MINI-REVIEW

Dietary monosodium glutamate enhances gastric secretion

Raisa Khropycheva[1], Hisayuki Uneyama[2], Kunio Torii[2], and Vasiliy Zolotarev[1]

[1]Laboratory of Physiology of Digestion, Pavlov Institute of Physiology of the Russian Academy of Sciences, St.-Petersburg, Russia ; and [2]Physiology and Nutrition Group, Institute of Life Sciences, Ajinomoto Co., Inc., Kawasaki, Japan

Abstract : Dietary L-glutamate (Glu), an amino acid abundant in many foodstuffs in a free form, is able to modulate physiological functions in the stomach, including secretion and motility. Recently, specific receptors for Glu were identified in the apical membrane of chief cells in the lower region of fundic glands and in the somatostatin-secreting D-cell fraction of the gastric mucosa. This Glu-sensing system in the stomach is linked to activation of the vagal afferents. Among 20 kinds of amino acid, luminal Glu alone activated the vagal afferents in the stomach through a paracrine cascade led by nitric oxide and followed by serotonin (5-HT). In dogs with Pavlov pouches, found that supplementation of an amino acid-rich diet lacking Glu with monosodium Glu (MSG) enhanced the secretion of acid, pepsinogen, and fluid. However, MSG did not affect these secretions induced by a carbohydrate-rich diet and it had no effect on basal secretion when MSG was applied alone without the diet. Enhancement of gastric secretion by MSG was abolished by blockage of the gastric afferents using intra-gastric applied lidocaine. This effect of MSG was due in part to stimulation of 5-HT$_3$ receptors in the gastric mucosa. J. Med. Invest. 56 Suppl. : 218-223, December, 2009

Keywords **:** *dietary glutamate, stomach, secretion, vagus, 5-HT$_3$ antagonist*

INTRODUCTION

The gastric mucosa recognizes a variety of chemical characteristics of food from simple, such as osmotic pressure and pH, to complex, such as molecules of macronutrients. These chemical characteristics of a meal signal quality as well as quantity. This information alters gastric secretomotor function by activating specific nervous and endocrine pathways and related mechanisms at the very beginning of digestive process (1, 2). Among other nutrients, amino acids and short hydrophobic peptides are known as the most active stimuli inducing gastrin release and acid secretion in the stomach (3, 4). The origin of free amino acids and short peptides in the gastric lumen is straightforward. Ingested dietary protein and peptides are cleaved by activated pepsin preferentially on the COOH-terminal sides of aromatic amino acids including L-Phe, L-Trp and L-Tyr (5). Thus, at the beginning of protein digestion some short peptides and amino acids are released before exiting the stomach. The only amino acid which is regularly ingested in a free form is glutaminic acid or its ionic form glutamate, well recognized for its characteristic umami taste.

Received for publication October 28, 2009 ; accepted November 4, 2009.

Address correspondence and reprint requests to Vasiliy Zolotarev, Ph.D., Laboratory of Physiology of Digestion, Pavlov Institute of Physiology, Makarova nab. 6, Saint-Petersburg 199034, Russia and Fax : +7-812-328-0501.

FREE GLUTAMATE IN GASTRIC LUMEN

L-Glutamate (Glu) in a free form is found at marked concentrations both in animal and plant foodstuffs such as green tea, seaweed, mushrooms, potato, Chinese cabbage, soybean, sardines, shrimps, and milk (6). High concentrations of Glu are found in ripe tomatoes (140 mg/100 g) and in Parmesan cheese (1200 mg/100 g). As a food additive, Glu is generally used as a sodium salt (monosodium glutamate, MSG). Average consumption for Europeans is 0.3-0.5 g/day individually ; in Asian countries the intake of added Glu is estimated to 1.2-1.7 g/day (7). An important potential application of free dietary Glu is to use it in supplements of hospital meals and diets for enteral nutrition. Glu is a major oxidative fuel and an important substrate for the synthesis of the other amino acids, glutathione, and protein in the intestine (8, 9) and is often applied to augment gut function. Addition of 3 g of Glu to daily hospital meals of patients with chronic atrophic gastritis for 24 days improved appetite, gastric acid secretion and secretion of gastrin (10). In parallel, this treatment reduced dyspepsia, and lipid peroxidation and caused an increase of body mass (11). Enteral Glu brought a survival advantage to hematological and oncological patients (12). In elderly patients, MSG supplementation of food caused an increase of food intake and improved nutritional status (13). Furthermore, moderate increase of luminal Glu may offer a therapeutic approach to stimulate gastroduodenal contractile activity and to reduce feeding intolerance in premature infants (14, 15).

GASTRIC MUCOSA SENSING OF GLUTAMATE

There is little doubt that the gastrointestinal (GI) mucosa is the main site for regulatory action of enteral Glu, because under normal circumstances of digestion, almost all ingested Glu is extensively metabolized in the mucosal cells and does not appear in the portal circulation (8). Several sites of interaction of dietary amino acids are described at the apical membranes of gastric mucosal cell, including calcium sensing receptors (CaSRs) (1, 4), metabotropic glutamate receptors type 1 (mGluR1) (16), T1R1/T1R3 peptides (17), and amino acid transporters (18). CaSRs are expressed in gastric acid-secreting parietal cells and pepsinogen-secreting chief cells (19, 20), as well as in surface mucus-secreting cells (21) and gastrin-secreting G-cells in the antrum (22). These receptors activated by divalent cations are also sensitized by several kinds of amino acids, *i.e.* aromatic, polar and acidic ones, but aromatic amino acids are the most potent among them (1). A specific taste receptor for Glu (mGluR1) was initially revealed immunohistochemically at the apical membrane of chief cells in the lower region of the fundic glands in the rat stomach (16). Quite recently, Gi-protein coupling mGluR subtypes were also identified in the somatostatin-secreting D-cell fraction of the gastric mucosa (23). The heterodimer T1r1/T1r3 is known as an umami taste receptor in the taste buds on the surface of the tongue. These dimer components were identified by PCR in the antral stomach tissues of mice (17). However, the precise localization of the T1r1 and T1r3 heterodimer in stomach mucosa is not yet been reported. Finally, the excitatory amino acid transporter 1 (GLAST) has been labeled along the luminal surface both mucus neck cells and parietal cell of the mouse stomach (18).

DIETARY GLUTAMATE AND DIGESTIVE FUNCTIONS

There is substantial evidence that dietary glutamate, identified by gustatory and gut receptors, modulates physiological functions in the GI tract. Oral uptake of MSG stimulates cephalic phase exocrine secretions of saliva, bile and pancreatic juice (24-26), in parallel with secretion of insulin (27). In the 1990s, a role of dietary Glu in control of the gastric secretion was first investigated in series of studies in dogs. Ingestion of 2.8 g of MSG elevated and prolonged secretion of gastric juice induced by either meaty food or injection of pentagastrin (28). However, aqueous MSG solution did not affect these basal levels nor secretion caused by sham feeding in dogs (29). Further, in healthy human volunteers, enrichment of liquid diets with 0.5% MSG (w/v) enhanced the gastric empting rate. However, intubation of aqueous MSG solution alone did not affect stomach motility as compared to water. Physiological functions of MSG in the stomach are varied depending on the co-existing macronutrients, *i.e.* protein, carbohydrate, fat and so on. For example, gastric empting rate of liquid diet is enhanced when MSG is co-applied with protein diet but does not in the case of protein free one. This permissive effect is coupled with recognition of individual macronutrient intake by the brain and control of consequent digestion in the intestine (30).

Glu-sensing systems in the stomach are linked to activation of the vagal afferents that transmit food signals to the brain. Short latency impulse discharges of both afferent and efferent fibers of the gastric branches of the vagus nerve were stimulated specifically by luminally applied Glu but not other natural amino-acids (2, 31). In contrast, hepatic afferents respond to all amino acids delivered into the portal vein (32). Luminal Glu activates the vagal afferents in the gastric submucosa through the paracrine cascade, led by nitric oxide and followed by serotonin (5-HT), which in turn interacts with 5-HT_3 receptors on afferent fibers (2, 33).

LUMINAL MSG AND GASTRIC SECRETION

As described above, luminally applied Glu modulates gastric functions via local mechanisms, by interacting directly with secretory cells in the gastric glands, or through neuroendocrine pathways. We have recently studied the role of enteral MSG in vago-vagal reflex control of gastric secretion. In this research we used the dog model with a surgically split stomach, known as a small gastric pouch, as originally described by Pavlov (34). The small gastric pouch was prepared from tissues of the fundus and the upper corpus preserving vagal branches. It was fully separated from the main stomach, so that solutions applied to the main stomach did not interact with mucosa of the pouch. Aqueous MSG solutions intubated through a fistula directly into the main stomach at concentrations of 10-100 mM did not affect basal secretion from the small Pavlov gastric pouch. In contrast, a small amount (20 mL) of liquid diet (Elental), containing 17 amino acids as the protein source (excluding Glu), or a carbohydrate-rich diet (based on decstrin) without amino acids (both manufactured by Ajinomoto Co., Inc, Tokyo, Japan) stimulated moderate acid and fluid output from the pouch. Supplementation of Elental with 10-100 mM MSG (equimolar NaCl used as control) enhanced secretion of acid and fluid in a concentration-dependent fashion. Furthermore, addition of MSG induced pepsinogen production in the pouch, which did not occur when the Elental liquid diet was infused alone. However, MSG had no enhancing effect on the secretory response to the carbohydrate-rich diet (Fig. 1). The stimulative effect of MSG in the Elental liquid diet was totally

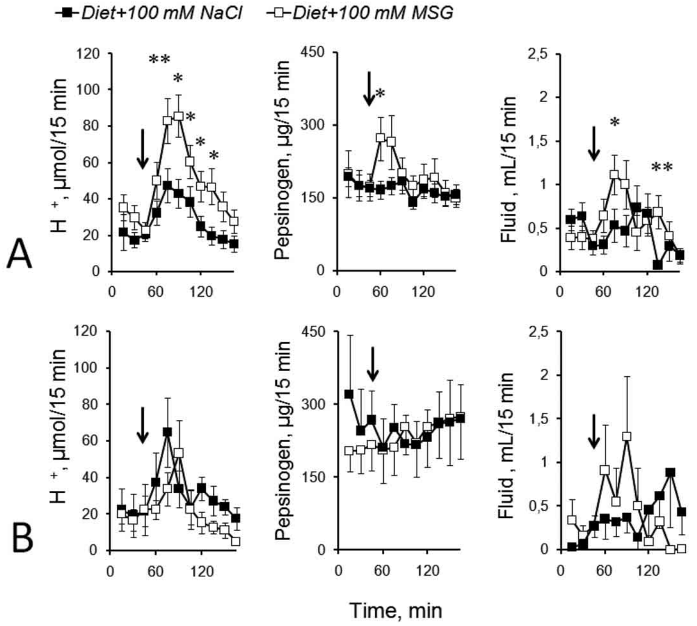

Fig. 1 Supplementation with 100 mM monosodium L-glutamate (MSG) enhanced gastric secretion induced by a high-caloric amino acid-rich diet, but it did not affect secretion induced by a carbohydrate-rich amino acid-free diet in Pavlov pouch dogs. A) Secretion of acid, pepsinogen and fluid in the small gastric pouch stimulated with an amino acid-rich diet (see details in the text). B) Secretion in the small gastric pouch induced by a carbohydrate-rich, amino acid-free diet. Both diets were infused through a fistula into the main stomach ; secretions were measured in the washes from the Pavlov pouch. Data are expressed as means± SEM. Solutions were intubated into the main stomach after a 45-min stabilization period ; bolus infusions are marked with arrows. Paired comparisons were made with Student's t test ; * : $p< 0.05$, ** : $p< 0.01$; $n=9$ in each group.

suppressed after intra-gastric infusion of a local anesthetic, lidocaine (5%), which blocked submucosal afferent responses. Recently it has been shown that antagonism of 5-HT_3 receptors with granisetron selectively attenuates Glu-specific impulse discharge in gastric branches of the vagus nerve associated with stimulation of mucosal mGluR1 (2). In our study, granisetron (20 μg/kg, *i.v.*) did not affect basal secretions from the Pavlov gastric pouch but it did attenuate increases in secretion when MSG was co-applied with Elental. Blockage of 5-HT_3 receptors totally abolished the MSG-induced increase of pepsinogen secretion and partially reduced the enhancement of acid and fluid output, indicating that the effect of dietary MSG on gastric secretion is partially mediated by 5-HT_3 receptors.

CONCLUSIONS

The regulatory role of umami substances in the process of digestion is not restricted to cephalic phase secretion of digestive juices and insulin which depend upon excitation of taste receptors in the oral cavity. Being the only amino-acid regularly ingested in a free form, Glu in the stomach induces physiological effects. It directly interacts with receptors on both exocrine and endocrine cell in the gastric mucosa, for example chief cells and probably also D-cells, and it stimulates nervous pathways. At doses not exceeding its typical concentrations in food, itragastrically applied Glu activates vagal afferent fibers in the stomach through production and release of nitric oxide and consequently serotonin in mucosal cells. We have shown that stimulation of the gastric afferent response by direct infusion of Glu into the stomach enhances gastric phase secretion, especially secretion of pepsinogen ; and that this effect partially depends on activation of 5-HT_3 receptors. In several experimental models it was demonstrated that aqueous solutions of MSG do not affect secretion or motility in the stomach. Instead, MSG becomes a moderate activator of gastric functions when it is co-applied with other nutrients. Importantly, Glu selectively interacts with nutrients, enhancing the effects of protein- or amino acid-rich diets but does not have this effect with a protein-free carbohydrate diet. New data concerning the expression of Glu receptors on D-cells allow us to speculate that nervous system effect induced by dietary MSG on gastric secretion is amplified by simultaneous MSG-induced reduction of somatostatin release (23). Finally, the success of the enteral feeding of patients may depend on the secretory state of the stomach (35). Our studies in combination with others previously published show that free Glu supplementation of elementary liquid diets should improve gastric secretory capacity and enhance motility. MSG supplement of liquid diets should be considered for patients with GI complications.

ACKNOWLEDGEMENT

Experimental study at the Pavlov Institute of Physiology was financially supported by Ajinomoto Co., Inc.

REFERENCES

1. Conigrave AD, Brown EM : Taste receptors in the gastrointestinal tract II. L-Amino acid sensing by calcium sensing receptors : implications for GI physiology. Am J Physiol 291 : G753-G761, 2006
2. Uneyama H, Niijima A, San Gabriel A, Torii K : Luminal amino acid sensing in the rat gastric mucosa. Am J Physiol 291 : G1163-G1170, 2006
3. Noto T, Nagasaki M, Endo T : Role of vagus nerves and gastrin in the gastric phase of acid secretion in male anesthetized rats. Am J Physiol 272 : G335-G339, 1997
4. Busque SM, Kerstetter JE, Geibel JP, Insogna K : L-type amino acids stimulate gastric acid secretion by activating of the calcium-sensing receptor in parietal cells. Am J Physiol 289 : G664-G669, 2005
5. Kageyama T : Pepsinogens, progastricsins, and prochymosins : structure, function, evolution, and development. Cell Mol Life Sci 59 : 288-306, 2002
6. Ninomija K : Natural occurrence. Food Rev Int 14 : 177-211, 1998
7. Beyreuther K, Biesalski HK, Fernstrom JD, Grimm P, Hammes WP, Heinemann U, Kempski O, Stehle P, Steinhart H, Walker R : Consensus meeting : monosodium glutamate-an update. European J Clin Nutrition 61 : 304-313, 2007
8. Reeds PJ, Burrin DG, Stoll B, Jahoor F : Intestinal glutamate metabolism. J Nutr 130 (4S

Suppl) : 978S-82S, 2000

9. Young VR, Ajami AM : Glutamate : an amino acid of particular distinction. J Nutr 130 (4S Suppl) : 892S-900S, 2000
10. Kochetkov AM, Shlygin GK, Loranskaya TI, Vasilevskaia LS, Kondrashev SYU : Utilization of monosodium glutamate in combined therapy of atrophic gastritis. Vopr Pitan (5-6) : 19-22, 1992
11. Shirina LI : A study of lipid peroxidation in patients with chronic gastritis during administration of a food additive monosodium glutamate. Vopr Pitan (4) : 34-36, 1996
12. Zielger TR, Bye RL, Persinger RL, Young LS, Antin JH, Wilmore DW : Effect of glutamine supplementation on circulating lymphocytes after bone marrow transplantation : a pilot study. Am J Med Sci 315 : 4-10, 1998
13. Yamamoto S, Tomoe M, Toyama K, Kawai M, Uneyama H : Can dietary supplementation of monosodium glutamate improve the health of the elderly? Am J Clin Nutr 90(3) : 844S-849S, 2009
14. Burrin DG, Soll B : Metabolic fate and function of dietary glutamate in the gut. Am J Clin Nutr 90(3) : 1S-7S, 2009
15. Neu J, Zhang L : Feeding intolerance in very-low-birthweight infants : what is it and what can we do about it? Acta Pediatr (Suppl) 94 : 93-9, 2005
16. San Gabriel AM, Maekawa T, Uneyama H, Yoshie S, Torii K : mGluR1 in the fundic glands of rat stomach. FEBS Letters 581 : 1119-1123, 2007
17. Bezencon C, le Coutre J, Damak S : Taste-signaling proteins are coexpressed in solitary intestinal epithelial cells. Chem Senses 32 : 41-49, 2007
18. Iwanaga T, Goto M, Watanabe M : Cellular distribution of glutamate transporters in the gastrointaestinal tract of mice. An immunohistochemical and in situ hybridization approach. Biochem Res 26(6) : 271-278, 2005
19. Cheng I, Qureshi I, Chattopadhyay N, Qureshi A, Butters RR, Hall EA, Cima RR, Rogers KV, Hebert SC, Geibel JP, Brown EM, Soybel DI : Expressions of an extracellular calcium sensing receptor in rat stomach. Gastroenterology 116 : 118-126, 1999
20. Hebert SC, Cheng S, Geibel J : Functions and roles of the extracellular Ca^{2+} -sensing receptor in the gastrointestinal tract. Cell Calcium 35 : 239-247, 2004
21. Rutten MJ, Bacon KD, Marlink KL, Stoney M, Meichsner CL, Lee FP, Hobson SA, Rodland KD, Sheppard BC, Trunkey DD, Deveney KE, Deweney CW : Identification of a functional Ca^{2+} -sensing receptor in normal human gastric mucous epithelial cells. Am J Physiol 277 : G662-G670, 1999
22. Buchan A, Squires P, Ring M, Meloche R : Mechanism of action of calcium sensing receptor in human antral gastrin cells. Gastroenterology 120 : 1128-1139, 2001
23. Nakamura E, Hasumura M, San Gabriel A, Uneyama H, Torii K : Functional roles of glutamate receptors/transporters on cultured D cell somatostatin release isolated from rat gastric mucosa. 36 IUPS Congress, Kyoto, P4PM-5-5, 2009
24. Ohara I, Otsuka S, Yugari Y : Cephalic phase response of pancreatic exocrine secretion in conscious dogs. Am J Physiol 254 : G424-G428, 1988
25. Spielman A : Interaction of saliva and taste. J Dent Res 69 : 838-843, 1990
26. Raybould H : Visceral perception : sensory transduction in visceral afferents and nutrients. Gut 51 : 11-14, 2002
27. Graham T, Sgro V, Friars D, Gibala M : Glutamate ingestion : the plasma and muscle free amino acid pools of resting humans. Am J Physiol 278 : E83-E89, 2000
28. Vasilevskaia L, Rymshina M, Shlygin G : Effect of glutamate and combined with inosine monophosphate on gastric secretion. Vopr Pitan 3 : 29-33, 1993
29. Slygin GK, Vasilevskaja LE : The mechanism of potentiative effect of glutamate on gastric secretion. Dokl Akas Nauk SSSR 312(4) : 1010-4, 1990
30. Zai H, Kusano M, Hosaka H, Shimoyama Y, Nagoshi A, Maeda M, Kawamura O, Mori M : Monosodium L-glutamate added to a high-energy, high-protein liquid diet promotes gastric empting. Am J Clin Nutr 89 : 1-5, 2009
31. Niijima A : Reflex effects of oral, gastrointestinal and hepatoportal glutamate sensors of vagal nerve activity. J Nutr 130 : 971S-973S, 2000
32. Niijima A, Meguid MM : An electrophysiological study on amino acid sensors in the hepatoportal system in the rat. Obes Res 3 : 741S-5S, 1995
33. Iijima J, Horie S, Hasegawa R, Yasui H, Takami

S : Immunohystochemical and morphologic basis for glutamate signaling in the rat stomach. Biol Pharm Bull 31(10) : 1838-1840, 2008

34. Zolotarev V, Khropycheva R, Uneyama H, Torii K : Effect of free dietary glutamate on gastric secretion in dogs. Ann NY Acad Sci 1170 : 87-90, 2009

35. Hamilton M, Chapman MV, Mutch M, Bennet-Guerrero E, Mythen MG : The relationship between a pentagastrin-stimulated gastric luminal acid production test (Gastrotest) and enteral feeding-related gastrointestinal complications in critically ill patients. Anesth Analg 100 : 1447-52, 2005