

Role of Dietary Free Glutamate in Gastrointestinal Function

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Abstract

Glutamate is a non-essential amino acid that confers umami taste. Recently, several taste receptors for umami taste have been identified in the oral cavity as well as in the gastrointestinal tract. Gustatory stimulation of the tongue by glutamate activates vagal gastric, pancreatic, and hepatic efferent nerves. In the gastrointestinal tract, glutamate excites afferent fibers of the abdominal vagus nerve. Recent data suggest the possibility that a chemosensory system similar to that found in the mouth is also present in the stomach and small intestine and that this system aids in regulating gastrointestinal functions. In this review, we have summarized the known effects of dietary free glutamate on gastrointestinal functions such as gastric secretion and gastrointestinal motility, and we explore the possibility of application of glutamate as a medical food supplement. Fortification of protein or amino acid rich diets with free glutamate enhances gastric secretion and promotes gastric emptying. Current results indicate that free glutamate modulates gastrointestinal functions, especially gastric digestion, via cephalic or gastrointestinal phase responses. Dietary supplementation of enteral nutrition with free glutamate could help to prevent complications of these diets, especially diarrhea.

Keywords: L-glutamate; Umami; Gastric secretion; Gastrointestinal motility; Gastric emptying; Diarrhea; Vagal nerve

Introduction

Glutamate is the most abundant amino acid and is widely distributed in vegetables, meats, and fish. Free glutamate imparts a distinctive taste, known as the umami taste (savory taste). Seasonings and food ingredients such as cheese, tomato, soy sauce, and dried mushrooms are especially enriched in free glutamate. In Japan, the estimated daily intake of free glutamate exceeds 1.6g per person.

Recent advances in molecular biology have allowed identification of several receptors for umami taste derived from glutamate. The taste buds on the tongue in the oral cavity are proposed to have a taste receptor (T1R1/T1R3 heterodimer) and metabotropic glutamate receptors (mGluR1 and mGluR4) for umami taste perception [1-5]. In the gastrointestinal tract of mice, rats and humans, mGluR1 and T1R receptors are also expressed in the gastric mucosa [6,7].

Current questions now focus on how umami taste signals are transmitted from the oral cavity or the gastrointestinal tract to the brain. The digestive system contributes to homeostasis by breaking down food into nutrients that can be readily absorbed and metabolized. Events that occur during food digestion are usually divided into two phases according to of the location in the digestive system that they occur; namely, cephalic and gastrointestinal phases. The cephalic phase is triggered by sensory exposure such as the taste, smell, or merely the sight and sound of food. This phase plays an important role in regulation of food digestion, nutrient absorption, and utilization [8]. Gustatory stimuli, such as those imparted by glutamate on the tongue, activate the vagal gastric, pancreatic, and hepatic efferent nerves [9-11]. This suggests that glutamate regulates several functions via the cephalic phase. Indeed, the stimulation evoked by umami promotes gastrointestinal secretions, such as saliva and pancreatic juice, as well as endocrine secretions (e.g., insulin) [12-15].

The gastrointestinal phase of digestion begins once food enters the stomach. This phase promotes gastric secretion and gastric motility, slows the exit of chyme from the stomach, and promotes the continued

digestion of foods that have reached the small intestine. Recently, we reported the possible existence of a unique glutamate-sensing system within the gastrointestinal tract, especially in the stomach [16]. Intra-gastric glutamate was found to excite afferent fibers of the abdominal vagus nerve. Sensory perception by the abdominal vagus is well known to initiate the coordinated processes of gastrointestinal motility, exocrine and endocrine secretion, immunity, and satiation [17-19].

In this review, we examine the evidence for effects of dietary free glutamate on gastrointestinal functions such as gastric secretion and gastrointestinal motility, and the possibility of application of free glutamate to promote digestion of medical diets.

Effects of dietary free glutamate on gastric secretion

Acidic gastric juices, which contain a protein-digesting enzyme (pepsin), help the digestion of protein in the stomach. Gastric juice secretion is triggered by both the cephalic and the gastrointestinal phases of digestion. The cephalic phase response reportedly contributes approximately 30-50% of the stimulation of acid secretion following the ingestion of a meal [20]. The gastrointestinal phase depends on a complex set of neural, hormonal, and cellular mechanisms that result from distension of the stomach and chemical stimuli, such as osmotic pressure, pH, and molecular interactions of macronutrients. The mechanism underlying glutamate modulation of gastric secretion is not yet known.

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The effect of dietary free glutamate on gastric secretion was originally reported in studies that used the Pavlov-pouch in dogs (a vagus nerve sparing pouch) [21]. Meat with or without umami flavor (glutamate + inosine 5'-monophosphate) was fed to dogs and changes in gastric juice were monitored. The umami flavor supplementation caused a rapid and prolonged 1.6 fold increase in the meat-stimulated gastric juice secretion. Kochetkov et al. [22] reported that supplementation of a daily hospital meal with free glutamate for 24 days improved gastric secretion and appetite in patients with atrophic gastritis suffering from loss of appetite due to gastric dyspepsia.

Recent reports have now shed new light on how free glutamate modulates gastric juice secretion. Khropycheva et al. reported that the effect of dietary glutamate on the gastrointestinal phase of gastric secretion depended on the characteristics of the co-applied macronutrients [22,23]. Supplementation of glutamate to an amino acid-rich diet enhanced the secretion of acid, pepsinogen (inactive form of pepsin), and fluids in dogs with Pavlov pouches. However, glutamate has no similar effect when added to a carbohydrate-rich diet and it had no effect on basal secretion when supplied alone without a diet. Our own research also indicated that supplementation of glutamate to a protein-rich liquid diet enhanced gastric juice volume and decreased gastric pH in rats (Somekawa, JPEN 2007). The effect of free glutamate could depend on the proportion of neural and humoral signals occurring during ingestion of different nutrients.

Effects of dietary free glutamate on gastrointestinal motility

Free glutamate promotes gastric juice secretion and may aid in protein digestion. Gastrointestinal motility plays several important roles, such as mixing food and gastric juice in the stomach, forcing digested food into the duodenum, and regulating the speed to match the capacity that the intestines can digest and absorb the food. The mechanism by which free glutamate modulates gastrointestinal motility is not yet clear.

Toyomasu et al. [24] reported that intragastric glutamate stimulated upper gastrointestinal motility (gastric body, antrum, duodenum, jejunum) via the vagus nerves in conscious dogs. They used force transducers chronically implanted on the serosal surface

of the gastrointestinal tract to show that addition of intraluminal free glutamate enhanced the contractile response in both the fed and fasted states. They also used an acetaminophen method to show that an intragastric supply of free glutamate stimulated postprandial motility and accelerated gastric emptying of dog food (solid diet). (Gastric emptying is the parameter where food empties from the stomach to the duodenum).

Free glutamate might also operate as a prokinetic agent in the upper gut. If the stomach sends undigested food too rapidly into the duodenum, this could create a sensation of discomfort sensation. We reported that when free glutamate is co-applied with a liquid diet, its effect on gastric emptying does not support its activity as a prokinetic agent and glutamate addition does not cause a discomfort sensation due to enhanced gastric emptying.

Gastric emptying has also been evaluated by the ^{13}C breath test, where $[1-^{13}\text{C}]$ sodium acetate was used as a standard tracer for liquid test meals [25,26]. Three types of liquid test meals (400ml) were used: a protein-rich liquid meal (12.5% dextrin and 12.5% casein-calcium, 400kcal), a carbohydrate liquid meal (25% dextrin, 400kcal) and non-caloric water. These test meals were used as a base and were supplemented with 0.5% w/v of monosodium L-glutamate (MSG), which is a concentration that would be typically ingested in a common diet and is also the optimal concentration sensed as "umami" (broth for clear soup, soba and udon, soup for ramen noodles, etc.) [27,28]. The results are shown in (Figure 1 and Table 1). The unit for the vertical axis of the graph in the figure (%dose/h) is that used in the breath test and, in this setting, it represents the rate of gastric emptying at each time interval. The parameter in the table ($t_{1/2\text{ex}}$) indicates the time at which half of the total (cumulative) amount of ^{13}C in the breath was exhaled. A smaller value indicates faster gastric emptying. The addition of glutamate accelerated gastric emptying only when the protein-rich liquid meal was ingested. Hosaka et al. have also recently showed that glutamate supplementation of a liquid-containing liquid meal (400ml/520kcal, Protein/Fat/Carbohydrate: 100/300/120kcal) did not affect gastric emptying (2011 Digestive Disease Week).

The reason for this inconsistency has not yet been identified, but possibly might involve gastric juice secretion, as gastric emptying

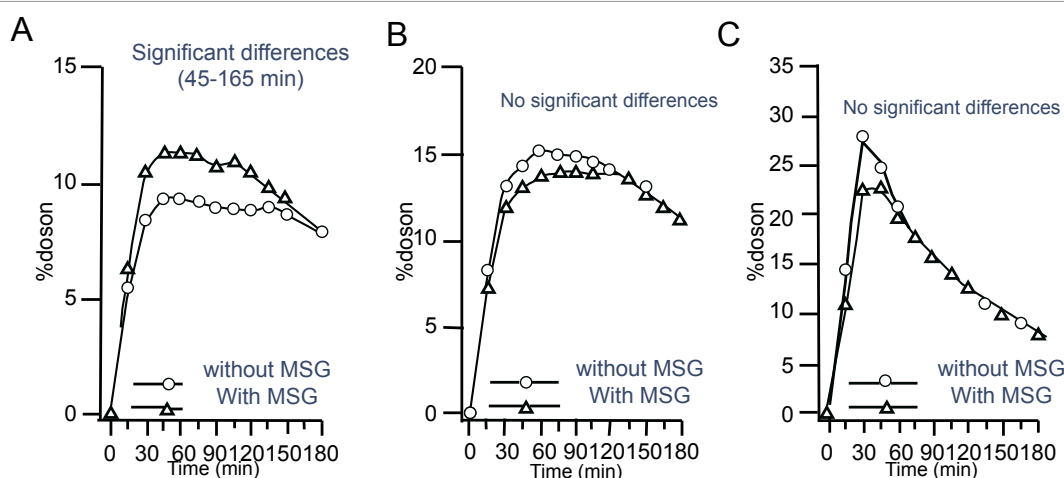


Figure 1: Effect of MSG on gastric emptying. a) Effect of MSG after ingestion of a protein-rich liquid meal (n=10). b) Effect of MSG after ingestion of a carbohydrate liquid meal (n=9). c) Effect of MSG after water intake (n=9). See text for detail. Reproduced from Zai et al. [46].

and gastric juice secretion are closely interrelated [29,30]. Gastric acid reducing agents (Proton pump inhibitors, PPIs) delay gastric emptying of solid meals, which involves a process of hydrolysis, and but can delay or have no effect on gastric emptying of calorie-containing liquids, which contain freely available nutritional factors or ingredients in undigested food [29]. Boutry et al. used ultrasonography in humans to show that free glutamate supplementation to a liquid diet (700kcal/600ml, Protein/Fat/Carbohydrate: 20/35/45%) raised the postprandial antrum distension [31]. They hypothesized that the gastric distension did not translate into a delay of gastric emptying but may involve acid secretion promoted by free glutamate. In addition, the effect of glutamate on gastric emptying may vary depending on other nutritional factors or ingredients in the undigested food.

The efficacy of acceleration of gastric emptying of high protein liquid diets in response to free glutamate has not yet been adequately explained. Tanaka et al. [32] reported that free glutamate supplementation of a protein-rich liquid diet reduced post-ingestive abdominal discomfort, such as stomach fullness and heaviness, in healthy adult volunteers >45 y age. These findings suggest that dietary free glutamate supplementation in elderly subjects, who experience clinically significant gastric disorders, might improve stomach function and overall nutrition.

Clinical application of glutamate to medical foods

Free glutamate modulates gastric juice and gastrointestinal motility, especially when included in a protein or amino acid rich meal. Protein malnutrition is a problem in many elderly individuals [33]. Enteral nutrition (EN) is a useful method for the patient whose gastrointestinal tract is functional but who cannot orally consume adequate amounts of nutrients. However, EN has some adverse side effects, such as gastrointestinal, metabolic, and mechanical complications. Diarrhea is the most common gastrointestinal side effect [34] and limits the clinical usage of the enteral liquid diets for many postoperative and elderly patients. In clinics, post-vagotomy diarrhea has been a major nutritional problem associated with abnormal GI functions such as abnormal regulation of gastric emptying of enteral liquid diets [35]. Normal gastric emptying requires adequate activation of the gastric as well as celiac vagus. Free glutamate supplementation of these diets could be a possible solution for the complications of EN, especially diarrhea.

We reported that free glutamate supplementation of a casein-protein liquid diet prevents the incidence of diarrhea during repetitive intra-gastric tube feeding in rats [36]. This is the first observation to indicate that fortification of an enteral liquid diet with a single nutrient can prevent postoperative diarrhea (Figure 2). A possible mechanism underlying this effect is shown in (Figure 3). The protein-rich liquid diet, by itself, did not induce the activation of gastric vagal afferents, but

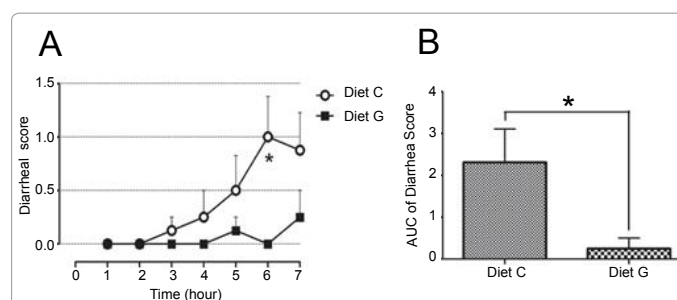


Figure 2: Effect supplementation of a protein-rich liquid diet with free glutamate on postoperative diarrhea. One day following gastrectomy, rats were administered a 2.7mL shot of a liquid diet once per hour for 7 hours. Rats injected with a liquid diet supplemented with 0.5% MSG [●] (Diet G, n=8); rats injected the diet without MSG [○] (Diet C, n=8). Diarrhea was scored every hour for seven hours for each animal (0=normal, 1=slight, 2=moderate, 3=severe). (A): Time course for diarrhea scores; (B): the area under the curve for the diarrhea scores. The data are means \pm SE. * $p < 0.05$ (by Mann-Whitney's U test) Reproduced from Somekawa et al. [36].

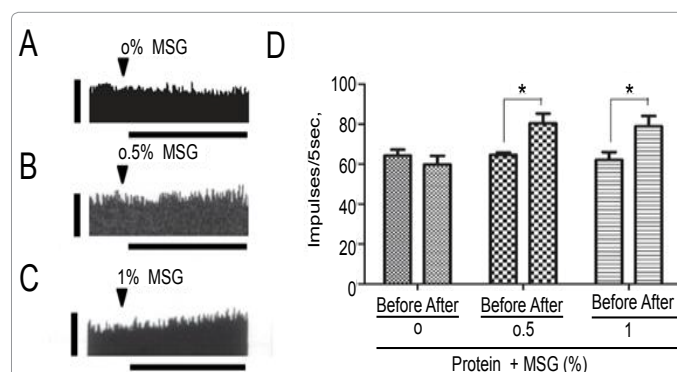


Figure 3: Vagal gastric activity following intra-gastric application of a protein-rich liquid diet, with or without free glutamate supplementation. (A)-(C): Representative recording of gastric afferent discharge, displayed as a sequential rate histogram, after intragastric administration of 2 mL of a liquid protein-rich (casein) diet supplemented with 0, 0.5, or 1% MSG. Arrowheads indicate the points at which the solution was infused. The vertical bar indicates 100 impulses/5 s. The horizontal bar indicates 30 min. (D): Summary of changes in discharge rate, showing the impulse values of diets containing 0, 0.5, and 1% MSG on gastric afferent activity measured before and after administration. Each point and vertical bar represents means \pm SE from 5 different rats * $p < 0.05$ (by a paired t-test). Reproduced from Somekawa et al. [36].

supplementation of the diet with free glutamate significantly enhanced the afferent activities. The result that purified casein protein alone could not induce the afferent activation of the gastric vagus may also indicate that protein is poorly recognized as a nutrient in the stomach. Supplemental free glutamate and glutamate released by the process of protein digestion cannot be distinguished when present in the oral cavity/gastrointestinal tract. Then, one hypothesis that might partly explain the physiological effects of glutamate upon the gastrointestinal tract is that glutamate in its free form will act upon physiological targets before glutamate will be released from alimentary (and endogenous) proteins in the lumen of the digestive tract.

Ohura et al. [37] reported clinical data showing that the frequency of diarrhea occurrence dropped when a Medi-F push care (MPC), a glutamate-added enteral nutrition product, was given. They used MPC in nutritionally depleted patients and found reduced severity of diarrhea in 7/8 cases, improved nutrition in 17/20 cases, and improvement in bedsores in 4/4 cases.

	Protein-rich liquid meal (n=10)	Carbohydrate liquid meal (n=9)	Water (n=9)
$t_{1/2ex}$ min. (mean \pm S.D.)			
Group without MSG	212.7 \pm 102.6	172.6 \pm 38.2	97.4 \pm 10.2
Group with MSG	153.0 \pm 34.6*	197.6 \pm 92.8	90.8 \pm 9.0

* $p < 0.05$

See text for detail. Reproduced from Zai et al. [46]

Table 1: Effect of MSG on gastric emptying.

Glutamate is thought to help the recognition of enteral nutrition products as food by the stomach and to promote appropriate digestion and absorption. To date, the physiological importance of the free glutamate that co-exists with natural proteins has been ignored, since the focus of enteral liquid diets developed so far has been on delivery of simple purified nutrients to patients. These results seen in rats and human strongly suggest that supplementation of the naturally occurring free amino acid, glutamate, to enteral liquid diets can improve the digestion, absorption, and utilization of these diets (and thereby leading to prevention of diarrhea), by transmitting visceral glutamate information from the stomach to the brain. Further research is in progress.

Perspectives

In this review, we showed evidence that dietary free glutamate modulates gastrointestinal function via cephalic and gastrointestinal phases. Decreased gastrointestinal function is a health issue for many people, including the elderly [38] and those with functional dyspepsia (FD). FD is a clinical syndrome that features abdominal symptoms centered in the upper abdomen without an organic disease [39]. Functional food could help these people. We recommend further studies to investigate both the cephalic and gastrointestinal phases.

Recently, aspects of the cephalic phase, including taste as well as smell and texture, have been tested in clinics [40-42]. Lunding et al. reported that vagal activation by sham feeding during the cephalic phase improves gastric motility in FD patients [43]. When the cephalic phase is absent or decreased, such as occurs with enteral and parenteral nutrition or in elderly people whose taste and smell capabilities have diminished, cephalic phase stimulation might be a useful method to increase nutrition. Preliminary evidence has also been reported in preterm infants, where oral stimulation with a latex pacifier during gavage feedings leads to enhanced growth efficiency [44].

In the field of taste physiology research, each basic taste is thought to have a physiological meaning with respect to ingestion and maintaining nutrient homeostasis (e.g., sweetness as an energy source, saltiness as minerals, sourness as spoiled foods, bitterness as poisons, and umami taste as proteins). Recently, Janssen et al. [45] reported that a bitter taste receptor agonist can regulate the secretion of ghrelin. The roles that taste receptors in the gastrointestinal tract play remain to be investigated.

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