Forum Minireview

New Frontiers in Gut Nutrient Sensor Research:
Monosodium L-Glutamate Added to a High-Energy, High-Protein Liquid Diet Promotes Gastric Emptying: a Possible Therapy for Patients With Functional Dyspepsia

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Abstract. Functional dyspepsia is a clinical syndrome that features abdominal symptoms centered in the upper abdomen without an organic basis. Three possible mechanisms of gastric dysfunction could be related to functional dyspepsia: 1) delayed gastric emptying, 2) impaired gastric accommodation to food intake, and 3) hypersensitivity to gastric distention. Delayed gastric emptying has been suggested to lead to prolonged antral distension that causes dyspeptic symptoms. Delayed gastric emptying is therefore a focal point of debate about anorexia caused by dyspepsia, and prokinetic agents are often administered in Japan for its treatment. Recently, we found that addition of monosodium L-glutamate (MSG) to a high-energy liquid diet rich in casein promoted gastric emptying in healthy men. Therefore, another potential method to improve delayed gastric emptying could be enhancement of chemosensors that activate the autonomic nervous system innervating the gastrointestinal tract. In conclusion, enrichment with glutamate promoted gastric emptying after intake of a high-protein meal, suggesting that free glutamate is important for protein digestion and that MSG may be helpful for management of delayed gastric emptying in patients with functional dyspepsia.

Keywords: 13C breath test, functional dyspepsia, gastric emptying, monosodium L-glutamate (MSG), Rome III criteria, gastrointestinal tract

Functional dyspepsia (FD) was defined by the Rome II criteria as a clinical syndrome characterized by chronic or recurrent symptoms centered in the upper abdomen, in the absence of underlying organic disease that is likely to explain the symptoms (1). The symptom complex of FD includes epigastric pain, bloating, postprandial fullness, early satiety, nausea, vomiting, belching, and anorexia. In the Rome III criteria, however, FD symptoms are reduced to only four categories, which are 1) bothersome postprandial fullness, 2) early satiation, 3) epigastric pain, and 4) epigastric burning. The relationship with food intake has been proposed as a distinguishing feature for FD subgroups such as epigastric pain syndrome and postprandial distress syndrome (2). Recently, it was reported that postprandial fullness is the most severe symptom in patients who report aggravation of their symptoms by a meal (3).

Although the pathophysiology of FD is still unknown, it has been suggested that there could be three possible mechanisms related to gastric dysfunction (4 – 10): 1) delayed gastric emptying, 2) impaired gastric accommodation to food intake, and 3) hypersensitivity to gastric distention. Delayed gastric emptying was initially considered to be the main cause of symptoms in patients with FD. In the clinical setting, it is assumed that delayed gastric emptying and consequent prolonged antral
distension could reduce hunger, increase satiety, and even cause gastric discomfort, all of which would pose a significant barrier to adequate nutrition. Accordingly, delayed gastric emptying is a focal point of debate about anorexia caused by dyspepsia, and prokinetic agents are often administered in Japan for its treatment.

Another method of improving delayed gastric emptying involves the enhancement of meals with flavors and seasonings that activate the autonomic nervous system innervating the gastrointestinal (GI) tract. Oral intake of the monosodium salt of l-glutamic acid [monosodium l-glutamate (MSG)], a known flavor enhancer, stimulates exocrine secretion, including saliva, gastric juice, bile juice, and pancreatic juice (11–15), as well as GI endocrine secretion of hormones such as insulin (16). Free l-glutamate binds to taste receptors on taste cells in the oral cavity and activates taste nerves to elicit the unique taste umami (17, 18).

Recently, genes encoding glutamate-sensing receptors have been identified in the oral cavity (T1R1–T1R3 heterodimers, ionotropic receptors, and different variants of metabotropic glutamate receptors) (19–24). These receptors are expressed in the taste buds and likely to contribute to detection of the ‘umami’ taste. Infusion of amino acids into the intestine has been shown to increase vagal afferent activity and antrroduodenal contraction (25). Interestingly, two groups of researchers have reported that T1Rs and mGluR1, receptors mediating the umami taste in the oral cavity, are expressed in the GI mucosa of humans, rats, and mice (26, 27). Intragastric administration of l-glutamate increases the firing rate of afferent fibers running in the gastric branch of the vagus nerve in rats (28). These reports suggest that the stomach is capable of sensing umami substances, which may help to regulate digestion and absorption.

Recently, we investigated whether enrichment with L-glutamate influenced the rate of gastric emptying in healthy humans, while searching for a possible new therapy for FD patients (29). Ten healthy volunteers without H. pylori infection were enrolled. All ten subjects underwent the high-protein meal test, while nine also underwent the carbohydrate meal test and water meal test. All tests were performed after an overnight fast. Two different control liquid test meals (400 kcal/400 ml) labeled with 100 mg of 13C sodium acetate were used. The high-protein meal consisted of 12.5% dextrin and 12.5% casein-calcium, while the carbohydrate meal contained 25% dextrin. MSG (0.5% w/v; Ajinomoto Co., Inc., Tokyo) was added to the control liquid test meal. All meals were flavored with the non-caloric sweetener aspartame (Ajinomoto Co., Inc.) and plum scent to mask the taste of glutamate. To investigate whether the presence of nutrients influenced the effect of glutamate, 400 ml of water was also ingested. For measurement of gastric emptying, a 13C breath test was performed (30, 31). Although scintigraphy is often considered the gold standard for measurement of the gastric emptying rate, the breath test we used has been validated against scintigraphy. For three hours after ingestion of the test meal, breath samples were obtained automatically via a special nasal cannula (Breath ID System and ID Kit; Oridion Medical, Jerusalem, Israel). The breath test data were expressed as the percent recovery per hour of the administered dose of 13C (%dose/h), and the curves that were drawn showed the velocity of gastric emptying at each point. The %dose/h was determined by calculating the ratio of 13CO2 to 12CO2 in the breath samples. Gastric emptying was evaluated by using two parameters. The first was the half-emptying time (t-1/2ex). The t-1/2ex is the time at which half of the dose of 13CO2 has been excreted when total 13CO2 excretion occurs at infinity. The other parameter was the cumulative %dose/h (area under the %dose/h curve) at 180 min. The following results were obtained.

1) Effect of adding MSG to the high-protein meal: When the %dose/h curve (gastric emptying flow curve) and the cumulative %dose/h curve were drawn, the %dose/h curve was shifted in an upward direction after intake of the high-protein meal with MSG. This change indicated acceleration of the velocity of gastric emptying. Adding MSG to the test meal significantly decreased t-1/2ex, while the cumulative %dose/h (area under the %dose/h curve) at 180 min was significantly increased. The t-1/2ex with/without MSG was 153.0 ± 34.6* / 212.7 ± 102.6 min (± S.D., *P < 0.05), while the cumulative %dose/h at 180 min was 28.6 ± 2.4 / 24.7 ± 3.4* (± S.D., *P < 0.05). Thus, MSG significantly accelerated gastric emptying. 2) Effect of adding MSG to the carbohydrate meal: The t-1/2ex with/without MSG was 197.6 ± 92.8 / 172.6 ± 38.2 min (± S.D.) and the cumulative %dose/h (area under the %dose/h curve) at 180 min was 36.4 ± 2.6 / 38.6 ± 3.2 (± S.D.). MSG had no effect on the gastric emptying rate after intake of the carbohydrate test meal. 3) Effect of adding MSG to water (n = 9): Following the ingestion of 400 ml of water, the %dose/h curve showed a rapid rise. The t-1/2ex with/without MSG was 90.8 ± 9.0 / 97.4 ± 10.2 min (± S.D.) and the cumulative %dose/h (area under the %dose/h curve) at 180 min was 42.7 ± 4.8 / 45.6 ± 1.7 (± S.D.). There were no significant changes of any of the gastric emptying parameters after adding MSG to water.

What is the mechanism underlying the improvement of gastric emptying by MSG after a high-protein meal? According to several reports, the oral intake of MSG stimulates exocrine secretion. Thus, the mechanism involved in the promotion of gastric emptying by MSG...
after a high-protein meal is likely to involve an increase of digestive juice secretion. Several recent reports have also suggested involvement of the gastric phase of digestion. Mucosal receptors for L-glutamate (umami substances) have recently been identified in the GI tract of mice, rats, and humans; and it has been suggested that luminal L-glutamate may activate these mucosal receptors or vagal nerve afferents.

Addition of glutamate improved gastric emptying after the high-protein test meal, but conversely caused slight slowing of gastric emptying after the equi-caloric carbohydrate test meal or non-caloric water test meal. This discrepant response suggests that L-glutamate acts on the GI tract in a different manner from prokinetic agents that uniformly increase motility by direct activation of the myenteric plexus (32 – 35). In general, water leaves the stomach most rapidly, while carbohydrate and protein meals are processed by the stomach at a similar rate; gastric emptying of the high-energy, high-protein liquid test meal in humans.

Our finding that a dose of MSG with the range of daily intake promotes gastric emptying after consumption of a high-protein liquid meal suggests that we should pay attention to the amino acid composition of foodstuffs to understand their influence on digestion.

In conclusion, we showed that addition of free L-glutamate promotes gastric emptying after intake of a high-energy, high-protein liquid test meal in humans. Although further studies of gastric emptying and post-prandial sensation are necessary, our findings suggest the potential use of glutamate for the improvement of GI dysfunction related to delayed gastric emptying.

References


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