Review Article

Physiological role of dietary free glutamate in the food digestion

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Gustatory and anticipatory cephalic stimuli during a meal yield nutritional information and aid efficient food digestion. Mammals, including humans, can detect the amount of dietary protein and its quality via cephalic relay to initiate proper digestion in the upper gastrointestinal (GI) tract. In addition to gustatory stimuli, visceral sensing by the abdominal vagus conveys primary afferent nutritional information from the digestive system to the brain. Electrophysiological studies indicated that abdominal vagal afferents, which were innervated into the stomach and intestine sending information to the brain, were activated by luminal glutamate. Histochemical analysis also revealed the existence of a glutamate signalling system (metabotrophic glutamate receptors) in the GI tract. Luminal glutamate in the stomach and intestine provides the efferent reflection of the abdominal vagus, supporting the modulation of exocrine and endocrine excretion during digestion. These results strongly indicate that glutamate has regulatory effects on the food digestive processes through the gut nutrient-sensing system. It plays physiological and nutritional roles and initiates digestion in the stomach as well as anticipates subsequent processes in the small intestine and the liver. We reviewed recent studies on glutamate physiology in the gut including our research, and discussed the physiological significance of dietary free glutamate in the regulation of gut function, focusing on the visceral sensation from the stomach.

Key Words: monosodium glutamate, visceral sensation, vagus afferent, gastric digestion

INTRODUCTION

The abdominal vagus consists of an afferent pathway which conveys nutrient information from abdominal organs to the brain, and an efferent pathway which conveys information from the brain to the internal organs. Afferent signals transfer the information of food volume, osmotic pressure, pH, and the nutrient composition within the alimentary tract. In rats, the vagus nerve involves 8000 afferent and 3000 efferent fibers. Dietary nutrient information is detected by afferent fibers in the stomach, intestine, and portal vein, and transmitted to the nucleus of solitary tract in the brain stem. It regulates food digestion, absorption and metabolic processes. Free glutamate itself is a widespread amino acid, which is found naturally in human body proteins and in protein-containing foods, such as chicken, beef and fish. Seasonings and food ingredients such as cheese, tomato, soy sauce and dried mushroom are especially enriched with free glutamate making daily meals delicious. In Japan, it is estimated that daily intake of free glutamate exceeds 1.6 g per person.

Niijima and collaborators firstly reported in 1991 that dietary free glutamate evoked a visceral sensation from the stomach, intestine and portal vein.[1] This report is essential for glutamate physiology because the evidence strongly suggest that dietary free glutamate might have a critical role in post-ingestive events such as food digestion and nutrient availability. In this paper, we reviewed recent studies on glutamate physiology in the gut, including our research, beyond that first discovery to present, and discussed the physiological significance of dietary free glutamate in regulatory functions of the gut, focusing on the visceral sensation in the stomach.

AMINO ACID-SENSING CARRIED BY THE ABDOMINAL VAGUS

Electrophysiological recording of abdominal vagal afferent fibers revealed how they can detect luminal amino acids in the alimentary tract. The intraduodenal administration of amino acids such as glutamate, isoleucine and phenylalanine activated vagal celiac afferents which carry predominantly the intestinal nutrient-sensing; whereas glycine inhibited nerve activation. Among the 20 amino acids that make up our body protein, celiac afferents could detect all amino acids within the intestine.[2]

In contrast to celiac afferents, rat gastric afferents responded differently to amino acids. While intra-gastric stimulation by glutamate was maintained, other amino acids (glycine, isoleucine and phenylalanine) could not stimulate afferents from the gastric branch of the vagus. In

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Manuscript received 9 September 2007. Accepted 3 December 2007.

figure 1, we summarized luminal amino acid-selectivity to gastric vagal afferents. Amazingly, glutamate alone could activate gastric afferents. This implies that free glutamate, among the 20 amino acids of dietary protein, could evoke nutrient information to the brain by itself.

It is well known in taste sensation at the tongue that glutamate responses in taste fibers could be markedly enhanced with the presence of 5'-mononucleotides such as inosine monophosphate (IMP) and guanine monophosphate (GMP). Thus, we examined the influence of GMP in the gastric vagus together with glutamate (Fig. 2A). The gastric response to glutamate could not be synergistically enhanced in the presence of GMP. Therefore, the sensation of glutamate in the stomach may differ from the mechanism for oral glutamate perception.

GLUTAMATE-SENSING IN THE STOMACH AND INTESTINE

What is the chemical transduction mechanism in the mucosa to sense luminal glutamate by the vagus nerve? It is known that serotonin (5-HT) or nitric oxide synthase (NOS) containing cells are densely distributed throughout the gastric mucosa. To identify the molecular mechanism involved in gastric glutamate-sensing, we examined the effects of mucosal 5-HT depletion on gastric vagal activation by glutamate (Fig. 2B). Maximal glutamate response was suppressed by intraperitoneal treatment of the 5-HT depletor, *p*-chlorophenylalanine (PCPA). It is well known that repetitive intraperitoneal dosing of PCPA abolishes mucosal 5-HT. The effect of glutamate in the stomach was likewise blocked by the 5-HT_3 receptor antagonist and the non-selective NOS inhibitor L-NAME.[3] Thus, within the gastric mucosa, luminal glutamate information translates into intrinsic bioactive substances such as nitric oxide and 5-HT that is later transferred to nerve endings of vagal afferents via 5-HT_3 receptor activation.

POSSIBLE DISTRIBUTION OF GLUTAMATE-SENSING RECEPTORS IN THE RAT GASTRIC MUCOSA

As for the hypothesis regarding gut chemical-sensing for nutrients, there is the "intestinal sensor cell hypothesis", originally proposed at 1970s by Fujita and others.[4] The hypothesis proposes that the nutrient-sensing cells are distributed in the gastric antrum or duodenal mucosa. When these cells interact with luminal nutrients, they release hormones in an endocrine or paracrine manner, to transfer luminal nutrient information to other organs, including the brain via endocrine or vagal pathways. Unfortunately, it has been unclear for long time what cells carry the gut nutrient perception. In 1996, a German research group suggested that taste-like cells, which molecular make up resembles to that of taste cells in the oral cavity, are found in the gastric and intestinal mucosa. They suggested that sensor cells correspond to taste-like cells.[5]

With the quick development of molecular biology in the field of taste research, several taste receptors for umami taste, derived from glutamate, have been identified. At least 2 different metabotrophic glutamate receptors such as type 1 and type 4 ($mGluR_1$ and $mGluR_4$), and one taste receptor (T1R1/T1R3 heterodimmer) have been linked with umami taste sensation.

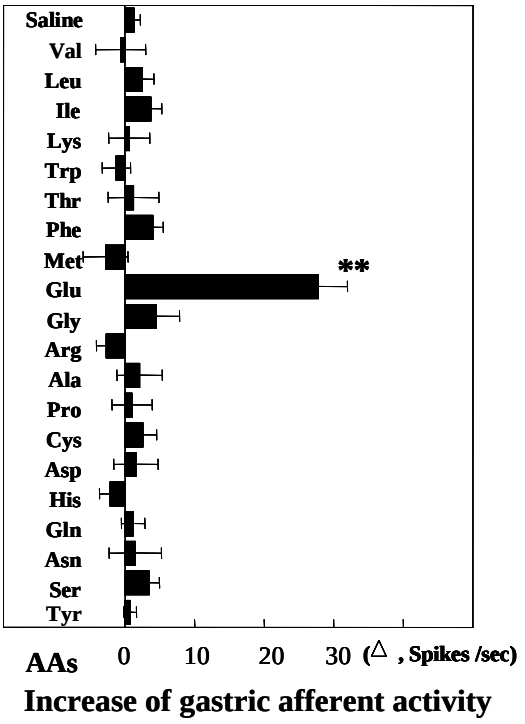

Figure 1. Luminal amino acid-sensing by the rat gastric vagus nerve.
Each aqueous solution (150 mmol/L, 2mL) was introduced into the rat stomach, and the mean discharge rate above baseline at 20 min plotted. Each column and horizontal bar represents mean ± SEM. **; $p<0.05$ *vs.* saline (Kruskal-Wallis test)

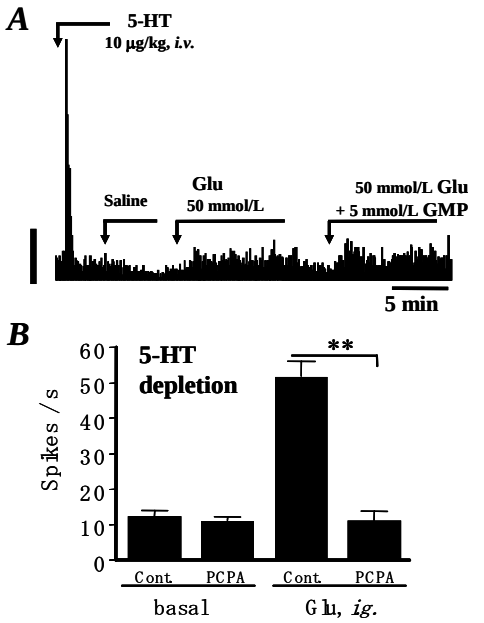

Figure 2. Feature of glutamate-sensing by rat gastric vagus.
A: Influence of 5-mononucleotide on the gastric glutamate sensation. GMP (guanosine 5'-monophosphate) and Glu (monosodium salt of glutamic acid) were applied directly into the stomach; B: Effect of mucosal 5-HT depletion on the gastric glutamate response. PCPA (*p*-cholorophenylalanine) was injected intraperitoneally twice per day for 2 days at a dose of 200 mg/kg. Each point and vertical bar represent mean ± SEM. (Data were modified from Uneyama *et al*[3]

The distribution of umami taste receptors within the rat gastric mucosa was identified with specific antibodies to these receptors, especially mGluRs. Positive-staining for

some mGluRs exists in the rat gastric mucosa. Interestingly, positive-mGluR$_1$ staining corresponded to the apical side of the gastric mucosal epithelium, indicating that mGluR$_1$ may interact with luminal nutrients.[6]

PHYSIOLOGICAL SIGNIFICANCE OF THE NUTRIENT INFORMATION CARRIED BY LUMINAL GLUTAMATE

To study weather glutamate stimulation in the stomach controls the reflex of alimentary organs; the rat vagal efferent nerve activity was monitored after intra-gastric administration of free glutamate in rats (Fig. 3). Intragastric application of glutamate (150 mmol/L) activated the gastric and pancreatic efferent nerve activities. Consequently, glutamate information from afferents of the stomach affects the stomach itself, the function of digestive organs such as the pancreas, and regulates food digestion evoking the vago-vagal reflex.

This effect of glutamate into the gastric function was originally reported by a Russian research group in 1992,[7] using the Pavlov-pouched dogs (Fig 4A). To monitor changes in gastric juice content, meat was fed to dogs with or without umami flavour, a mixture of 92% monosodium glutamate and 8% inosine monophosphate. Supplementation with umami flavour enhanced gastric secretion by 1.6 times approximately.

In a collaborative study with the Pavlov institute of physiology, the direct effect of free glutamate in gastric secretion, using Pavlov's-pouched dogs, was further verified with a liquid diet of free amino acids instead of meat. A gastric fistula and a gastric pouch were made, and the liquid diet was directly applied into the main stomach. Collected gastric juice from the pouched stomach and its pepsinogen content were measured. As a result, only the amino acid mixture that included free glutamate enhanced gastric acid secretion. From this, it became clear that the gastric-sensing of dietary glutamate is important in triggering the gastric secretion. We propose that without free glutamate the stomach is unable to trigger the normal phase of gastric digestion.

To estimate the efficacy of free glutamate in the medical diets based on the oral and gastric sensation of glutamate, medical doctors and dieticians were involved in several clinical trials. For instance, Kochetkov *et al*[8] reported the effect of free glutamate fortification to daily hospital meals on gastric secretion and appetite in patients with chronic atrophic gastritis (Fig. 4B). Patients with atrophic gastritis suffer from loss of appetite due to gastric dyspepsia. They monitored the basal and maximal capacity of gastric acid secretion after the daily meal supplemented with free glutamate during 24 days, and observed that fortification with free glutamate improved gastric secretion and appetite in these patients. In the other hand, Zai *et al* studied how protein-rich liquid diets supplemented with free glutamate affected healthy volunteers using a stable isotope.[9] The oral intake of a protein-rich meal (a mixture of 50 % casein calcium and 50% dextrin) delayed the gastric emptying rate leading to postprandial dysesthesia such as heavy stomach and abdominal fullness. The breath test is a common clinical measurement to evaluate gastric emptying monitoring the content of ^{13}C-labelled carbon dioxide in normal respiration

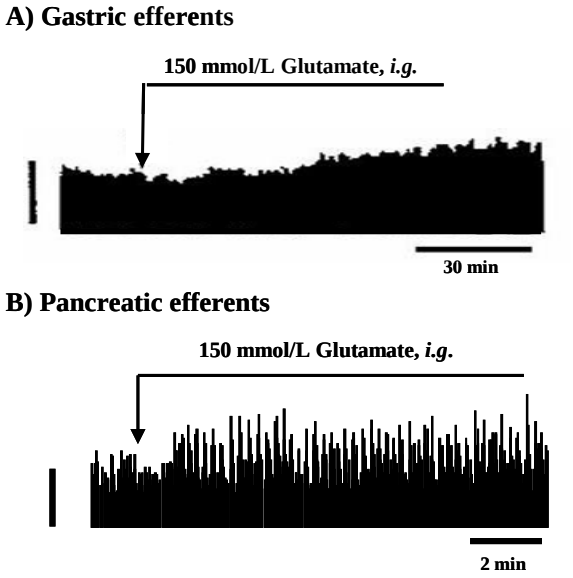

Figure 3. Reflex control of digestive organs by gastric glutamate-sensing in rats.
Efferent nerve activities of the gastric (**A**) and pancreatic (**B**) branches of the abdominal vagus were monitored after the intragastric *(i.g.*) administration of an isotonic 150 mmol/L glutamate solution.

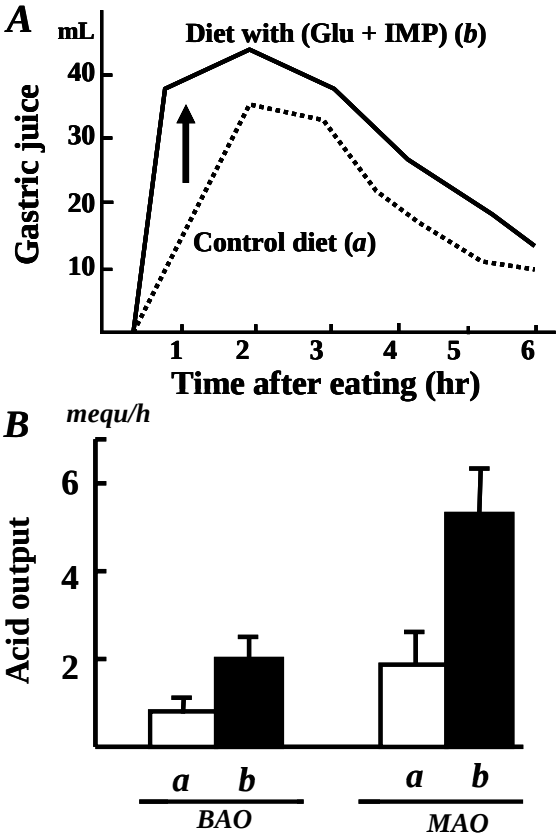

Figure 4. Effects of free glutamate from the diet on stomach digestive functions.
A: Effect of umami substances, containing free glutamate, on canine gastric secretion. Experiments were performed with 3 dogs that had the Pavlov's gastric pouches. Umami substances (2.8g) were supplemented to the meat of the diet (100g); B: Free glutamate fortification of hospital's meals. Basal acid output (BAO) and maximal acid output (MAO) capacities in patients with chronic atrophic gastritis were measured before and after glutamate fortification (2-3g/day). (All data were quoted from ref. 7 and ref. 8.)

after ingesting a mixture of ^{13}C-labelled sodium acetate. With this technique, it was shown that the supplementation of 0.5% of free glutamate to the protein-rich liquid diet significantly increased the delayed gastric emptying rate. As a result, the free glutamate-enriched meals attenuate the symptoms of maldigestion or functional dyspepsia and could be applied to improve these processes.

PERSPECTIVES

The industrial significance of free glutamate was noticed in the food industry after the discovery of sodium glutamate in 1908 by Kikunae Ikeda of Tokyo Imperial University in Japan. He wanted to commercialize the component of *kombu* (a type of seaweed) that produces umami taste as seasoning. Up to date, umami taste has been established as one of the five basic tastes, distinct from the other basic tastes such as saltiness, bitterness, sourness and sweetness.

Behind the establishment of the new taste conception, scientific evidence for the physiological significance of free glutamate-containing foods has accumulated over a century since its first discovery. Oral stimulation by free glutamate evokes cephalic phase of food digestion, such as an induction of pancreatic juice secretion.[10] In healthy and elderly volunteers, oral intake of free glutamate simulates salivation which is essential for mastication and swallowing.[11,12]

In this review, we showed that foods with free glutamate evoke umami taste in the tongue and, after swallowing, visceral detection that induces the activation of gastric vagal afferents. Gastric glutamate information is then transferred to the brain stem via vagal afferents that controls the digestive function of abdominal organs, especially the stomach. This gastric glutamate-sensing mechanism helps with the digestion of foods by modulating gastric secretion, emptying and intestinal absorption. In the taste research field, it has been believed that umami taste, free glutamate, acts as a marker for protein intake. We propose that the palatability of umami taste may reflect its physiological need for protein digestion.

AUTHOR DISCLOSURES

Hisayuki Uneyama, Ana San Gabriel, Misako Kawai, Miki Tomoe and Kunio Torii, no conflicts of interest, except that this paper is authored in part from the Ajinomoto Co, Inc.

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