

## MINI-REVIEW

# Taste, visceral information and exocrine reflexes with glutamate through umami receptors

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**Abstract :** Chemical substances of foods drive the cognitive recognition of taste with the subsequent regulation of digestion in the gastrointestinal (GI) tract. Tastants like glutamate can bind to taste membrane receptors on the tip of specialized taste cells eliciting umami taste. In chemical-sensing cells diffused through the GI tract, glutamate induces functional changes. Most of the taste-like receptor-expressing cells from the stomach and intestine are neuroendocrine cells. The signaling molecules produced by these neuroendocrine cells either activate afferent nerve endings or release peptide hormones that can regulate neighboring cells in a paracrine fashion or travel through blood to their target receptor. Once afferent sensory fibers transfer the chemical information of the GI content to the central nervous system (CNS) facilitating the gut-brain signaling, the CNS regulates the GI through efferent cholinergic and noradrenergic fibers. Thus, this is a two-way extrinsic communication process. Glutamate within the lumen of the stomach stimulates afferent fibers and increases acid and pepsinogen release ; whereas on the duodenum, glutamate increases the production of mucous to protect the mucosa against the incoming gastric acid. The effects of glutamate are believed to be mediated by G protein-coupled receptors expressed at the lumen of GI cells. The specific cell-type and molecular function of each of these receptors are not completely known. Here we will examine some of the glutamate receptors and their already understood role on GI function regulation. *J. Med. Invest.* 56 Suppl. : 209-217, December, 2009

**Keywords :** *Umami taste receptor, exocrine regulation, gastrointestinal tract*

## INTRODUCTION

Glutamate is a non-essential amino acid that confers umami taste (savory or meaty) when is found free within foodstuffs (1). Many foods such as meats, seafood, seaweed and vegetables contain free glutamate, which plays a central role in the palatability and acceptability of food (1, 2). Psychophysical human experiments, neurophysiological,

conditioned taste aversion and genetic studies suggest that umami has unique taste properties (3-10). Glutamate is also the most abundant amino acid among the 20 free amino acids in human breast milk (11). The effect of glutamate on the tongue is mediated by several G protein-coupled receptors that have been isolated from taste receptor cells : T1R1 (taste receptor type 1, member 1) and T1R3 (taste receptor type 1, member 3) (12-17), and several metabotropic glutamate receptors (mGluRs) (18-24). N-methyl D-aspartate (NMDA) and non-NMDA ionotropic glutamate receptors (iGluRs) are also found in taste cells (25-29). Agonists for iGluRs and mGluRs evoke umami taste in humans (30-31), and variations in taste receptor genes have been

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recently found to correlate with umami taste perception (32-34).

## UMAMI RECEPTORS IN THE TONGUE

There is a clear advantage in the conscious recognition of taste. Not only because different taste qualities are distinctively perceived in the brain, but also because allows the association of a particular chemical signal with specific visceral responses (35). Taste sensation on the tongue and nutrient chemosensing in the gut seem to share similar molecular mechanisms. Both, taste and the GI cells, express a class of G protein-coupled receptors (GPCRs) that belong to family C of seven transmembrane receptors (7TM). This family of receptors has diverse functions that in fact involve nutrient-like sensing, including amino acids, ions, or sugars (36). One of the main properties of umami taste is the synergism between glutamate and nucleotides so that the taste of glutamate is enhanced by the addition of 5'-ribonucleotides (37, 38). Among the known umami receptor-candidates, 5'-ribonucleotides stabilize the binding of glutamate only on T1R1 (39), with some differences in receptor-specificity between humans and rodent T1R1/T1R3. The rodent heterodimer binds to various amino acids, whereas the human binds specifically to glutamate (15, 16), and in both species 5'-ribonucleotides enhances the response of glutamate. The most direct evidence that links T1R1/T1R3 with umami taste is the correlation between variations in the umami taste perception with changes in receptor genes (32-34). A small percentage of the population (3.5%) has been described to suffer ageusia for L-glutamate (40) and Single Nucleotide Polymorphisms (SNPs) at the predicted N-terminal extracellular binding domain of T1R1 or T1R3 are the most common (32). Genetically modified mice that lack either the T1R1 or T1R3 lose all responses to 5'-ribonucleotides (inosine 5'-monophosphate, IMP) and the behavioral attraction to a brief exposure to L-glutamate and L-amino acids (17). However, T1R3 knock out (KO) mice are still able to recognize the taste of umami substances during a 48-hour two-bottle preference test (41). Since neuronal and behavioral responses to L-glutamate in the second filial generation (F2) between the inbred mouse C5BL/6ByJ and 129P3/J with allelic variations of T1R3 were not affected (42-43), and the functional responses to L-glutamate with Ca<sup>2+</sup> imaging in slice preparations

from the vallate of T1R3 (KO) mice persists (44), umami taste detection seems to depend on multiple receptors (45). Certain mutations in the mGluR1 gene have been also associated with phenotype variations in the perception of monosodium glutamate (MSG) in humans (32, 34). Altogether, it has been suggested that there could be additional receptors for different umami substances or not well-understood interactions among the already cloned ones (45). Others proposed that T1R1/T1R3 might play a role in the anterior tongue, whereas mGluRs work in the posterior tongue contributing to the discrimination among umami and other taste qualities (46, 47).

## SIGNAL TRANSDUCTION OF GPCRS INVOLVED IN UMAMI SENSING

Upon activation of the heterodimer T1R1/T1R3 in taste cells the predominant G trimeric protein that couples to the receptor separates and the  $\beta\gamma$  subunit activates phospholipase C  $\beta 2$ , which in turns produces inositol triphosphate (IP<sub>3</sub>) and diacylglycerol (48-52). IP<sub>3</sub> binds to IP<sub>3</sub> receptors (IP<sub>3</sub>R3) that release Ca<sup>2+</sup> from intracellular stores (53); and the increase of intracellular Ca<sup>2+</sup> activates the monovalent-selective cation channel TRPM5 (54-56), which depolarize taste cells with the consequent release of ATP and stimulation of purinergic receptors of facial afferent nerve fibers (57-60). Taste receptor cells express gustducin that is a G-protein composed of  $\alpha$ -gustducin, G $\beta 3$ , and G $\gamma 3$  (51, 61). Other G proteins that have been found in taste cells include G $\alpha i 2$ , G $\alpha 14$ , G $\beta 3$  and G $\gamma 13$  (52, for review 62). Gustducin is a key molecule for umami signal transduction in the anterior region of the tongue, fungiform papillae (63), whereas in the circumvallate papillae (CV), the posterior region of the tongue, G $\alpha 14$  is the G protein co-expressed with T1R3 (52). mGluR1 shares this T1R1/T1R3 pathway relaying on the G protein Gq (64), but phospholipase C  $\beta 2$  is not the only signal transduction cascade for L-glutamate in taste cells. L-Glutamate in the CV strongly reduces the production of cAMP (65-66). Interestingly, taste-mGluR4 couples negatively with cAMP (19, 67) and mGluR1 also is associated to adenylate cyclase, tyrosine kinase, and map kinase cascades in different types of cells (64). Changes in cAMP seem to play a role for umami taste at the back of the tongue (65, 68).

## TASTE SIGNALING MOLECULES IN THE GI TRACT

The expression of taste receptors and taste-signaling molecules in the GI tract and the fact that only L-glutamate among the 20 amino acids can stimulate afferent endings of the vagus nerve from the stomach provides the bases for a hypothetical nutrient sensing system on the lumen of the stomach (69, 70). Indeed there are subpopulations of cells in the GI that express some of the taste signaling molecules such as  $\alpha$ -gustducin,  $\alpha$ -transducin and sweet, bitter and umami taste receptors (71-78) that have shown to regulate gastrointestinal function and release of signaling molecules (75-78). The chemical composition of chyme is detected on the lumen of the GI where enteroendocrine cells are the most likely first nutrient-sensing integration site. Enteroendocrine cells are diffused throughout the GI tract and secrete a great variety of hormones or signaling molecules such as gastrin (G cells), ghrelin (P or X cells), somatostatin (D cells), cholecystokinin (CCK) (I cells), serotonin (enterochromaffin cells), glucose-dependent insulinotropic peptide (GIP) (K cells), glucagons-like peptides (GLPs) and peptide YY (PYY) (L cells) (for review 70). These hormones are implicated in secretory processes at the stomach, intestine and pancreas as well

as motility, blood flow and satiety (79). G cells, for instance, play a key role in acid secretion (78). They are mostly located at the mid-basal portion of gastric glands in the antrum and express the extracellular calcium-sensing receptor (CasR) (80). CasR belongs to the same GPCR family of taste receptors. We have recently localized CasR in taste cells (81) where it seems to modulate taste perception (82-84). The release of gastrin from G cells is regulated by  $Ca^{2+}$  and CasR agonists. Gastrin targets enterochromaffin-like cells through CCK-2 receptor stimulating the release of histamine that in turn induces acid secretion from parietal cells. Thus, as shown in figure 1, the chemosensory system requires either an open endocrine cell with cytoplasmic projections to the lumen from where to detect the chemical content (green) with taste receptors that can identify the chemical composition of chyme, or closed endocrine cells (yellow) that are activated by signaling molecules secreted by neighboring cells. Both types of cells can secrete hormones or neuropeptides to the local micro circulation or afferent neurons (mostly vagal) that regulate many functions including water and electrolyte secretion. In the particular case of luminal glutamate, the vagus nerve electrophysiological activity appears to be regulated by nitric oxide (NO) and serotonin release in a cascade of events upon receptor activation that

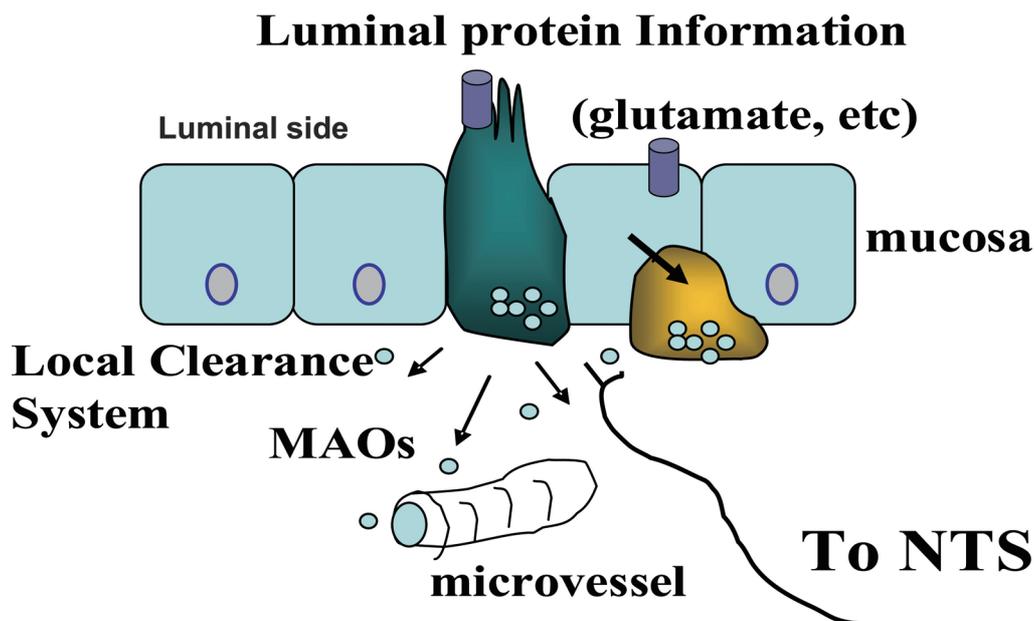


Fig. 1 Nutrient sensing in the gastrointestinal tract. Nutrients are sensed on the surface of cells. When tastants and chemicals contact taste receptors (blue cylinder) on the apical membrane of open enteroendocrine cells (green) that are in contact with the lumen content, there is a release of hormones that reach the microcirculation or activate afferent neurons sending the message to the central nervous system (nucleus of the solitary tract, NTS). These bioactive molecules can also act on neighboring cells. The yellow cell is a closed endocrine cell.

is not completely understood yet (85). However, neuroendocrine cells are not the only cells that can detect the chemical content of the lumen. It is known for some time that gastric parietal cells can be activated by L-amino acids such as L-phenylalanine (L-Phe) through the receptor CasR. L-Phe has a high affinity for CasR and causes a significant decrease of gastric pH in a gastrin independent manner (86). We also found that the apical membrane of gastric chief cells (and possibly parietal cells, unpublished data) contain mGluR1, which could be partially responsible for the release of pepsinogen during the gastric phase of protein digestion in the presence of free L-glutamate (85, 87). Moreover, luminal L-glutamate also increases mucus gel thickness and bicarbonate secretion in the duodenum (77). The protective layer of the mucous gel of the intestinal mucosal is constantly replenished from the continuous secretion in goblet cells in a process that seems to be regulated by various glutamate receptors such as mGluR4 and CasR. What we do not understand yet is the specific location of each receptor and their molecular regulation mechanism.

## SPECIFIC GLUTAMATE RECEPTORS AND THEIR FUNCTION IN GI

L-Glutamate can bind to many receptors that

function as chemical sensors in the GI tract. Some like the metabotropic glutamate receptors (mGluR1 and mGluR4) are selective to glutamate, whereas others are promiscuous receptors that interact with a wide range of amino acids (Table 1) (T1R1/T1R3 and CasR) (36). What they all have in common is that belong to the same GPCR family of nutrient sensing receptors, are found in taste tissue and evoke or modulate umami taste, and have been linked to GI function regulation. This explains how a single amino acid like L-glutamate could support a broad range of functions within the GI. The capacity to bind to several receptors located in different cells makes glutamate a versatile amino acid. Glutamate can evoke umami taste, regulate gastric acid, mucous and bicarbonate secretion, intracellular pH, and influence the speed of gastric emptying upon a rich protein meal among other functions (88). Unfortunately, the exact cell-distribution in the GI tract for each receptor has not been unraveled yet probably because of the following reasons: 1) GPCRs are not highly expressed in GI cells although they are physiologically active, thus many have been only uncovered by transcript analysis; 2) because of the very low expression level, their study requires very specific antibodies; and 3) enteroendocrine cells that form a diverse cell population represent less than 1% of gut epithelial cells. A detail study of the specific distribution of these

**Table 1** Known G coupled-receptor candidates that mediate the action of luminal L-glutamate, their cell distribution within the GI tract, agonists and functions they regulate, and the studies where these functions were evaluated

Receptor	Location within GI	Affinity	Function	Reference
T1R1/T1R3	taste cells, stomach, intestine	L-glutamate, L-aspartate, L-alanine... (5'-ribonucleotide synergism)	umami taste, bicarbonate secretion	15,16,17, 39,41,74, 77
mGluR1	taste cells, chief, parietal cells, and intestine	L-glutamate	umami taste, acid and pepsinogen secretion(?), cellular alkalinization	21,23,24, 77,85
mGluR4	taste, intestine, enterochromaffin cells	L-glutamate	umami taste, mucous secretion	18,19,77, 89
CaSR	taste, stomach (G-cells, parietal cells), intestine	all L-amino acids except branched chain and positively charged amino acids	calcium taste and taste modulation, gastrin, gastric acid, bicarbonate, and mucous secretion	77,81,84, 86

receptors will aid to elucidate whether glutamate supports the release of gut hormones, besides the activation of vagal afferents.

## CONCLUSION

Glutamate induces the umami taste in the oral cavity and in the GI regulates gastric acid, pepsinogen, mucous and bicarbonate secretion. mGluRs, T1R1/T1R3 and CaSR are the receptors that seem to regulate those responses by sensing free glutamate in the lumen. Taste sensation and nutrient chemosensing share similar molecular systems such as taste receptors, G proteins and intracellular signaling cascades. Enteroendocrine cells are specialized cells that have taste-like properties and release signaling molecules upon activation, but they are not the only cells that can 'taste' the chyme. Chief and parietal cells of the stomach also express receptors that can bind to free glutamate. At the end, glutamate seems to potentiate protein digestion by stimulating pepsinogen and gastric acid secretion while protecting the mucosa with a thicker mucous gel and bicarbonate release at the same time. Future studies may clarify the molecular mechanisms of all these effects and the cells that mediate them.

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