

Amino acid sensing in the gastrointestinal tract

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Abstract Rapid progress in gastroenterology during the first part of the last century has shown that gastrointestinal (GI) function is regulated by neuroendocrine, paracrine and endocrine signals. However, recent advances in chemical sensing, especially in the last decade, have revealed that free L-amino acids (AA), among other nutrients, play a critical role in modifying exocrine and endocrine secretion, modulating protein digestion, metabolism and nutrient utilization, and supporting the integrity and defense of the GI mucosa. Many of the mechanisms by which AAs elicit these functions in the GI has been linked to the traditional concept of hormone release and nervous system activation. But most these effects are not direct. AAs appear to function by binding to a chemical communication system such as G protein-coupled receptors (GPCRs) that activate signaling pathways. These intracellular signals, although their molecular bases are not completely elucidated yet, are the ones responsible for the neuronal activity and release of hormones that in turn regulate GI functions. This review aims to describe the distribution of the known GPCRs from the class 3 superfamily that bind to different kinds of AA, especially from the oropharyngeal cavity to the stomach, what kind of taste qualities they elicit, such as umami, bitter or sweet, and their activity in the GI tract.

Keywords Amino acids · Taste receptors · Gastrointestinal tract · Chemical sensing · Gastric phase · Umami · Glutamic acid · Monosodium glutamate

Abbreviations

AA	Amino acids
CaSR	Extracellular calcium-sensing receptor
ECL	Enterochromaffin-like cells
GI	Gastrointestinal
GPCRs	G protein-coupled receptors
HEK	Human embryonic kidney (cells)
mGluR1	Metabotropic glutamate receptor type 1
mGluR4	Metabotropic glutamate receptor type 4
NO	Nitric oxide
5-HT	Serotonin

Introduction

For many years, food proteins have been judged by their L-amino acid (AA) content, digestibility, bioavailability, and efficiency to support protein deposition and nitrogen balance (Reeds and Garlick 2003). In average, 11–14 % of total energy intake comes from vegetal or animal proteins that in Western diets represent about 70–100 g of protein per day (Humayun et al. 2007; IOM 2005; Silk 1980). However, it is now widely recognized that AAs by themselves influence a wide range of nutritional and biological functions that go beyond their role in protein metabolism (Jahan-Mihan et al. 2011; Wu 2010; Hundal and Taylor 2009). These emerging biological activities include taste perception and modulation of gastrointestinal (GI) functions by binding to a superfamily of guanine nucleotide-binding protein-coupled receptors (GPCRs) that belong to class C and work as nutrient-sensing systems. From what is

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known so far, the most relevant GPCRs for AA sensing in the mouth and GI are the extracellular calcium-sensing receptor (CaSR), taste receptor 1 (T1R) family, metabotropic glutamate receptors (mGluRs) and the GPCR family C subtype 6A (GPRC6A) receptor (Liou et al. 2011; Bystrova et al. 2010; Feng et al. 2010; Nakamura et al. 2010; Akiba et al. 2009; San Gabriel et al. 2007, 2009a, b; Zolotarev et al. 2009; Conigrave and Brown 2006; Uneyama et al. 2006; Wellendorph et al. 2005; Nelson et al. 2002; Chaudhari et al. 2000). This group of seven transmembrane (7TM) receptors contains a characteristic large extracellular venus flytrap (VFT) domain necessary for receptor dimerization and binding to agonists (for a review, see Wellendorph et al. 2009).

Only free AAs, not AAs bound to proteins, can interact with receptors on the oral and gastric mucosa. Non-protein AAs in foods impart distinctive tastes (Kawai et al. 2012; Ninomiya et al. 2010; Sorrequieta et al. 2010; Koutsidis et al. 2008; Drake et al. 2007; Oruna-Concha et al. 2007; Martin et al. 2001; Ninomiya 1998). In fact, the particular taste of snow crabmeat or scallops is due to the combination and relative amounts of glycine, alanine, arginine and glutamate in the presence of salt and nucleotides (Fuke and Konosu 1991). We are starting to recognize the taste properties of AAs, which seem to depend on the size, hydrophobicity, chemical structure of the radical group and concentration (Kawaki et al. 2012). AAs impart complex taste qualities that can modify the flavor of foods (Schiffman et al. 1979). Some AAs are added to improve the quality of a protein or improve the flavor of a particular dish (Ghosh et al. 2010; Laska 2010). In other cases, AAs are used to replace proteins that cause food allergies (Niggemann et al. 2001). Overall, the profile of free AA varies according to the kind of food and the procedure of preparation. For instance, fermentation, an ancient technology that has been used to preserve, increase the digestibility of and enrich the flavor of foods, and releases protein-bound AA; therefore, it provides a complex profile of free AA (Caplice and Fitzgerald 1999; Yoshida 1998; Cordoba et al. 1994) and as a result a complex taste. Traditional seasonings such as bean paste, soy or fish sauces were developed very early in human culinary history (Curtis 2009; Yoshida 1998). Another method to extract non-protein-bound AAs from food ingredients consists of heating meats and vegetables like in soups (Ninomiya et al. 2010; Ninomiya 1998). Also, the ripening process of some vegetables involves an increase of certain amino acids such as glutamate and aspartate that impart an umami taste (Sorrequieta et al. 2010). There are even free AAs in human milk, which is considered the perfect food for infant nutrition during the first 6 months of life. The fraction of free AAs in human milk constitutes 5 % of the total AAs (Chuang et al. 2005; Agostini et al. 2000; Sarwar et al.

1998; Svanberg et al. 1977); in addition, milk from other species, such as non-human primates, pigs, horses, seals and sea lions, are similarly abundant in free AAs (Sarwar et al. 1998; Wu and Knabe 1994).

Role of free AAs in the diet

The relevance of free AAs in foods is that they can bind directly to GPCRs in the oral cavity and the gastric wall before proteins breakdown. The initial step of protein digestion does not start until they reach the stomach, and even in the stomach under acid pH the release of free AAs is not quantitatively significant (Sampath-Kumar and Fruton, 1974; Voynick and Fruton 1971). This is the reason why AA sensing in the upper region of the GI and its consequent regulation of oral and gastric processes seem to depend almost entirely on the free AA content in the diet and the availability of chemo-receptors on the gastric surface. The proteinase pepsin, which is the best-known representative of the acid proteinase family with optimal activity to cleave peptide-ester bonds of protein substrates in the pH range 2–5, is produced in the stomach and preferentially attacks bonds next to aromatic AAs such as phenylalanine, tryptophan and tyrosine. After gastric protein digestion, only free aromatic AAs and a sizeable bulk of hydrophobic polypeptides remain even after pepsin cleaves large portions of proteins in the stomach (Taylor et al. 1982; Voynick and Fruton 1971). Gastric polypeptides are not further hydrolyzed to a large pool of free, di-, tri- and oligo-AA until they enter the duodenum and are attacked by pancreatic proteases such as trypsin, chymotrypsin, elastase and carboxypeptidase (Caspary 1992; Silk 1980; Adibi and Mercer, 1973). The distribution, location and function of AA receptors in the oropharyngeal cavity and the stomach will be discussed in detail later.

The taste system

The sense of taste is the guardian mechanism that monitors and drives our feeding behavior, which ranges from aversion to noxious or toxic compounds to attraction to foods that provide caloric energy. Therefore, taste disorders in humans cause health problems linked to feeding, nutrition and quality of life (Stewart et al. 2010; Pepino et al. 2010; Tomoe et al. 2009; Schiffman and Graham 2000; Graham et al. 1995; Deems et al. 1991). The machinery of taste consists of onion-like clusters of 50–100 specialized cells, called taste buds, distributed through the oral cavity, soft palate, epiglottis, larynx and pharynx (Sbarbati and Osculati 2005). Taste-bud cells are divided into at least four types of sensory cells that are exposed to tastants at a porus

region with apical microvilli where taste receptors are localized (DeFazio et al. 2006; Lindemann 1996). For the purpose of this review, the most relevant cell types are II and III. Type II cells exist in distinct subsets of sweet (T1R2/T1R3), bitter (T2Rs) and umami receptors (mGluR4, mGluR1 and the heterodimer T1R1/T1R3), besides the essential molecules for signal transduction (San Gabriel et al. 2009a, b; Bachmanov and Beauchamp 2007; Roper 2007; Toyono et al. 2003, 2007; Clapp et al. 2004; Zhang et al. 2003; Li et al. 2002; Nelson et al. 2001, 2002; Perez et al. 2002; Chandrashekar et al. 2000; Chaudhari et al. 2000). Type III or “presynaptic” cells have direct synapses with primary sensory neurons and have sour receptors (ASIC and PKDL channels) (Ishimaru et al. 2006; Ugawa et al. 2003; Kinnamon et al. 1993). Salty taste seems to depend on a different population of taste cells still to be categorized (epithelial Na channel, ENaC) (Chandrashekar et al. 2010; Yoshida et al. 2009a, b; Shigemura et al. 2008). Thus, it is well established that humans have five different taste sensations: sweet, bitter, sour, salty and umami, the taste of glutamate, aspartate and ribonucleotides such as inosine-5'-monophosphate (IMP) and guanosine-5'-monophosphate (GMP) (Ikeda 2002; Yamaguchi 1998; Ninomiya and Funakoshi 1989).

Gustatory sensation of L-AA

In relation to the taste of amino acids, while the majority of proteins are tasteless, with few exceptions (Niccolai et al. 2001), the chemical perception of AAs and short peptides is especially complex (Table 1). Most amino acids elicit more than one basic taste although one taste tends to prevail (Kawai et al. 2012; Birch and Kemp 1989; Kato et al. 1989). Ikeda first documented the importance of free amino acids to food taste in 1908 with the discovery that the taste-active compound of sea tangle, a traditional Japanese soup ingredient, was the sodium salt of L-glutamate, the prototypical substance for umami taste (Ikeda 2002). Today, the taste properties of L-glutamate are the best known among all AAs, and its functions have been extensively studied. We know that salts of L-glutamate induce salivary secretion, which initiates digestion of starches and fats, and improve the palatability of certain foods. As a result, salts of L-glutamate can be used to partly replace sodium chloride without compromising the taste of low-sodium foods (Sasano et al. 2010; Hodson and Linden 2006; Yamaguchi, 1998; Bellisle et al. 1991; Giduck et al. 1987). In fact, The Institute of Medicine Committee on Strategies to Reduce Sodium Intake in the US recognized using monosodium glutamate as one possible strategy to lower the total sodium content in foods (2010).

Table 1 Predominant taste qualities of amino acids and sensing mechanisms known so far

Amino acid	Human taste perception	Potential binding to GPCRs
L-Alanine	Sweet	GPRC6A
L-Arginine	Bitter	GPRC6A
L-Asparagine	Bitter	(?)
L-Aspartic acid	Umami, sour	T1R1/T1R3
L-Cysteine	Sulfurous	(?)
L-Glutamic acid	Umami, salty	T1R1/T1R3, mGluRs
L-Glycine	Sweet	GPRC6A
L-Histidine	Bitter	CaSR
L-Hydroxyproline	Sweet	(?)
L-Isoleucine	Bitter	(?)
L-Leucine	Bitter	(?)
L-Lysine	Bitter, salty, sweet	GPRC6A
L-Methionine	Bitter, sulfurous	GPRC6A
L-Phenylalanine	Bitter	CaSR
L-Proline	Sweet	(?)
L-Serine	Sweet	GPRC6A
L-Threonine	Sweet	(?)
L-Tryptophan	Bitter	CaSR
L-Tyrosine	Bitter	(?)
L-Valine	Bitter	(?)

GPCR G protein-coupled receptors, *GPRC6A* GPCR family C subtype 6A receptor, *CaSR* extra calcium sensing receptor, *T1R* taste receptor type 1, *mGluR* metabotropic glutamate receptor

(?) still unknown

Potential taste receptors for L-AA

Specific GPCRs that bind to AA have been described in type II taste receptor cells (Table 2), such as the heterodimer T1R1/T1R3, whereas other glutamate receptors such as mGluRs still need to be localized among different cell types (San Gabriel et al. 2009a, b; Toyono et al. 2003, 2007; Li et al. 2002; Nelson et al. 2002; Chaudhari et al. 2000). Emerging evidence indicates that the dietary niche drives the evolution of the sensory system. Consequently, AA affinity for T1R1/T1R3 differs depending on the species (Jiang et al. 2012; Jin et al. 2011; Roura et al. 2011; Li et al. 2005; Beauchamp et al. 1977). The human T1R1/T1R3 is very specific to glutamate, whereas the mouse T1R1/T1R3 responds to many amino acids when expressed in human embryonic kidney (HEK) cells, and in both species the activity is enhanced by IMP (Li et al. 2002; Nelson et al. 2002; Xu et al. 2004). However, it is not yet well understood why there is a need for multiple receptors to detect L-glutamate, or whether T1Rs and mGluRs are located in the same subset of taste cells and perhaps form heterodimers with other GPCRs or contribute equally to the

Table 2 Distribution of GPCRs in the oropharynx and stomach and their predominant functions in taste and the GI tract

Organ	Type of cell	GPCRs	Function
Oral cavity	Type II cells	T1R1/T1R3	umami taste
Taste cells	Type II & III	CaSR	taste modifier
	Type II & III	GPRC6A	?
	To determine	mGluR1 & mGluR4	umami taste
Stomach	Parietal cells	CaSR (mGluR1?)	↑ acid secretion
	Chief cells	mGluR1	↑ pepsinogen
	G cells	CaSR, GPRC6A	↑ gastrin release
	D cells (antrum)	CaSR, GPRC6A	(?) somatostatin
Duodenum	To determine	mGluR4	mucus secretion
	To determine	T1R1	duodenal bicarbonate secretion
	To determine	T1R3	

↑, increase; (?), not known yet

perception of umami taste, or, if this is so, how their signals are integrated in the brain (Yasumatsu et al. 2009).

Other AA receptors that have been described in the tongue are promiscuous CaSR and GPRC6A (Bystrova et al. 2010; San Gabriel et al. 2009a, b; Wellendorph et al. 2007). CaSR contributes to a wide range of biological functions because it is expressed in different tissues particularly in the parathyroid and kidney, where it supports extracellular calcium homeostasis (Brown et al. 1993). The principal agonist of CaSR is calcium (Ca^{2+}), but other divalent and trivalent cations, aminoglycoside antibiotics and polyamines are capable of activating the receptor (Saidak et al. 2009; Brown and MacLeod 2001). Free AAs are considered allosteric modulators for CaSR because activating CaSR AA requires the presence of a threshold Ca^{2+} concentration. The AAs with a higher affinity for CaSR are the aromatic amino acids L-tryptophan, L-phenylalanine, L-tyrosine and L-histidine, whereas basic and branch-chain amino acids are the least effective (Saidak et al. 2009; Conigrave et al. 2000, 2007). Small peptides like glutathione and other gamma-glutamyl peptides also bind to CaSR with a high affinity (Wang et al. 2006). They were recently described as potent taste enhancers, but without taste by themselves, a property that has been designated as *kokumi* (Maruyama et al. 2012; Ohsu et al. 2010). In fact, *kokumi* substances have been proven to activate CaSR-expressing taste cells (Maruyama et al. 2012). What's more, there are gustatory nerve fibers that respond to the sensation of calcium and magnesium (Ninomiya et al. 1982). However, it is not known whether the calcium and magnesium signal comes from the activation of CaSR or other receptors, or how they relate to AA

sensation. Tordoff et al. (2008) has proposed through genetic analysis that the calcium and magnesium taste is mediated primarily by T1R3, which is a component of the umami and sweet taste receptors. However, calcium and magnesium, like L-phenylalanine and L-histidine, have strong bitter qualities; thus, it is difficult to explain how the bitter properties of those AAs combine with their potential function as *kokumi* substances. Moreover, calcium can also bind to other GPCRs like mGluRs, which bind exclusively to glutamate (Kubo et al. 1998).

Another AA receptor recently described in taste tissue is the GPRC6A. It has been found to be a sensor for L-arginine and L-lysine and small neutral AAs, such as L-alanine, L-glycine or L-serine, apparently binds to osteocalcin, mediates some of the non-genomic effects of testosterone and like CaSR is also activated by Ca^{2+} and other cations (Pi and Quarles 2012; Pi et al. 2005, 2010; Kuang et al. 2005; Wellendorph et al. 2005). However, not much is known yet about its function in taste tissue.

Possible associations between L-AA taste sensations and taste receptors

The matter now is to investigate how different tastants elucidate each taste quality according to receptor affinity and cell distribution in the sensory system. Bystrova et al. (2010) attributes the different taste properties of CaSR agonists to the differential expression of the receptor in subpopulations of taste cells (San Gabriel et al. 2009a, b). However, this doesn't take into account the potential binding of CaSR agonists to other receptors like T1R3. For

instance, certain AAs with large radicals and high hydrophobicity might have higher affinity for GPCRs linked to bitter taste perception (T2Rs; Chandrashekar et al. 2000), also expressed in a population of type II cells, than for CaSR. Unfortunately, to our knowledge, there are no molecular studies for the systematic characterization of AA interaction with either the bitter taste receptor T2Rs or the sweet receptor T1R2/T1R3, taking into account that bitter and sweet are the most frequent taste sensory attributes for AAs (Kawai et al. 2012).

GPRC6A has been proposed to be a functional receptor in type III taste cells; despite the similar taste properties of the agonists L-lysine and L-arginine (sweet/bitter), it is too early to link GPRC6A to any particular taste quality, especially with sweet or bitter, because they are not commonly transduced from type III cells but rather type II cells. Thus, further studies are necessary to characterize the taste quality that GPRC6A and other GPCRs evoke after being stimulated by L-AA.

Regulation of gastric acid secretion

The major function of the stomach is to secrete acid for the facilitation of protein digestion, iron, calcium and vitamin B12 absorption, and deter the overgrowth of bacteria (Shubert 2009). Gastric hydrochloric acid secretion is closely regulated by neuronal, hormonal and paracrine signals. It is released from parietal cells that are the hallmark of the oxyntic mucosa, the acid-secreting gastric mucosa that occupies about 80 % of the gastric surface (Goo et al. 2010; Konturek et al. 2008). Between meals, parietal cells are under the paracrine inhibition of somatostatin, which originates from D cells in the stomach (Goo et al. 2010; Shubert 2009). D cells can be found in the oxyntic mucosa as well as the antral mucosa with pyloric or antral glands that also contain gastrin-secreting G cells. Antral glands represent the other 20 % of the gastric surface (Konturek et al. 2008), and gastrin activates gastric secretion directly on parietal cells or through the stimulation of the parietal cell agonist histamine from enterochromaffin-like cells (ECL) (Goo et al. 2010; Shubert 2009). ECL cells are also located in the oxyntic mucosa, in close vicinity with parietal cells. Thus, under the paracrine negative influence of somatostatin, the acid secretion by parietal cells is partially blocked together with the inhibition of gastrin and histamine, which maintains only a basal acid secretion (Fig. 1a).

When a meal is initiated, sensory cues such as taste and smell or even thought (cephalic phase) trigger neuronal autonomic reflexes that lead not only to salivary secretion (Kitamura et al. 2010), but also prepare the stomach for the meal-stimulated gastric secretion (Power and Schulkin

2008). Vagal efferent fibers secrete acetylcholine, which blocks the release of somatostatin from D cells and activates parietal and G cells by binding to muscarinic M3 receptors (Goo et al. 2010). During the gastric phase when the meal reaches the stomach, the gastric wall stretches and foods interact with nutrient receptors at the surface of the lumen. Both mechanisms contribute to the further stimulation of gastric acid secretion. Thus, foods not only supply necessary nutrients but also modulate physiological functions in the GI (Shimizu 2010). In other words, the GI tract can adapt its motility, acid secretion and hormone release according to the chemical composition and volume of the luminal contents in the stomach (Steinert and Beglinger 2011).

Gastric L-AA sensing

In the same way free AAs provide biological cues for the taste system, they are also chemical signals in the stomach (DeIValle and Yamada 1990). However, in the stomach, the function of AA depends on two major factors: the availability and concentration of free AA from the diet and digestive process, and the presence and distribution of accessible chemosensory mechanisms. Fujita et al. suggested the “intestinal sensor cell hypothesis” based on the existence of nutrient-sensing cells, distributed along the antral or duodenal mucosa, that release bioactive compounds to inform other tissues of the chemical composition of the GI contents. During this process, cells release hormones or activate the vagus nerve (Fujita et al. 1980). Hofer et al. (1996) reported that the gastric and intestinal mucosa contain taste receptor-like cells similar to taste cells in the oropharyngeal cavity. Nowadays, we know that the chemosensory system in the GI consists of the activation of either chemo-sensitive afferent fibers from the vagus nerve (Blackshaw et al. 2007; Iggo 1957) or GPCRs on the luminal surface of nutrient-sensing cells (Rasomanana et al. 2012; Hofer et al. 1999).

Gastric vagal afferent nerve

Afferent fibers of the vagal gastric branch can differentiate mechanical signals, such as stretch during a meal, from cues of individual nutrients in the luminal contents (Richardson et al. 1976). In regard to AAs, the gastric chemical perception of the vagus afferent nerve seems to be very selective to L-glutamate and IMP, another umami substance (Kitamura et al. 2010, 2011; Uneyama et al. 2006). Concerning the rest of the AAs, glucose or isotonic saline solutions do not activate the vagal gastric afferent nerve in rats (Uneyama et al. 2006; Clarke and Davison 1978). This

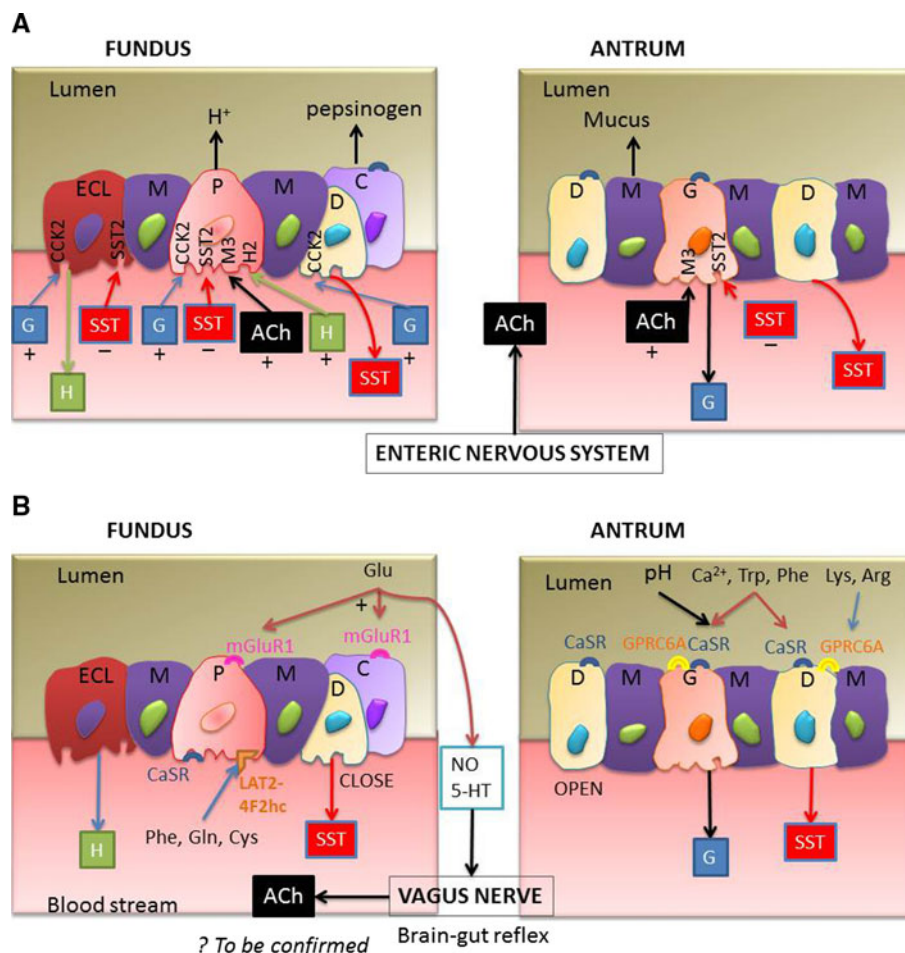


Fig. 1 Regulation of acid gastric secretion in the stomach. **a** Between meals, gastric acid is kept at basal levels by somatostatin inhibition from D cells in the antrum and the fundus. During a meal, gastrin from G cells activates the proton pump of parietal cells (P) and binds to CCK2 receptors of ECL cells that secrete histamine. Histamine and acetyl choline (ACh) from enteric neurons, like gastrin, are potent activators of the proton pump in P cells (adapted from Goo et al.). **b** P and chief (C) cells in the fundus, and G and D cells (open-type) in the antrum express GPCRs on the surface that are in contact with gastric luminal contents. Free L-glutamate (Glu) can potentially

bind to metabotropic glutamate receptors (mGluR1) in C cells and possibly in P cells at the same time, which activates the afferent vagal neurons that most likely drive ACh release as a result of the brain-gut reflex, which increases acid secretion. Other amino acids such as Trp and Phe bind to CaSR on G and D cells, probably causing gastrin release and modulating the secretion of somatostatin. pH and calcium ions may play a role in CaSR activity in G cells, too. The same cells that contain CaSR also express GPCR6A, which binds to Lys and Arg among others; thus, these amino acids may regulate gastric acid secretion as well

L-glutamate vagal stimulation can be blocked by the anesthetic lidocaine or by either the depletion of serotonin (5-HT) or the inhibition of 5-HT₃ receptors (Uneyama et al. 2006). The inhibition of the nitric oxide (NO) synthase enzyme also interferes with vagal stimulation by luminal L-glutamate, whereas a 5-HT₃ blocker can reverse the activation of the vagus afferent-nerve induced by a NO donor (Uneyama et al. 2006). On the other hand, the afferent nerve of the vagal intestinal branch (celiac nerve) responds to oligopeptides and all AAs, either by excitation or depression, suggesting that the duodenum contains sensors for all AAs in contrast to the stomach, which only responds to L-glutamate (Kitamura et al. 2010; Easwood et al. 1998).

Function of free AA in the stomach

Early studies showed that intragastric administration of aromatic AAs such as L-phenylalanine and L-tryptophan promotes the secretion of gastric acid (Taylor et al. 1982; Strunz et al. 1978). With recent studies, we have learned that CaSR and GPCR6A are present in a subpopulation of G cells and some D cells of the antral region, both exposed to the lumen contents (open type) (Haid et al. 2011, 2012). CaSR and GPCR6A are thought to act as physiological sensors to protein breakdown products and CaSR as a pH and calcium sensor as well (Fig. 1b). This way free AA can regulate gastrin and somatostatin secretion in G and D

cells, respectively (Feng et al. 2010; Geibel and Hebert 2009; Ray et al. 1997). However, given that they control opposite functions, Haid et al. (2012) speculate that the same receptor repertoire should elicit different effects in G and D cells. It is expected that the stimulation of gastrin release by G cells, which in turn induces pepsinogen and hydrochloric acid secretion, will be coordinated with the inhibition of somatostatin release by D cells in early stages of digestion (Saffouri et al. 1984). However, it is also known that gastrin can stimulate the release of somatostatin only from the D cells of the antrum region; therefore, an excess of gastrin secretion will ultimately modulate the somatostatin-associated inhibition of gastrin release (Schubert et al. 1991). The importance of CaSR in the antral region is that luminal pH and the concentration of free aromatic AAs may modulate the cross talk between G and D cells in the antrum region that in the end influence the progress of the gastric phase of secretion. Hydrochloric acid secretion by parietal cells from oxyntic glands can also be regulated by the intravenous concentration of free AAs via either CaSR or the amino acid transporter comprised of the dimer LAT2-4F2hc and L system AA transporter (Kirchhoff et al. 2006; Busque et al. 2005). This would constitute a completely different regulation mechanism since both are located at the basal membrane and are specific to different AAs, CaSR to aromatic AAs and the L system AA transporter to L-cysteine and L-glutamine.

Regarding L-glutamate, when it is infused in the stomach with protein-rich foods or after the administration of penta-gastrin, a gastrin-like polypeptide, it also substantially potentiates the gastric phase secretion (Zolotarev et al. 2009). However, L-glutamate was not found to affect basal gastric secretion with an aqueous solution or influence the secretion of a carbohydrate-rich diet (Khropycheva et al. 2011).

There are several glutamate receptors that could mediate the effects of L-glutamate in the stomach. Among them, we found mGluR1 transcripts in rat chief cells (pepsinogen-secreting cells) and localized the receptor facing the luminal membrane of the gastric glands (San Gabriel et al. 2007). The luminal activation of mGluR1 by dietary L-glutamate may mediate the secretion of pepsinogen. In fact, L-glutamate increases pepsinogen release in the presence of an AA mixture (Khropycheva et al. 2011). However, no direct link has been established so far between mGluR1 on chief cells and ultimate afferent-nerve stimulation, which seems to be the mode of action of L-glutamate. Other GPCRs to which L-glutamate can bind have been reported in the stomach, such as the components of the AA receptor T1R1 and T1R3, the glutamate receptor mGluR4 as well as the taste signal transduction markers α -gustducin and phospholipase C β 2 (Akiba et al. 2009; Bezecon et al. 2007). However, they have not been fully localized in the gastric mucosa or linked to a particular physiological

function. Up to now, glutamate receptors have been associated in general to the promotion of defense factors by L-glutamate, but in the duodenum (Akiba et al. 2009). It is still unknown what type of gastric cells are responsible for the L-glutamate-dependent release of 5-HT and NO, which activate the afferent vagal nerves.

Conclusion and perspectives

There is a mounting body of proof that the same receptors that function as taste receptors for AAs (e.g., T1Rs, mGluRs, CaSR and GPRC6A) in the oropharyngeal cavity also regulate GI functions such as gastric secretion and therefore protein digestion; we are now starting to understand the specific roles of AAs according to their affinity to GPCRs. With the continuously advancing deorphanization process of GPCRs and their molecular characterization, we will better comprehend their interactions and some of their functions. Much of this knowledge has come from screening methods in heterologous systems like HEK cells or by using cell lines such as the enteroendocrine cell line STC-1 that already express taste GPCRs. However, more gastro-physiological studies are necessary to further determine the specific anatomical location of T1Rs or mGluR4 receptors in human gastric mucosa as well as how their function is coordinated to the gastric phase, NO and 5-HT secretion. A better understanding of these processes may help to understand the specific role of free AAs in foods in digestion and ultimately the biological importance of their taste perception.

Most L-AAs either taste sweet or bitter with the exception of L-glutamic and L-aspartic acid, and yet we still don't have evidence at the molecular level of all the receptors that support those taste qualities. Similarly, little is known about whether AA taste disorders could be linked to GI diseases; therefore, AA GPCRs are potential pharmaceutical targets for GI dysfunctions.

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