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Insights on modulators in perception of taste modalities: a review

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Abstract

A major challenge in taste research is to overcome the flavour imperfections in food products and to build nutritious strategies to combat against obesity as well as other related metabolic syndromes. The field of molecular taste research and chemical senses has contributed to an enormous development in understanding the taste receptors and mechanisms of taste perception. Accordingly, the development of taste-modifying compounds or taste modulators that alter the perception of basic taste modalities has gained significant prominence in the recent past. The beneficial aspects of these substances are overwhelming while considering their potential taste-modifying properties. The objective of the present review is to provide an impression about the taste-modulating compounds and their distinctive taste-modifying properties with reference to their targets and proposed mechanisms of action. The present review also makes an effort to discuss the basic mechanism involved in oro-gustatory taste perception as well as on the effector molecules involved in signal transduction downstream to the activation of taste receptors.

Key words: **Cluster of differentiation 36: CD36: G protein-coupled receptors: Transient receptor potential melastatin 5: Taste modulators: T1R: T2R**

Introduction

Taste perception plays a significant role in food preference and determines the intake of foods with pleasurable taste while evading those that are unpleasant. Taste perception is mediated through binding of tastants with their specific receptors and this process is altered by the molecules that interrupt their interaction. Processing of taste information is crucial for facilitating food preference and creating familiar dietetic habits[1]. Taste modalities such as umami and sweet contribute to an evolutionary role in nutrition as a selective supplier of proteins and energy-rich diet, respectively. Sour and bitter tastes are involved in the evasion of detrimental or spoiled foods[2]. Salty taste ensures proper dietary electrolyte balance. In addition, recent compelling evidence demonstrates that lipids can be perceived by definite receptors in taste cells and, hence, fat taste is slowly attaining the status of a sixth taste modality[3–5].

The incidence of obesity and obesity-associated disorders such as type 2 diabetes and the metabolic syndrome has increased pointedly in the previous decades, attained epidemic levels and consequently is becoming a most important worldwide health issue[6]. Increasing concerns regarding the health and quality of life have inspired individuals to prevent the consumption of foods that are rich in fat or sugar[7,8]. Hence, identifying taste in food choice and analysing consumption behaviour will help in understanding the fundamentals involved in body weight maintenance and the development of obesity.

A taste mimetic is a substance that possesses the distinctive organoleptic qualities of a food product. On the other hand, taste modulators are substances that could either enhance or inhibit the perception of a specific taste modality[9]. Modulation of taste responses may occur at numerous phases throughout the course of taste perception, which includes the interaction of tastant molecules with saliva[10]. Both taste mimetics and taste modulators are being discovered as tools for basic taste research and have some absolute applications in the food industry as well as in the pharmacological industry. Drug discoveries for various medical conditions including asthma and respiratory tract infections[11–13], CVD[14] and metabolic disorders[15] are based on taste modulators. In the present review, we focus on both the taste mimetics and taste modulators that reliably modify various taste responses at the receptor level.

Sweet taste

The taste receptors T1R2 and T1R3 (human taste receptor type 1 members 2 and 3) are the principal receptors for sweet taste. These receptors can sense numerous, chemically varied sweetened compounds including both the natural and artificial non-energetic sweeteners, sweet-tasting proteins, natural sugars and certain specific D-amino acids[16–18]. In the absence of T1R2, homodimers of T1R3 respond to both monosaccharides

Abbreviations: CALHM1, Ca homeostasis modulator 1; CD36, cluster of differentiation 36; GPCR, G protein-coupled receptor; IP_3, inositol 1,4,5-trisphosphate; L-Arg, L-arginine; MSG, monosodium glutamate; PKD2L1, polycystic kidney disease 2-like 1 protein; PLC $\beta 2$, phospholipase C $\beta 2$; PROP, 6-*n*-propylthiouracil; T1R, taste receptor type 1; T2R, taste receptor type 2 (bitter taste receptor); TRPM5, transient receptor potential melastatin 5.

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as well as to disaccharides. These receptors belong to the class C G protein-coupled receptors (GPCR) family that has definite structures including an N-terminal extracellular domain linked to the seventh transmembrane domain through a sharp cysteine-rich domain[19,20]. This family of GPCR contain a bilobate domain with two lobes being separated by a cleft[21,22]. The stimulation of sweet taste receptors, irrespective of their expression pattern either in the taste bud cells of the tongue or in other areas of the oral cavity, results in the activation of α-gustducin. Phospholipase C β2 is subsequently stimulated, leading to the release of stored intracellular Ca^{2+} and activation of transient receptor potential melastatin 5 (TRPM5) (Fig. 1). This sequence results in membrane depolarisation and the release of neurotransmitters, which can then activate afferent sensory neurons that send signals to brain centres involved in taste perception[23].

Sweet tastants and sweet taste modifiers

Sweeteners or sweet inducers are extensively used as dietary supplements, food additives and pharmaceuticals[24]. Sweeteners can be classified into distinctive types according to their intrinsic properties, origin (artificial or natural), nutritional value (energy-containing or non-energy-containing), sweetness potency and their stability[25].

The most common natural sweeteners are neohesperidine, steviol glycosides, thaumatin and dihydrochalcone. A bioengineered synthesis pathway concerning glucosyltransferase optimisation using *Saccharomyces cerevisiae* has led to a new generation of stevia sweeteners[26]. Among steviol glucosides, two molecules, namely, rebaudioside A and stevioside, have been established as standard sweeteners[27,28]. In addition, cycloartane-type saponins, namely, abrusosides from the leaves of *Camellia sinensis* and *Abrus precatorius* L., could serve as effective sweet tastants[29]. Accordingly, the sweet-tasting proteins can also be perceived as promising natural sweeteners due to their high sweet effectiveness and sensory properties. The plant proteins, namely, brazzein, thaumatin, neoculin, monellin and miraculin, have been recently identified as sweet-tasting molecules[30]. Among these, miraculin and neoculin have the uncommon, rare property of adapting sourness into sweetness. Moreover, sensory analysis has revealed that miraculin could represent a natural sugar mimetic used in ancillary beverages[31]. However, the leading problem deterring in the use of sweet-tasting proteins in diet applications is the obstacle of gaining proteins from their natural source.

In addition to the natural sweeteners, artificial sweeteners are also currently in use and the prominent ones are acesulfame K, cyclamates, aspartame, saccharin, neotame and sucralose[32]. Among these, sucralose and neotame are chlorinated derivatives of sucrose and aspartame, respectively (Table 1). In addition, a recently developed dipeptide, advantame, is an excellent heat-stable sweetener that is 20 000 times sweeter than sucrose[33].

Sweet taste receptors are subjected to both positive and negative allosteric modulation. Screening of the compound library for molecules that positively regulate the *in vitro* responses of the heterologous sweet taste receptors led to the identification of a sweet taste-enhancing molecule[34,35]. This substance, termed as 'SE-1', predominantly enhanced the stimulation of the sweet taste receptor if intensified with sucralose; however, it displayed inadequate or negative modulation when tested with other sweet taste substances[34]. The structural variation of SE-1 developed by molecular modelling and site-directed mutagenesis gave rise to strong derivatives, which are labelled as SE-2 and SE-3, that are slightly increased in sweetness compared with sucrose[35]. In addition, polyols are the larger consumed fraction of sweet enhancers due to their lack of cariogenic properties[36,37]. Therefore, polyols have been used as food additives that effect the hydrogenation of reducing sugars which are found naturally in vegetables and fruits. Many of the polyols including sorbitol, maltitol, mannitol, isomaltose, lactitol, erythritol and xylitol act as effective sweet modifiers.

In contrast, some other compounds inhibit the activity of sweet taste receptors (Table 1). Lactisole is one such compound that inhibits the human sweet taste receptor but not that of the rodent[38]. It was shown that this substance does not bind to the sweet taste receptor subunit T1R2, but instead interacts with T1R3[39]. In addition, compounds isolated from the leaves of the plant *Gymnema sylvestre*, namely, gymnemic acid and gurmarin peptide, are also sweetness-suppressing molecules that act specifically on rodent sweet taste receptors[40,41].

Bitter taste

Bitter taste is normally considered to be an unfavourable taste attribute in most food products and elicits a stereotypical innate response by mammals to avert consumption of harmful food constituents. Bitter taste is identified by the receptors that are encoded by the *Tas2r* gene family expressed in type II taste bud cells and have a sequence length of about 300–330 amino acids with a short extracellular N-terminus. Bitter taste receptors (taste receptors type 2; T2R) belong to class A GPCR and have ligand-binding sites in their transmembrane sections[42]. In taste bud cells, T1R (which sense umami and sweet tastes) and T2R are generally expressed in a non-overlapping array[43], implying a partition of receptor cells that detect appetitive *v.* aversive stimuli. In contrast to T1R, the T2R are commonly believed to act as monomers; nevertheless, current evidence proposes that they may also form heterodimers[44]. The broad and overlapping range of ligand sensitivities of T2R assures that this family of receptors responds to an enormous range of bitter-tasting chemicals.

Bitter taste signalling is initiated by the interaction of the ligand with its cognate T2R that brings a conformational change in the receptor and triggers the heterotrimeric intracellular G-protein complex[45]. When activated, G_{α}-gustducin becomes relieved from the complex and activates phospholipase C $\beta 2$ (PLC $\beta 2$)[46] (Fig. 1). PLC $\beta 2$ further acts on phosphatidylinositol-4,5-diphosphate to generate diacylglycerol and inositol 1,4,5-trisphosphate (IP_3). The generated IP_3 releases Ca^{2+} ions from the endoplasmic reticulum and opens the TRPM5 which leads to membrane depolarisation and subsequent neurotransmitter release[45,47].

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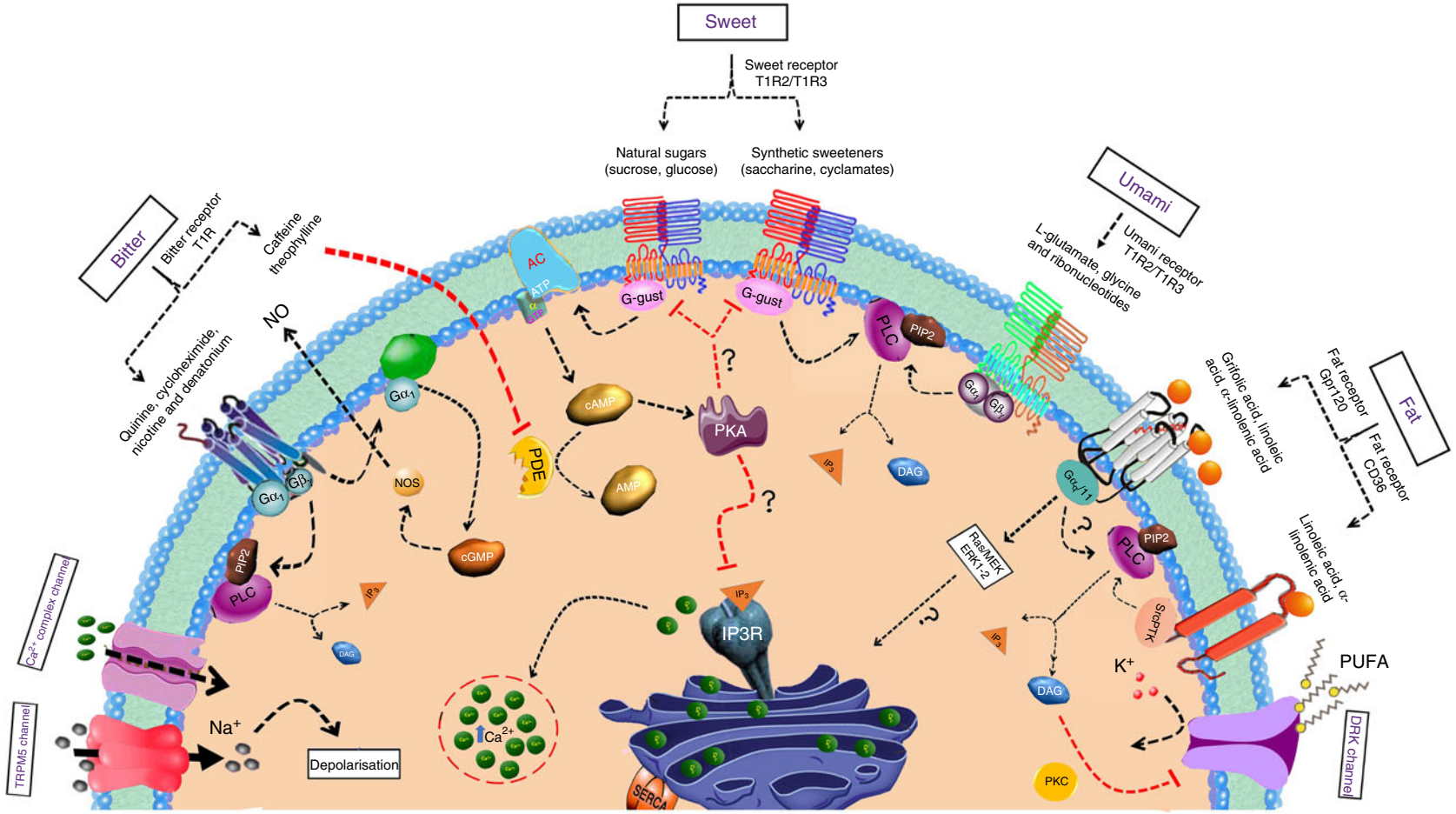

Fig. 1. Mechanisms of sweet, umami, bitter and fat taste perception by taste bud cells. The taste qualities of sweet, umami or bitter are sensed by the G protein-coupled receptor (GPCR) expressed on type II taste bud cells. Whereas, fat taste perception is mediated by both GPCR and cluster of differentiation 36 (CD36). Upon activation of GPCR, the signal is transmitted through βγ subunits Gβγ and α-gustducin to the downstream effectors phospholipase C $\beta 2$ (PLC) and adenylate cyclase (AC), respectively. PLC $\beta 2$ activation generates two second messengers, namely, diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP_3). IP_3 acts on IP_3 receptors on endoplasmic reticulum (ER) and increase the intracellular calcium levels. Whereas the AC mediates cyclic AMP (cAMP) production, which block the potassium channels on the plasma membrane. Both these pathways ultimately lead to the depolarisation of the taste receptor cells which lead to the opening of the transient receptor potential melastatin 5 (TRPM5) ion channel. Consequently, ATP is released through the Panx1 hemichannel into the extracellular space, which stimulates multiple targets including the gustatory afferent nerve fibres or the adjacent presynaptic cells which releases the neurotransmitters including serotonin (5-hydroxytryptamine; 5-HT) and noradrenaline into the synaptic cleft. PIP2, phosphatidylinositol 4,5-bisphosphate; T1R, taste receptor type 1; PDE, phosphodiesterase; PKA, protein kinase A; MEK, MAPK/ERK; MAPK, mitogen-activated-protein kinase; ERK, extracellular signal–regulated kinase; PKC, protein kinase C; DRK, delayed rectifying potassium; IP3R, IP_3 receptor; SERCA, sarcoendoplasmic reticulum calcium transport ATPase. For a colour figure, see the online version of the article.

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Table 1. Characteristics of candidate sweet and bitter taste modifiers/tastants and their associated mechanism of chemoreception

Compounds	Form	Mode of action	Source	Application/properties	Reference
Sweet tastants/modifiers					
Agonists – cyclamates, glucose, sucrose and saccharin					
Rebaudioside A and stevioside	Natural stevia sweetener	Involves the synergetic effect of steviols and their aglycone steviol glycosides on taste receptors and signal through interaction with TRPM5	*Stevia rebaudiana Rebaudiana bertoni*	Reduce postprandial blood glucose levels Enhance glucose-induced insulin secretion in TRPM5-dependent manner	Philippaert *et al.* (2017)[140]; Anton *et al.* (2010)[141]
MCL	Natural sugar mimetic	The taste-altering effect of MCL was mediated through T1R2	*Richadella dulcifica* *Synsepalum dulcificum*	Promised low-energy sweetener Modify the taste of sour fruits	Sanematsu *et al.* (2016)[142]; Misaka *et al.* (2013)[143]
NCL	Taste-modifying protein	Acts through T1R2/T1R3 in a pH-dependent and -independent stimulation interface with histidine and Tyr65/Val72, respectively	*Curculigo latifolia*	Alter sourness into sweetness Sweeten amino acid-enriched foods	Koizumi *et al.* (2015)[144]; Nakajima *et al.* (2011)[145]
ACK, ASP, neotame, etc.	Artificial sweeteners	Through binding to the heterodimeric GPCR (T1R2 and T1R3)	Sucralose and neotame are chlorinated derivatives of sucrose and aspartame	ACK combined with other sweeteners to give added sucrose-like taste Neotame is between 7000 and 13 000 times sweeter than sucrose	Li *et al.* (2002)[146]
Lactisole and gymnemic acid	Sweet-suppressing molecules	Block the T1R3 monomer of the sweet taste receptor T1R2/T1R3	Colombian arabica coffee beans and *Gymnema sylvestre*	Production of jams and jellies Block the sweetness of natural and artificial sweeteners	Jiang *et al.* (2005)[39]; Sanematsu *et al.* (2014)[147]
Bitter tastants/modifiers					
Agonist – alkaloids (for example, nicotine, quinine, caffeine, strychnine), terpenoids (for example, iso-α acid, amarogentine, limonoids) and flavonoids (for example, neohesperedin, epigallocatechin gallate)					
GIV3727 (T2R inhibitor)	Bitter receptor antagonist	Acts as an orthosteric antagonist of *h*T2R31	Derived by high-throughput screening approach	Decrease bitter taste potential of pharmaceuticals and food products	Slack *et al.* (2010)[51]
Probenecid	Bitter taste blocker	Blocks *h*T2R16 by allosteric mechanism and inhibits pannexin 1 channels as well as ATP release	A benzoic acid derivative with antihyperuricaemic property	Treating gout and hyperuricaemia Increase uric acid excretion in the urine	Greene *et al.* (2011)[54]
Enterodiol	Masker for caffeine bitterness	Through interaction with the bitter pharmacophore proton acceptor site F9	A lignan formed on lignan precursors in plants by the action of intestinal bacteria	Reduced bitterness of caffeine solution by about 30 %	Ley *et al.* (2012)[55]
GABA, BCML and ABA	Competitive inhibitors of T2R4	GABA acts as an antagonist, whereas BCML acts as an inverse agonist on T2R4 Pharmacological characterisation led to the identification of ABA as an antagonist for T2R4	GABA synthesised from glutamate via the enzyme glutamate decarboxylase ABA, derivative natural plant hormone	GABA masks the bitter taste of quinine, caffeine, coca and chocolate Aid in exploring the T2R molecular pathways in various tissues	Pydi *et al.* (2014)[56]; Pydi *et al.* (2015)[148]

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Table 1 *Continued*

Compounds	Form	Mode of action	Source	Application/properties	Reference
ACK and ASP	Bitter taste masker	Combination of ASP and ASK had a synergistic bitterness-masking effect of more than 54 % against E-bitartrate	ASP is a methyl ester of natural amino acids – L-phenylalanine and L-aspartic acid, whereas ACK is from the reaction of fluorosulfonyl isocyanate	Act as a valuable bitter masker Efficient bitter taste inhibitor for E-bitartrate	Rachid *et al.* (2010)[149]
Zinc sulfate and sodium cyclamate	Bitter taste inhibitors	Combination of zinc sulfate and sodium cyclamate effectively inhibited denatonium benzoate bitterness (86 %)	Cyclamate is the Na or Ca salt of cyclamic acid	Efficient bitter taste inhibitor for the drug quinine-HCl, denatonium benzoate	Keast *et al.* (2005)[150]
β-Cyclodextrin	Bitter taste masker	The bitter intensities of the drug and its fixation between their β-cyclodextrin complexes show that in the presence of cyclodextrins the bitter taste is minimised	From starch by enzymic conversion	Masking the undesired bitter taste of coffee	Szejtli *et al.* (2005)[151]
Umami peptide (Glu-Glu)	Bitter taste inhibitor	Inhibiting the binding of the bitter ligand to the human taste receptor, hTAS2R16	Soyabean-derived umami peptide	Strongest inhibitor, more effective than probenecid, a *h*T2R16 antagonist	Kim *et al.* (2015)[152]

TRPM5, transient receptor potential melastatin 5; MCL, miraculin; T1R2, taste receptor type 1 member 2; NCL, neoculin; ACK, acesulfame K; ASP, aspartame; GPCR, G protein-coupled receptor; GIV3727, 4-(2,2,3-trimethylcyclopentyl) butanoic acid; T2R, taste receptor type 2 (bitter taste receptor); GABA, γ-aminobutyric acid; BCML, *N*α,*N*α-bis (carboxymethyl)-l-lysine; ABA, abscisic acid.

Bitter tastants/modifiers

A widespread variety of structurally diverse compounds can trigger T2R; however, the efficacy of most of them remains to be pharmacologically determined[48,49] (Table 1). A recent assessment of a bitter compound library comprising both synthetic and natural bitter substances gave rise to the classification of twenty-eight T2R46 agonists, thirty-three T2R14 agonists, and thirty-two T2R10 agonists. The collective activity of all the three receptors is sufficient to perceive half of the tested substances, signifying that these receptors work as 'generalists' in the detection of most bitter substances[43].

A recent study analysed both the promiscuity and selectivity of bitter ligands for human T2R[50]. In this report, the authors proposed that promiscuous bitter compounds activate all the selective T2R while both selective and promiscuous compounds can activate promiscuous T2R. However, no compound is known to activate all twenty-five T2R or no unique compound towards a selective T2R[43,50].

4-(2,2,3-Trimethylcyclopentyl) butanoic acid (GIV3727) was the first T2R inhibitor discovered by employing the high-throughput screening approach of 17 854 compounds, which specifically acts as a competitive inhibitor for T2R31 against acesulfame K[51]. The site-directed mutagenesis and molecular modelling revealed that the binding site of the bitter taste receptors is overlaid with that of the bitter agonists and therefore, this finding describes the competitive mechanism of action and the perceived selectivity of GIV3727 for an individual subset of the human bitter taste receptors[52]. Additionally, probenecid, which was formerly known as an anion transporter channel inhibitor, mostly used as a uricosuric drug[53], was suggested as a bitter taste blocker[52,54]. Moreover, enterodiol, a T2R inhibitor that has appeared to conceal the bitter taste of caffeine, inhibits numerous human bitter taste receptors[55]. This molecule was recognised by the examination of compounds structurally related to the known bitter masking molecule homoeriodictyol. In addition, 3β-hydroxydihydrocostunolide (3HDC) and 3β-hydroxypelenolide (3HP), natural sesquiterpene lactones from edible plants, were recognised as bitter taste receptor blockers which block the responses of T2R46[52]. Ley *et al.*[55] in their *in silico* docking experimentations proposed that the attachment of enterodiol to T2R10 may make an impact on the observed bitter masking effect. Recently, *Nα,Nα*-bis (carboxymethyl)-L-lysine (BCML), γ-aminobutyric acid and (+)-*S*-abscisic acid are suggested as competitive inhibitors of activated T2R4[56]. Among them, BCML was considered as a highly effective T2R antagonist reported until now. Besides, studies classified various effective bitter taste inhibitors such as 5'-AMP, sodium acetate, monosodium glutamate (MSG), and sodium gluconate to inhibit whey protein hydrolysate and offer insights on potential bitter taste inhibitors for the product applications associated with whey protein hydrolysate.

More recently, Kim *et al.*[57] reported on the active umami fraction (F05) of modernised Korean soya sauce and its bitter masking effect on human bitter-taste sensory receptor-expressing cells. This active umami fraction (F05) reduced the human-perceived bitterness along with efficient repression of the intracellular Ca^{2+} response induced by caffeine in the *h*T2R46 and *h*T2R43 bitter taste receptor-expressing cells. Both Glu-enriched oligopeptides and free amino acids are proposed to be vital in the effect of F05 on bitter taste receptors; F05 was also mixed with other bitter components like magnesium chloride and Gly-Leu that partly modulate the action of human bitter taste receptors.

In contrast, bitter-tasting tri-peptides are shown to be more effective in T2R1 stimulation. Among the peptides examined, the bitter tri-peptide Phe-Phe-Phe is the most potent in activating T2R1 with a half maximal effective concentration (EC_{50}) value in the micromolar range[58]. In addition, Melis & Tomassini Barbarossa[59] examined the taste perception of bitter, sweet and umami with the modifications triggered by L-arginine (L-Arg) supplementation. The outcome proposes that L-Arg could be used as a strategic tool to modify taste responses that are related to eating behaviours. L-Arg can enrich the bitterness intensity of 6-*n*-propylthiouracil (PROP), whereas other reports[60,61] have established a suppression of quinine's bitterness.

Umami taste

The term 'umami' was coined in 1909 by Japanese chemist Kikunae Ikeda, and means 'delicious savoury taste'[62]. Binding of the umami tastant, such as free glutamate, in foods to the oral umami taste receptor triggers the umami taste sensation. The typical model of the umami receptor T1R1+T1R3 was reported by Temussi[63] and Chandrashekar *et al.*[17]; it was stated that T1R1 is considered critical for sensing umami taste[64]. The heterodimeric GPCR complex of T1R1 and T1R3 elicits the umami taste when interacting with amino acids, typically MSG, and this interaction occurs synergistically with the 5′-ribonucleotides GMP, IMP and AMP[65]. Furthermore, mGluR1 and mGluR4 were also be identified as the probable receptor candidates for umami taste.

Ligand binding to the T1R1/T1R3 receptor activates Gβ3γ13, which in turn activates PLC $\beta 2$ that catalyses the production of the second messengers IP_3 and diacylglycerol. IP_3 binds with IP_3 receptor IP_3R3 to induce the release of Ca^{2+} from intracellular stores (Fig. 1). The increase in intracellular Ca^{2+} subsequently activates TRPM5, which results in taste cell depolarisation and release of ATP that activates ionotropic purinergic receptors on gustatory afferent nerve fibres[66].

Brain mechanisms underlying the oral perception of umami taste have been well documented. Animal studies revealed that the facial (chorda tympani and greater superficial petrosal), glossopharyngeal and vagus (superior laryngeal) nerves, which make synapses with taste cells, convey umami taste information to the first relay nucleus, the rostral part of the nucleus of the solitary tract, and then the taste information is finally transferred to the insular cortex[67]. The umami tastants such as MSG and IMP activate the same regions of the insular cortex that is known as a primary taste cortex in humans, suggesting that both umami tastants could be similarly recognised[68].

Umami tastant/modifiers

Umami tastants are very important for food seasoning and are widely used in food production. They show many health

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benefits, including reduction in fat deposition, inhibition of weight gain, and decrease in plasma leptin levels in rats[69,70]. Umami tastants were also found to regulate gastrointestinal functions and to decrease the risk of stroke and CHD in adults by reducing Na intake in their diets[71,72]. The umami taste preference is native and associated with protein-rich food uptake[17,45]. Several recent efforts motivated further studies to evaluate the taste properties of umami ingredients and to find new umami substances[73,74] (Table 2).

MSG was the first molecule reported to have umami taste[75]. Later, certain ribonucleotides such as IMP and GMP were discovered to have synergistic properties with MSG[76,77]. In addition, theanine, gallic acid, theogallin[78], *N*-acetylglycine[79], pyroglutamyl peptides[80], glycopeptides[81] and succinoyl amides of amino acids[82] were all reported to have umami taste. Alapyridaine[83], which is a product of the Maillard reaction, and morelid[84] found in morel mushrooms were also found to enhance umami taste.

Cairoli *et al.*[85] evaluated umami taste enhancement by the positive effect of sulfur substitution, where the umami taste enrichment was amplified if the methylene function of the alkyl chain linked to the exocyclic amino function of 5'-GMP was replaced by a sulfur atom. Furthermore, the umami-enhancing potential was declined if there was an oxidation of sulfur atoms to consequent sulfoxides[86].

Moreover, along with these natural and synthesised umami taste-enhancing compounds[69,70], several other investigations demonstrated that a few peptide molecules produced from hydrolysates of fish protein, beef bouillon, or other foods, have umami taste[87–89]. Recently, Rhyu & Kim[90] found that low-molecular-weight acidic peptides (F-IV; 1000> MWP500) were the constituent that contributed to the umami taste of doenjang water extract. Further, Su *et al.*[91] found two novel umami taste-enhancing peptides, an octapeptide and an undecapeptide, from groundnut hydrolysate. Bagnasco *et al.*[92] reported that medium-to-small size polypeptides contributed to the umami taste of hydrolysate of rice middlings.

Fat taste

Recently, there has been a massive upsurge of information and evidence on the oro-gustatory perception of fat taste. Reports indicate that improper oral fat detection may be associated with several complications, including obesity-induced lipotoxicity, diabetes, arterial hypertension, atherosclerosis, etc.[93]. The detection of fat stimuli was thought to depend mostly on olfactory, textural and post-ingestive cues[94]. However, recently, research conducted predominantly on rodent models exposed an additional gustatory element for the detection of long-chain fatty acids[94,95]. In mammals, oro-gustatory sensing of dietary fat is facilitated by fat taste receptors, namely, cluster of differentiation 36 (CD36) and GPR120/40, which are expressed in taste bud cells on circumvallate papillae, fungiform papillae and foliate papillae of the tongue epithelium[4,5]. Fat taste perception involves Ca signalling downstream to the activation of CD36 and GPR120/40, stromal interaction molecule 1-mediated opening of store-operated Ca channels, the release of neurotransmitters from taste bud cells and, finally, stimulation of afferent nerve fibres that transmit the signals to the brain[4,96]. Our recent report suggests that the activation of extracellular signal-regulated kinase signalling cascade downstream to the activation of CD36 by fatty acids regulates Ca homeostasis modulator 1 (CALHM1)-mediated Ca signalling in both human and mouse taste bud cells[5]. TRPM5, a monovalent, non-selective cation channel, is reported to be a probable contributor of fat taste signalling[97]. In addition, the delayed rectifying K channels expressed in taste bud cells are inhibited by PUFA in the diet and this supports their involvement in fat taste perception (Fig. 1). Moreover, toll-like receptor 4 signalling has recently been reported to stimulate consumption of obesogenic foods that are rich in fat and sugar[98].

Fat tastants/modifiers

Like sweet tastants, fat tastants are molecules that may be synthesised in the laboratory or purified from plants that imitate the purpose of fat taste by binding to fat taste receptors (online Supplementary Table S1). Recent research had foreseen that the fatty acid-activated CD36 and GPCR might be the potential target of plant-driven tastants eliciting the fat taste sensation devoid of having any energy value[99]. CD36 and GPR120 agonism with grifolic acid (GA) has been shown to elicit intracellular Ca signalling in both human and mouse taste bud cells[4]. Several selective ligands for free fatty acid (FFA) receptors have subsequently advanced as plausible remedies for type 2 diabetes[100–102]. Therefore, many enduring academic programmes and industries are driven by the aim of improving selective and potent agonists for FFA receptors. Godinot *et al.*[103] synthesised effective agonists for the fat taste receptors GPR120 and GPR40 in mice, which trigger the glossopharyngeal nerve through binding to the receptor. In humans, various reports derived from triangle tests and two-alternative forced choice, and sensory profiling demonstrate that GPR40 agonists were perceived in sip-and-spit tests and bring out a taste similar to that of linoleic acid[103]. A vastly convincing FFA1 agonist TUG-770, with its promising pharmacokinetic and physico-chemical properties, displayed increased glucose tolerance in diet-induced obese mice[104]. Further, through mutational and modelling efforts, the dual synthetic agonists of GPR120/40, including GW9508, NCG21 and NCG46, are emerging as novel ligands with improved pharmacological properties for the fat receptors.

In 2018, Melis *et al.*[105] showed that the alterations of oleic acid perception stimulated by the administration of L-Arg are associated with the PROP taster status of subjects and common variants in *CD36*. Moreover, the low concentration supplementation of L-Arg governed an upsurge in perceived intensity of oleic acid, mostly in medium tasters and PROP non-tasters. Sihag & Jones[106] found that oleoylethanolamide, which acts as an effective agonist of PPAR-α, potentially modifies the expression of CD36 and thereby alters fat taste perception. Consequently, a certain group of hybrid composites of thiazolidinedione PPARγ agonists also revealed therapeutic prospective beyond antidiabetic activity[107]. In addition, Sasaki *et al.*[108] identified that both intraperitoneal (IP) and orally administered D-serine affect feeding behaviour; especially, IP-injected D-serine

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Table 2. Characteristics of candidate umami and salt taste modifiers/tastants and their associated mechanism of chemoreception

Compounds	Form	Mode of action	Source	Application/properties	Reference
Umami tastants/modifiers					
Agonists – L-glutamic acid and L-aspartate					
MSG	Umami taste enhancer	mGluR4 could be a possible chemosensory receptor in taste buds involved in transducing the taste of MSG	Fermentation from sugarbeet molasses and carbohydrate sources	Used to reduce the Na content by 35 % through mixing of low-concentrated NaCl solution with the tastant, MSG	Chaudhari *et al.* (1996)[153]
IMP and GMP	Umami taste enhancers	GMP may operate via ligand-binding domain of the T1R1	Dried *shiitake* mushrooms	Glutamate and 5'-inosinate are contained naturally in various foods, and enhancing umami taste	Kurihara *et al.* (2015)[154]; Zhang *et al.* (2008)[155]
Amides	Umami enhancers	Rubemamine and rubescenamine are able to directly activate T1R1/T1R3 and synergistically modulate the activation of T1R1/T1R3 by MSG	*Chenopodium album* *Zanthoxylum rubsecens*	Release agent migrating from food packaging	Backes *et al.* (2015)[156]
Alapyridaine	Umami enhancer	Relies on GMP synergism with other umami-flavoured food to strengthen taste	Heated sugar/amino acid mixtures as well as in beef bouillon	Might open new opportunities for the manufacture of umami-type savoury foods with low L-glutamate contents	Soldo *et al.* (2003)[83]; Ottinger *et al.* (2003)[157]
Umami peptides	Umami taste modulators	Novel umami peptides constantly reported to show umami taste and elicit signal transduction through the activation of T1R1/T1R3	Fish protein, soya sauce and groundnut hydrolysate	Beneficial to finding new umami substances It will also be useful to investigate the flavour interactions with taste receptor responses	Zhang *et al.* (2017)[158]
Lactisole	Umami taste suppressor	Inhibits *h*T1R2/*h*T1R3 by binding to the TMD of *h*T1R3	Roasted Colombian arabica coffee beans	Production of jams and jellies Enhance fruit flavours by suppressing sweetness of sugar	Xu *et al.* (2004)[159]; Jiang *et al.* (2005)[39]
Clofibric acid	Inhibits umami savoury taste of glutamate	Inhibits glutamate taste perception, presumably via T1R1/T1R3 by allosteric mechanism	A metabolite of the cholesterol-lowering drug clofibrate	Acts as a lipid-lowering drug through inhibition of T1R	Kochem *et al.* (2017)[160]
Salt tastants/modifiers					
Agonists – sodium chloride, lithium chloride, potassium chloride, ammonium chloride					
Sodium aspartate	Salt taste enhancer	Asp-Na act by significantly suppressing the glossopharyngeal nerve response to quinine hydrochloride	A non-essential amino acid in sugar cane and sugarbeets	The mixture of NaCl and KCl containing Asp-Na can be used as a salt substitute	Nakagawa *et al.* (2014)[131]
NGCC	Salt taste enhancer	NGCC acts as a salt taste enhancer by modulating the amiloride/benzamil-insensitive Na^+ entry pathways	A synthetic compound made by International Flavors & Fragrances Inc.	NGCC directly activates *h*TRPV1; thereby acts as an effective salt taste enhancer	Dewis *et al.* (2013)[161]; Kim *et al.* (2014)[132]

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Table 2 *Continued*

Compounds	Form	Mode of action	Source	Application/properties	Reference
Maillard reacted peptides	Salt taste modifiers	Maillard reacted peptides modulate salt taste by a direct action on the Bz-insensitive TRPV1t salt taste receptor	Soya protein hydrolysate	Offers advantage over most of the TRPV1t agonists as possible salt taste modifiers	Katsumata *et al.* (2008)[162]; Schindler *et al.* (2011)[163]
Salt mixture and AlgySalt®	NaCl replacer	Saltiness coded within the CNS in cells whose receptive fields include the NaCl-sensitive receptor cells is determined by its ability to drive salt taste receptors	Salt mixture: mixture of KCl, $MgCl_2$ and $CaCl_2$ AlgySalt®, a commercial replacer based on seaweed extracts	Reducing the use of added NaCl in processed meat products	Triki *et al.* (2017)[164]
KCl	Salt substitute	KCl increased the salt perception via depolarising the basolateral membrane of type III taste cells by passing through the tight junctions into the interstitial fluid of the taste buds	KCl is extracted from minerals sylvite, carnallite, and potash	Recommended as a valuable, safe replacer for NaCl in foods products	van Buren *et al.* (2016)[165]
Amiloride	Salt taste inhibitor	Considerably inhibits taste responses to NaCl without affecting other taste modalities in by blocking ENaC	A chemical pyrazine compound inhibiting ENaC	In humans, amiloride suppresses salt taste by about 20 %, indicating that human salt taste perception is mediated, at least in part, by ENaC	Ninomiya *et al.* (1998)[113]; Nagai *et al.* (2001)[166]

MSG, monosodium glutamate; T1R, taste receptor type 1; TMD, transmembrane domain; NGCC, *N*-geranylcyclo propylcarboxamide; TRPV1t, transient receptor potential vanilloid 1; CNS, central nervous system; ENaC, epithelial Na channel.

prevented the acquisition of a preference for high-fat diets. Furthermore, Murtaza *et al.*[109] presented the first evidence for the modulation of fat taste perception in human taste bud cells (hTBC) by ziziphin, purified from the edible fruit of *Zizyphus lotus*, indicating the possibility of using these compounds as a fat taste modifier/fat taste mimetic.

Salt taste

Salty taste in mammals is triggered by two different pathways termed as the amiloride-sensitive (AS) pathway and the amiloride-insensitive (AI), or high-salt, pathway. The former selectively reacts to Na and Li salts, which is facilitated by the epithelial Na channel (ENaC)[110–112]. However, the latter reacts to a wide scale of Na and non-Na salts[113,114]. In rodents, about 65 % of fungiform papillae cells and 35 % of foliate papillae cells displayed efficient amiloride-sensitive Na^+ currents, whereas the circumvallate papillae cells are absolutely insensitive to amiloride even though amiloride-sensitive Na^+ channel proteins and ENaCα mRNA have been spotted in those cells[115]. The AI pathway responses have been described in both a subpopulation of type II bitter taste cells and polycystic kidney disease 2-like 1 protein (PKD2L1)-expressing type III taste cells, which is essential for sour taste perception[116].

The degree of co-occurrence between sour and AI salt responses in type III taste cells is still undefined due to the frequency of cell-to-cell signal transmission in the taste bud[117]. Earlier reports have shown that the type III taste cells are essential for both AI salt taste and sour taste[116,118–120]; nevertheless, it was uncertain whether the expression of these taste receptors was exhibited by distinct or similar populations of taste cells. Furthermore, previous studies have shown that the AI salt taste responses originated in a subset of both sour-responsive taste cells and bitter-sensitive type II cells[116,121]. These findings suggest that the AI salt taste response perception depends mostly on the collective stimulus of different taste cell populations which determine further distinct bitter or sour taste qualities.

Several reports indicated that NaCl-mediated induction and its relative contributions depend on the concentration of Na[122,123]. Accordingly, at lower Na concentrations, there is no direct association of CALHM1 but there is an infusion of Na within ENaC located in taste bud cells[124,125] (Fig. 2). At higher Na concentrations, CALHM1 participates in an even more vital role in the neural response. However, further studies will be required to ascertain whether this is due to the stimulation of elevated thresholds of salt receptors in type II cells or due to other Na-receptive cell types that cooperate with type II cells.

Salt tastants/modifiers

The extreme consumption of salt in the diet is a universal health issue. Various efforts have been made to focus on this issue, involving the evolution of salt substitutes (Table 2) and mounting strategies to lower salt intake[126]. Salty taste is chiefly prompted by Na^+, which is the simple cation known to elicit a pure salt taste transduction in humans. Other than sodium chloride, various mineral and organic salts provoke a salty taste but to a minor extent[127]. Potassium chloride is a promising candidate that acts as a substitute for sodium chloride in low-salt foods[128–130]. However, it has a vulnerable salty taste compared with sodium chloride and, in addition, when used in excessive quantities, it is often linked with bitterness. Other substitutes such as sodium gluconate and ammonium chloride are also recommended but reveal the similar complication of association with bitterness when reacting with KCl, which limits their usage.

Nakagawa *et al.*[131] reported that sodium aspartate is a potent enhancer of salt taste perception. They proposed a research model based on their study results that the sodium aspartate-induced conformational change on ionic channels enhance NaCl and KCl perception. The enhancement of salt taste transduction by sodium aspartate was also confirmed by human sensory assessments.

The compound (+)-(*S*)-alapyridaine has universal taste-enhancing properties. When alapyridaine was introduced in the sensory triangle test, the threshold concentrations for the umami taste of MSG and GMP, for the sweet taste of sucrose and glucose, along with the salty taste of NaCl, were considerably decreased. However, on the other hand, the bitter taste perception of L-phenylalanine and caffeine, along with the sour taste of citric acid, was unaltered[83]. Hence, the taste-enhancing properties of alapyridaine in umami and saltiness prompt developments in the production of low-Na foods for hypertensive patients. Furthermore, Kim *et al.*[132] proposed a unique synthetic compound (*N*-geranylcyclopropylcarboxamide), which modulates amiloride-insensitive Na^+-opening pathways, thereby characterised as a salt taste enhancer. More importantly, as per their report, the *N*-geranylcyclopropylcarboxamide concentration at which it greatly enhanced the benzamil-insensitive Na^+ chorda tympani response in rodents also improved the taste perception of NaCl solutions (60–80 mM) in human subjects. Additionally, choline chloride is also proposed to be a salt taste enhancer[133] and several choline-containing compounds were synthesised to be used as salt taste enhancers[134]. Nevertheless, chlorhexidin (an antiseptic compound) has been revealed to impede salt taste perception generated by the chloride salts of Na, K, ammonium and Li.

Taste-enriching peptides are also used to enhance salt taste perception and hence diminish the usage of sodium chloride content in foods. Kino & Kino[135] synthesised an effective salty taste-enriching dipeptide, Met-Gly, using L-amino acid ligase (Lal) of BL00235 (Lal from *Bacillus licheniformis*) or TabS (Lal from *Pseudomonas syringae*) by site-directed mutagenesis based on the perceived crystal structure.

Sour taste

Weak organic acids tend to diffuse through the plasma membrane as neutral molecules in sour taste transduction and dissociate inside the cytoplasm, which causes intracellular acidification[136]. However, strong acids depolarise the sour taste receptor cells either by the inhibition of K^+ channels or by the stimulation of voltage-gated Na^+ channels[45] (Fig. 2). However, both these mechanisms might result in the opening of voltage-gated Ca^{2+} channels and stimulate the discharge of neurotransmitters against adjacent afferent nerves.

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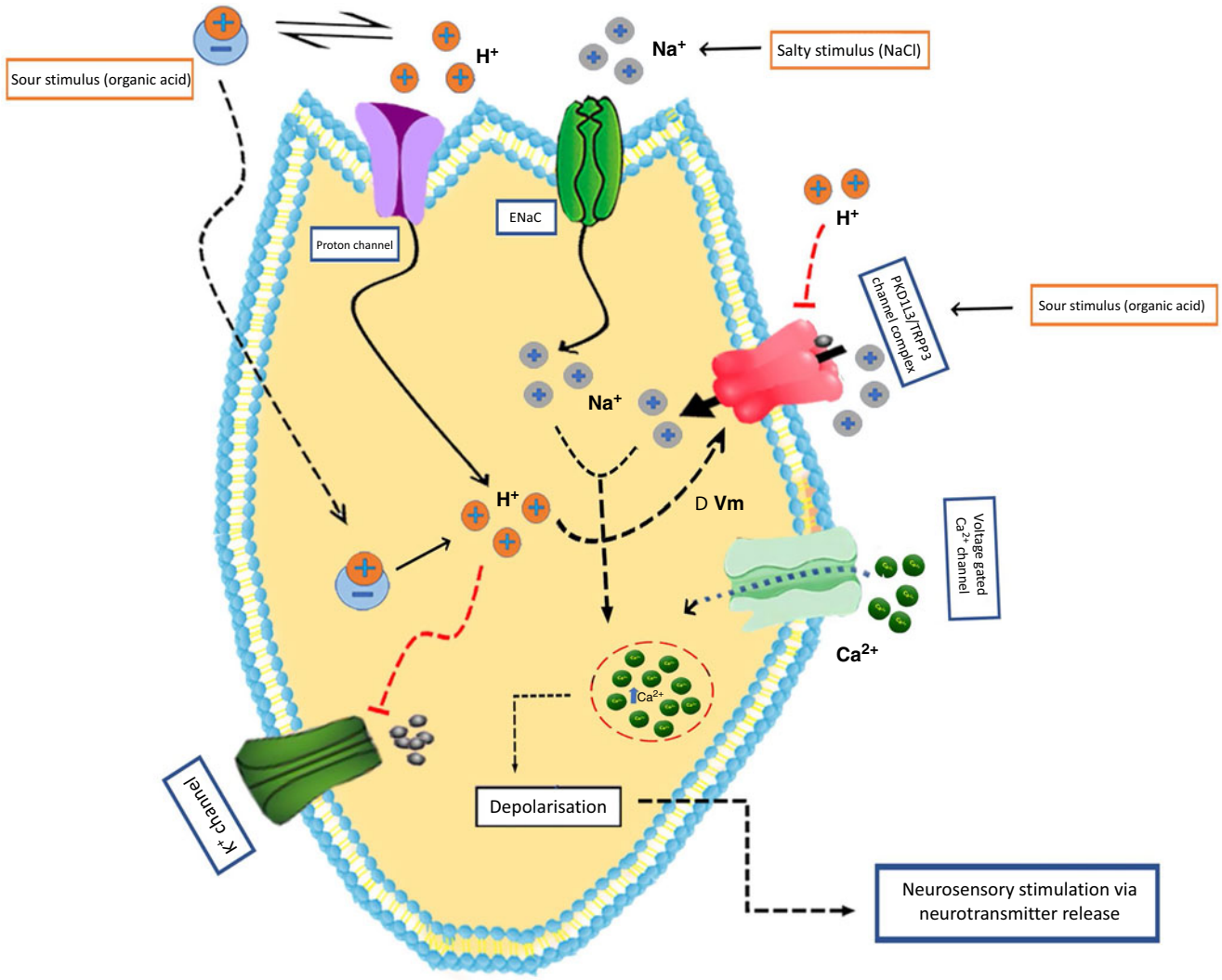

Fig. 2. Mechanisms of sour and salt taste perception by taste bud cells. Sour taste is triggered in type III cells by the intracellular proton concentration change triggered by protonated acids. In addition, several channels, including polycystin 2 like 1 (PKD2L1; transient receptor potential cation channel) and PKD1L3 have also been associated with sour taste. For salt taste, the putative candidate is the epithelial-type sodium channel (ENaC). The principal salt stimulus (sodium ion; Na^+) can permeate through these cation channels on the apical surface of taste bud cells and trigger depolarisation. ΔVm, membrane potential change; TRPP3, transient receptor potential polycystic 3. For a colour figure, see the online version of the article.

Sour tastants/modifiers

In sour taste transduction, several ion channels have been predicted to function as mediators despite the fact that the genetics of sour taste perception are inadequately recognised. Although protons signify a dominant part of the sour stimulus, the precise nature of the sour taste stimulus is still under dispute. It was established that weak organic acids in their undissociated form can competently pervade the taste cell plasma membrane and possibly will reduce the intracellular pH values near the cell surface[137]. Recently, Ohishi *et al.*[138] examined the potentials of the bortezomib-induced taste condition in mice and reported that the sensitivity of sour taste was drastically increased by the administration of bortezomib (online Supplementary Table S1). Moreover, PKD2L1 expression was increased in bortezomib-administered mice, and on cessation of its administration its effect reverted to the control level. Hence, these effects propose that the increase in PKD2L1 protein expression develops sour taste sensitivity in bortezomib-administered mice, and this modification is reversed on termination of its administration. Alternatively, Ishii *et al.*[139] suggested that capsaicin can be exploited as an inhibitor of PKD2L1 and PKD1L3, which signifies that in a medical condition, pre-treatment with capsaicin will probably lessen sour taste sensitivity.

Conclusions and future perspectives

Our diets differ based on numerous influences such as environment, our culture and health. At the molecular level, individuals perceive different taste modalities with the help of a range of specified tissues that direct sensory receptors to control nutritious value. In general, the interplay between trigeminal, olfactory and gustatory sensation is interpreted as taste perception like sweet, bitter, umami, salty and sour. Apart from these five

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principal taste behaviours, the taste system perceives certain non-canonical senses of orosensory taste stimuli such as fat, kokumi, complex carbohydrates and water that prove the existence of additional taste modalities. Current investigations foretold the plant-driven taste modulators which possibly target fatty acid taste receptors (CD36 and GPCR) and provoke a taste sensation devoid of any energy value that may be used against dietary-induced obesity.

Moreover, while the molecular characterisation of modulators and activators for the umami and sweet taste receptors has been carried out, the precise relationship among the T1R heteromeric subunits has yet to be characterised. In the near future, to combat against obesity and other related metabolic syndromes, rigorous strategies should be developed to construct libraries of plant-derived or chemical taste modifiers that would adhere to taste receptors and prompt a façade gustatory sense. In order to achieve this goal, we should attain a comprehensive understanding of the entire oro-gustatory receptors and their respective plant-derived/chemical compounds that are able to activate the gustatory system at the cellular and neurological levels. Likewise, the further understanding of combined biochemical properties of tastants and their inter-species transformations in chemosensory signal detection could be improved.

Furthermore, there is a need for modern contemporary analytical technologies to accelerate the detection of unidentified active chemosensory molecules present in nature and to recognise their physico-chemical relations on a molecular level with food matrix ingredients. The existing complication to gain sensors with suitable sensitivity and selectivity for the examination of taste modulators is directed to the concept of electronic tongues. For example, the electronic bio-mimetic tongue is capable of validating the projected taste intensity of unidentified taste modulators.

Advancement in examination and screening of specific taste-modulating compounds may offer novel platforms for checking the taste of drug candidates and in food quality control. Nowadays, a major challenge in taste research is to overcome the flavour defects in nutritious food products and production of natural or biosynthetic, non-energy-containing fat/sugar mimetics as well as bitter maskers. Moreover, thorough understanding is needed in distinctive age-dependent chemosensory genotypic and phenotypic variances in sensory preference for aversion against food flavours. Further research is essential to enhance our understanding towards the molecular adaptations of salivary composition upon stimulation with tastants along with the receptor proteins included in perceiving tastants. This knowledge will help in developing methodological questions regarding the sequential profile of taste modulators and their biased agonism, which may lead to recognise broadly adjusted enhancers like positive allosteric modulators or inhibitors such as negative allosteric modulators for industrial or commercial applications.

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Supplementary material

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