metabolic pathway for insulin release, as it does not require the sweetener to be metabolized by the β-cell to generate ATP.6 The physiological significance of this direct pancreatic sweet sensing is that it allows the β-cell to respond to the presence of certain sugars or their mimics even before substantial changes in blood glucose occur, or to fine-tune insulin release in response to specific nutrient profiles. This effect is dependent on functional T1R receptors, as it can be abolished by T1R3 inhibitors or in T1R2-knockout mice.6

4.3. Neuro-Gustatory Pathways and Central Regulation

The journey of a sweet taste signal from the tongue to conscious perception and behavioral response involves complex neural pathways that also interface with central systems regulating homeostasis.

Ascending Gustatory Pathways:
Taste information originating from T1R activation in TRCs is conveyed by afferent fibers of the facial (VII), glossopharyngeal (IX), and vagus (X) cranial nerves to the rostral portion of the nucleus of the solitary tract (NST) in the medulla oblongata.7 From the NST, signals ascend via the parabrachial nucleus (PBN) in the pons to the ventral posteromedial nucleus, pars parvicellularis (VPMpc) of the thalamus. Thalamic neurons then project to the primary gustatory cortex, located in the frontal operculum and anterior insula, where taste quality is identified, discriminated, and associated with memory.13
Limbic Projections and Hedonics:
In parallel to the pathway leading to conscious taste perception, gustatory signals from the PBN also project to various limbic system structures, including the lateral hypothalamus (LH), the central nucleus of the amygdala (CeA), and the bed nucleus of the stria terminalis (BNST).13 These projections are crucial for imbuing taste stimuli with hedonic value (i.e., pleasantness or unpleasantness) and for driving motivated behaviors such as food seeking and consumption. The connections between the insular cortex and the amygdala are thought to be particularly important in mediating the emotional and appetitive impact of taste.38
Central T1R Receptor Functions:

The expression of T1R2/T1R3 receptors within the brain itself, particularly in hypothalamic nuclei like the ARC and PVN, allows for direct central sensing of glucose and potentially other sweet compounds.1 These hypothalamic T1Rs function as nutrient sensors that contribute to the regulation of energy balance, glucose homeostasis, and food intake, complementing the peripheral signals received from the gut and pancreas. The expression of these central T1Rs can be modulated by the nutritional state of the animal, such as during food deprivation or in conditions of obesity, indicating their dynamic involvement in energy regulation.4

Neural Plasticity in Taste and Metabolic Sensing:

The gustatory system is not static but exhibits considerable neural plasticity. Environmental factors, including dietary composition and hormonal status, can induce structural and functional changes in taste receptor cells and downstream neural pathways, particularly during critical developmental periods.40 These plastic changes are heavily influenced by the body's homeostatic systems, suggesting that the way an organism perceives and responds to taste can adapt to its internal physiological state and external nutrient availability.40 Such adaptations can have long-lasting consequences for food preferences, eating behavior, and metabolic health.

4.4. Emerging Roles in Diverse Physiological Systems

The functional relevance of T1R receptors is continually expanding beyond their roles in classical gustation and gut-pancreatic metabolic control.

Musculoskeletal Health:

Recent studies have unveiled an unexpected role for T1R family members in the musculoskeletal system. T1R3, for instance, appears critical for nutrient status detection in skeletal muscle, influencing pathways like mechanistic target of rapamycin complex 1 (MTORC1) signaling and autophagy, processes vital for muscle protein balance.1 Both T1R1 and T1R3 are implicated in myogenesis (muscle formation). In bone, the T1R2/T1R3 sweet taste receptor system has been shown to regulate postnatal bone mass and remodeling. Global loss of either T1R2 or T1R3 in mice can lead to increased cortical bone mass, suggesting these receptors normally play a role in bone resorption or formation, possibly by influencing the lineage commitment of mesenchymal stem cells in the bone marrow towards osteoblasts (bone-forming cells) or adipocytes.1 These findings link systemic nutrient sensing directly to the maintenance of muscle and bone health, with potential implications for age-related

conditions like sarcopenia and osteoporosis.

Adipose Tissue Biology:

T1R2 and T1R3 receptors are functionally expressed in adipocytes, where they are proposed to regulate adipogenesis and lipolysis.1 Studies in T1R2 knockout mice subjected to high-fat diets have shown alterations in fat mass accumulation and energy expenditure, suggesting that these receptors contribute to the body's response to nutrient surplus and the development of obesity.20

Immune Modulation:

An intriguing, non-canonical role for T1R receptors has emerged in the immune system. In the airway epithelium, T1R2/T1R3 receptors participate in innate immune responses by detecting bacterial products and triggering defense mechanisms.5 Furthermore, the expression of T1R3 in lymphocytes and thymus suggests a broader, though less defined, role for these "taste" receptors in immune surveillance and modulation.6

The collective evidence underscores that T1R receptor activation initiates a "sweet reflex arc," a multi-layered, integrated physiological response. This arc begins with sensory detection (oral or extra-oral T1Rs), proceeds through afferent signaling (nerves, hormones), involves central processing (brainstem, hypothalamus, cortex), and culminates in diverse efferent outputs (hormone secretion, altered gut motility, metabolic adjustments, behavioral modifications). This intricate system ensures an optimized and coordinated response to sweet/energy-containing nutrient intake, from anticipation through digestion and post-absorptive utilization. Moreover, T1R systems, particularly those involving the versatile T1R3 subunit, appear to function as "chemostats" for critical energy substrates like glucose and amino acids. They not only detect the presence of these molecules but also actively participate in feedback loops that regulate their flux, absorption, and utilization, thereby contributing to the maintenance of metabolic equilibrium. Given these extensive and critical roles in normal physiology, it is logical to infer that dysregulation of T1R expression or function—whether due to genetic predispositions, chronic dietary habits, or underlying disease states—could be a significant contributing factor to the pathogenesis of various metabolic disorders, including obesity, type 2 diabetes, and potentially conditions like sarcopenia and osteoporosis. For instance, altered T1R

signaling in the gut or pancreas could impair incretin and insulin responses, while dysregulation in hypothalamic T1Rs could disrupt appetite control and energy balance. Indeed, disordered expression of sweet taste receptors has been observed in patients with type 2 diabetes [6], highlighting the clinical relevance of these chemosensory pathways.

Table 3: Key Hormones and Physiological Processes Regulated by T1R Activation

Physiological System/Process	Key Hormones/Mediators Involved	Primary Site of T1R Action (Sweet/Umami)	Effect of T1R Activation (Sweet unless specified)	Overall Physiological Consequence
Glucose Homeostasis	Insulin, GLP-1, GIP	Oral Cavity (CPRs), Gut EECs (L, K-cells), Pancreatic β-cells	$\uparrow$Insulin secretion (cephalic & direct), $\uparrow$GLP-1 secretion, $\uparrow$GIP secretion	Improved glucose tolerance, Preparation for nutrient load, Enhanced glucose disposal
Appetite Regulation	GLP-1, PYY, Serotonin (5-HT), Ghrelin (potential), Leptin (modulator)	Gut EECs, Stomach, Hypothalamus	$\uparrow$Satiety signals (GLP-1, PYY, 5-HT), $\downarrow$Hunger signals (potential ghrelin modulation), Direct	Reduced food intake, Meal termination, Long-term energy balance regulation

			hypothalamic nutrient sensing	
Gut Motility	GLP-1, PYY, Serotonin (5-HT), GLP-2, CGRP (Umami)	Gut EECs, Enteric Neurons, Colon (Umami)	$\downarrow$Gastric emptying, $\downarrow$Intestinal transit (ileal brake via hormones), $\uparrow$Peristalsis (Umami, direct in colon), GLP-2 mediated effects	Optimized nutrient exposure time, Satiety, Coordinated nutrient passage
Nutrient Absorption	SGLT1, GLUT2, GLP-1, GIP, GLP-2, PKCβII	Gut Enterocytes, Gut EECs	$\uparrow$SGLT1 expression/activity, $\uparrow$Apical GLUT2 trafficking/activity, Enhanced glucose absorption	Optimized uptake of dietary carbohydrates
Bone Metabolism	(complex, involves local factors)	Bone (Osteoblasts, Osteoclasts, Marrow Stromal Cells)	Regulation of bone mass & remodeling (KO studies show $\uparrow$bone density), Modulates osteoblast/adipo	Maintenance of bone health, Potential link to osteoporosis pathogenesis

			cyte differentiation in marrow	
Muscle Function	MTORC1, Autophagy regulators	Skeletal Muscle	Nutrient status detection, $\uparrow$Myo genesis (T1R1/T1R3 for umami), Regulation of protein balance	Muscle maintenance and growth, Potential link to sarcopenia pathogenesis
Adipose Tissue Biology	(complex, involves local factors)	Adipocytes	Regulation of adipogenesis & lipolysis	Modulation of fat storage and metabolism, Potential role in obesity development
Innate Immunity	Nitric oxide, Antimicrobial peptides	Airway Epithelium	Detection of bacterial compounds, Initiation of local immune defense	Protection against respiratory pathogens
Male Fertility	(local testicular factors)	Testes (Spermatozoa)	Essential for normal sperm function and fertility (T1R3)	Reproductive competence

CPRs: Cephalic Phase Responses; EECs: Enteroendocrine cells; CGRP: Calcitonin Gene-Related Peptide. This table provides a summary; many mechanisms are complex

and involve multiple interacting factors.

5. Nutritive vs. Non-Nutritive Sweeteners (NNS): Differential Physiological Consequences via T1R Pathways

Both nutritive sweeteners (caloric sugars like glucose and sucrose) and non-nutritive sweeteners (NNS, such as saccharin, sucralose, and aspartame) exert their sweet taste by activating the same T1R2/T1R3 receptor complex in the oral cavity.[2] This shared activation extends to extra-oral T1Rs located in the gut, pancreas, and other tissues.[14] However, despite this common initial molecular interaction, the downstream physiological consequences of consuming nutritive versus non-nutritive sweeteners can differ significantly, primarily due to the presence or absence of calories and the subsequent metabolic feedback.

A key distinction lies in the "uncoupling" of sensory input from metabolic consequence with NNS. Sweet taste has evolved as a reliable indicator of caloric content, primarily carbohydrates.[6] Nutritive sweeteners fulfill this expectation by providing both the sweet sensation and the subsequent energy. NNS, however, activate the sweet taste receptors but deliver negligible or no calories.[37] This sensory-metabolic mismatch, particularly with chronic exposure, is hypothesized to disrupt learned associations between taste and energy, potentially leading to maladaptive physiological and behavioral responses.[32] The body's predictive homeostatic mechanisms, which rely on consistent cue-consequence relationships, may be "confused" or "degraded" by the repeated experience of sweetness without caloric reward.

Cephalic Phase Responses (CPRs):
Nutritive sweeteners like glucose are generally effective at eliciting CPRs, including pre-absorptive insulin (CPIR) and GLP-1 release.30 These responses are thought to optimize the handling of incoming nutrients. The effects of NNS on CPRs are more contentious. Some acute studies suggest that NNS can trigger GLP-1 release 37 or even CPIR. However, other

studies, particularly those involving repeated exposure or specific NNS, report no significant CPIR 31 or even an impairment of CPRs over time.32 It has been proposed that chronic NNS consumption may weaken the validity of sweet taste as a predictor of caloric intake, thereby diminishing the magnitude or reliability of CPRs, even when caloric sweeteners are subsequently consumed.32

Gut-Level Effects:

In the gut, both sugars and NNS can stimulate T1R2/T1R3 on EECs, leading to the release of incretin hormones like GLP-1 and GIP.3 Both types of sweeteners have also been shown to influence the expression and activity of glucose transporters such as SGLT1 and GLUT2.4 However, the long-term physiological impact of stimulating these pathways with NNS, in the absence of a significant nutrient load to be processed, is not fully understood and could lead to adaptive changes in receptor sensitivity or hormone effectiveness.

Pancreatic Effects:

NNS can directly activate T1R2/T1R3 receptors on pancreatic β-cells, stimulating insulin secretion.6 For example, sucralose ingestion prior to a glucose load has been reported to increase insulin concentrations in obese individuals compared to water.37 This insulin release occurs without a concomitant rise in blood glucose from the NNS itself. While potentially beneficial acutely in some contexts, chronic stimulation of insulin release without appropriate glycemic signals could contribute to β-cell stress or insulin resistance over time.

Metabolic and Homeostatic Outcomes:

The long-term impact of NNS consumption on overall metabolic health is a subject of intense research and debate. While NNS are often used with the goal of reducing calorie intake and managing body weight, some animal studies and human observational data have paradoxically linked chronic NNS use to adverse metabolic outcomes, including weight gain, increased adiposity, insulin resistance, and glucose intolerance.32 The mechanisms proposed to explain these effects include the aforementioned weakening of CPRs, disruption of the taste-calorie relationship leading to compensatory overeating of caloric foods, direct effects of NNS on extra-oral T1Rs, and alterations in the gut microbiota.37

The chronic activation of extra-oral T1Rs by NNS, without the accompanying nutrient load and its associated metabolic feedback, represents a sustained physiological perturbation. For instance, repeated, "inappropriate" stimulation of GLP-1 or insulin release (i.e., in the absence of significant hyperglycemia to manage) by NNS could,

over time, lead to receptor desensitization, impaired signaling efficiency, or other maladaptive cellular responses in the gut, pancreas, or even the brain. These subtle, chronic effects on systemic T1R pathways may contribute to the metabolic dysregulation observed in some studies of long-term NNS use, distinct from the acute uncoupling of oral taste from calories.

Gut Microbiota:
NNS can significantly alter the composition and function of the gut microbiota.37 These changes, sometimes referred to as dysbiosis, can independently influence host metabolism, contributing to glucose intolerance and other metabolic disturbances. While not a direct effect of T1R activation, these NNS-induced shifts in the gut microbial ecosystem represent an important indirect pathway through which NNS can impact systemic physiology.
The inconsistent findings across NNS studies—some indicating benefits, others harm, and some neutral effects—may be partly attributable to considerable individual variability. Factors such as genetic polymorphisms in *TAS1R* genes (which could alter receptor sensitivity or function), baseline gut microbiome composition (which influences NNS metabolism and host response), duration and type of NNS exposure, and underlying metabolic status of the individual likely play significant roles in determining the ultimate physiological impact of NNS consumption. This highlights the complexity of NNS effects and suggests that a "one-size-fits-all" conclusion regarding their health impact may be inappropriate.

6. Conclusion and Future Perspectives: T1R Receptors as Integrated Physiological Modulators

The journey of T1R sweet taste receptors from specialized sensors in the oral cavity to multifaceted players in systemic physiology represents a significant evolution in our understanding of nutrient sensing and metabolic regulation. It is now evident that these receptors serve a dual capacity: mediating the conscious perception of sweet taste, which guides food choice and elicits anticipatory metabolic responses [1], and acting as direct chemosensors in a wide array of extra-oral tissues, where they initiate

local and systemic physiological adjustments to nutrient availability.[6] The interconnectedness of these oral and extra-oral T1R functions forms an integrated system that is crucial for managing nutrient intake, optimizing digestion and absorption, and maintaining overall energy homeostasis.

The widespread physiological roles of T1Rs, particularly in the regulation of glucose metabolism, hormone secretion, appetite control, and even musculoskeletal and adipose tissue biology, position them as intriguing potential therapeutic targets for a range of conditions, including obesity, type 2 diabetes, sarcopenia, and osteoporosis.[1] However, translating this potential into effective therapies is fraught with challenges. The systemic expression of T1Rs means that interventions targeting oral receptors (e.g., with taste modifiers) could have unintended off-target effects elsewhere in the body. Conversely, developing strategies for tissue-specific modulation of extra-oral T1Rs will require a much deeper understanding of their localized functions and regulatory mechanisms. The complex and sometimes paradoxical effects of NNS further underscore the difficulties in predictably manipulating these pathways.

Despite considerable progress, many questions remain, paving the way for exciting future research. Key areas include:

- **Elucidation of Extra-Oral Signaling:** A comprehensive characterization of the precise signaling pathways downstream of T1R activation in all extra-oral tissues is needed, along with identification of their full range of endogenous and exogenous ligands.
- **Long-Term NNS Effects:** Rigorous, long-term studies in humans are essential to clarify the systemic consequences of chronic NNS consumption on various T1R-expressing tissues and overall metabolic health.
- **Genetic Variability:** Investigating the impact of *TAS1R* gene polymorphisms on individual differences in sweet taste perception, food preferences, NNS responses, and susceptibility to metabolic diseases is crucial for personalized nutrition and medicine.[10]

- **T1R-Microbiome Interactions:** The interplay between T1R signaling, dietary sweeteners (nutritive and non-nutritive), and the gut microbiome warrants further exploration, as this axis likely plays a significant role in metabolic outcomes.
- **Neural Circuitry of CPRs:** Further delineation of the precise vago-vagal reflex pathways and central neural circuits that mediate cephalic phase responses triggered by oral T1R activation is necessary.[30]
- **Alternative T1R Complexes:** The physiological relevance and functional characteristics of potential T1R3 homodimers or T1R3 in complex with other, as-yet-unidentified partners, need to be established.

T1R signaling pathways are not merely passive detectors of external nutrient cues; they are dynamically modulated by the body's internal metabolic and hormonal milieu. For example, factors like leptin, insulin, and overall nutritional status can influence T1R expression and sensitivity, particularly in central regulatory sites like the hypothalamus.[3] This indicates that T1Rs function as critical integration points where external sensory information is interpreted within the context of the body's current energy status, allowing for highly adaptive and fine-tuned physiological and behavioral responses. This bidirectional communication is fundamental for maintaining homeostasis.

The diverse physiological effects initiated by T1R activation in response to dietary components underscore how food constituents can act with a specificity akin to pharmacological agents, exerting distinct molecular and systemic effects through these receptor pathways. This "pharmacology of food" perspective, where nutrients and even non-nutritive compounds are viewed as bioactive molecules interacting with specific cellular targets like T1Rs, could inform more precise dietary recommendations and spur the development of functional foods or nutraceuticals designed to selectively modulate T1R pathways for targeted health benefits.

Given the extensive distribution and multifaceted roles of T1R receptors, future research must increasingly adopt a systems physiology approach. While studies

focusing on isolated tissues or specific pathways provide valuable mechanistic insights, they are often insufficient to capture the integrated role of T1Rs in overall health and disease. Understanding how T1R-mediated signals from disparate locations such as the gut, pancreas, and brain converge, interact, and are modified by chronic dietary patterns or disease states requires integrative experimental designs and computational models. Such an approach will be paramount to fully unraveling the complexities of this sophisticated chemosensory network.

In conclusion, the study of T1R receptors has transitioned from the realm of taste physiology to become a central theme in understanding systemic nutrient sensing and metabolic control. Continued exploration of this intricate network holds considerable promise for developing novel strategies to promote health and combat a spectrum of metabolic and other chronic diseases.

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