Monosodium l-glutamate added to a high-energy, high-protein liquid diet promotes gastric emptying

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INTRODUCTION

A wide variety of factors affect rates of gastric emptying. For example, the ingredients and energy density of meals are known to influence gastric emptying significantly. In clinical circumstances, delayed gastric emptying and subsequent prolonged antral distension (1) can reduce hunger, increase satiety, and, in some cases, cause stomach discomfort, all of which pose significant barriers to adequate nutrition (2–4). In such situations, delayed gastric emptying is a focal point of debate about anorexia caused by dyspepsia, and prokinetic agents are administered widely for treatment.

Other methods to improve delayed gastric emptying may involve the chemosensory (gustatory and olfactory) enhancement of meals with flavors and seasonings, which activate the autonomic system that innervates the gastrointestinal (GI) tract. Oral intake of a monosodium salt of l-glutamic acid [monosodium l-glutamate (MSG); a flavor enhancer] is known to stimulate secretions from the exocrine system (saliva and gastric, bile, and pancreatic juices) (5–9) and those from the GI endocrine system (such as insulin) (10). Free l-glutamate binds to receptors on taste cells in the oral cavity, activating taste nerves that elicit the unique taste known as umami (11, 12).

Genes encoding glutamate-sensing receptor molecules were recently identified in the oral cavity (T1R1-T1R3 heterodimers, ionotropic, and different variants of various metabotropic glutamate receptors) (13–18). Interestingly, several recent reports have shown that T1Rs and mGlur1 are also expressed in the upper GI mucosa of humans, rats, and mice (19, 20). Furthermore, intragastric administration of l-glutamate has been shown to increase the firing rate of afferent fibers in the gastric branch of the rat vagus nerve (21). These reports suggest that the stomach is capable of sensing umami substances that help regulate digestion and absorption.

Knowing that free l-glutamate coexists naturally with dietary proteins and that l-glutamate activates the autonomic nervous system by both taste and GI luminal stimulation, we investigated whether l-glutamate enrichment could affect the rate of gastric emptying. This study tests the effect of l-glutamate enrichment on gastric emptying in 3 groups of healthy men who consumed protein-rich liquid meals, equicaloric carbohydrate liquid meals, or equivolume noncaloric water meals.

SUBJECTS AND METHODS

Healthy volunteers

Before the study, Helicobacter pylori infection was assessed by serology (Mitsubishi Kagaku Bio-clinical Laboratories Inc, 1 From the Department of Medicine and Molecular Science, Gunma University Graduate School of Medicine, Maebashi, Japan (HZ, HH, AN, MM, OK, and MM), and the Department of Endoscopy and Endoscopic Surgery, Gunma University Hospital, Maebashi, Japan (MK and YS).

2 The experimental diets and monosodium l-glutamate used in this study were kind gifts from Ajinomoto Co, Inc.

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Tokyo, Japan) at a laboratory in central Japan. Ten healthy male volunteers (mean age: 32.4 y; range: 27–45 y) without H. pylori infection were enrolled. The following exclusion criteria were applied: 1) no previous abdominal surgery (except appendectomy), 2) no regular medication use, and 3) no intake of medications during the previous week that could alter GI motor function.

Experimental protocol
The Institutional Review Board of Gunma University Graduate School of Medicine approved the study protocol, and all subjects gave written informed consent. All examinations were performed after an overnight fast (the subjects could drink water freely until 30 min before examination). When the same subject participated in ≥2 different examinations, the examinations were conducted ≥1 wk apart. The schedule of examinations was set as a double-blind study, and the order of test diets was randomized. The subjects were asked to ingest the test meal in the first 3 min of the examination and were then instructed to lie in supine position during the examination.

Test meals
Three types of liquid test meals (400 kcal/400 mL) labeled with 100 mg [13C]sodium acetate (Cambridge Isotope Laboratories Inc, Cambridge, MA) were prepared: one meal (protein-rich diet) consisted of 12.5% dextrin (TK16; Matsutani Chemical, Itami, Japan) and 12.5% casein-calcium (EN9N; DMV International, Veghel, Netherlands), another (carbohydrate diet) contained 25% dextrin, and the third was a water control to determine whether nutrients influence the glutamate effect. Monosodium L-glutamate (MSG; 0.5% wt:vol; Ajinomoto Inc, Kawasaki, Japan) was either added to or withheld from liquid test meals. To mask the taste of the glutamate, all meals were flavored with the noncaloric sweetener aspartame (Ajinomoto Inc) and plum odor (GIV010790; Givaudan Japan KK, Tokyo, Japan). The dose of MSG to be used in these experiments was chosen to be a normal habitual concentration (22, 23) and that it is similar to half the effective concentration (EC50) value for taste receptors (15, 17, 18, 23). Nine of the 10 subjects included in the study ingested all test meals with and without MSG, and the remaining subject ingested only the protein-rich meals with and without MSG.

Measurement of gastric emptying
During the 3 h after ingestion of a test meal, a [13C] breath test was performed (24–27) on breath samples obtained by using an exclusive nasal cannula connected to an infrared spectrometer (Breath ID System; Exalenz Bioscience Ltd, Modiin, Israel; http://www.exalenz.com) that analyzes the ratio of 13CO2 to 12CO2 in each breath sample. This system, mechanically identical to Microstream capnography for monitoring end-tidal CO2 (Et-CO2), collects each subject’s breath automatically under continuous suction, with virtually no subject cooperation (28–31). The Et-CO2 monitoring system is used widely to monitor the respiration of patients receiving critical care or anesthesia. Breath samples were stored in intermediate cells with built-in capnography to regulate carbon dioxide concentrations, which were subsequently passed on continuously and in sequence to an analysis chamber. The total number of breath samples ranged from 60 to 70 per subject. Ratio data obtained from breath tests are expressed as the rate of 13CO2 recovery (ratio of 13CO2 to 12CO2) per hour of each initially administered [13C] substrate (%dose/h). In plots of %dose/h values, the slope of the resulting curve corresponds to the velocity of gastric emptying between data time points. Values in %dose/h were determined by calculating the ratio of 13CO2 to 12CO2 in the breath samples. Benefits of stable-isotope techniques that use [13C]-labeled test meals for the breath test include ease of performance, noninvasiveness, and high sensitivity for the quantitative assessment of gastric emptying (25, 26, 32–37).

Data analysis
Gastric emptying was evaluated by using 2 parameters: half the gastric excretion (emptying) time (t1/2ex) and total excretion of 13CO2 during 180 min (cumulative %dose/h over 180 min). The t1/2ex indicates the time at which half of the [13C] dose, in relation to cumulative 13CO2 excretion when time is infinite, is excreted (29). For the reasons stated above, t1/2ex and scintigraphic half-emptying time are not identical; however, there is a linear correlation between t1/2ex in the [13C] breath test and scintigraphic half-emptying times (26, 35). Total excretion of 13CO2 during 180 min was calculated by measuring the area under the %dose/h curve.

Statistical analysis
The effects of glutamate enrichment on t1/2ex and total excretion of [13C]CO2 during 180 min were compared, with serving sequence and subject as variables, in an analysis of variance (ANOVA). A repeated-measures 2-factor ANOVA with interactions was used to analyze treatment and time effects in 10 participants ingesting the protein meal and in 9 participants in each of the other meal groups. If a significant interaction between treatment and time was indicated (P < 0.05), pairwise comparisons were performed after a Bonferroni correction. Analyses comparing liquid test meals were carried out by using a repeated-measures 3-factor ANOVA (time, treatment, and meal) with interactions, with significance defined as a P value <0.05. A Bonferroni correction was applied to 3 pairwise comparisons of meals. Statistical analyses were carried out by using SPSS16.0J for Windows (SPSS Inc, Chicago IL). Results are expressed as mean ± SD, and statistical significance is defined as P values <0.05.

RESULTS
Effect of MSG on gastric emptying after a protein-rich meal
The time courses of [13C] excretion (%dose/h curves) for 10 subjects who were used to estimate gastric emptying rate and total excretion of [13C]CO2 during 180 min (Cum-%dose/h during 180 min) after a protein-rich meal are shown in Figure 1. After the protein-rich meal was ingested, the %dose/h curve ascended rapidly, reaching the plateau of 9.4 ± 1.4%dose/h at 45 min. The %dose/h curve after a protein-rich meal with MSG (0.5% wt:vol) ascended further, with a maximum mean (± SD) of
11.4 ± 2.0% dose/h at 60 min. The %dose/h curve for a protein-rich meal showed a significant interaction between time and treatment (P < 0.001). Partial tests showed a significant difference in %dose/h after protein-rich meals with and without MSG (Figure 1A). Total excretion of $^{13}$CO$_2$ (Cum-%dose/h) during 180 min was also significantly higher after a protein meal with MSG than after a meal without MSG (28.6 ± 2.4 compared with 24.7 ± 3.4; P < 0.05) (Table 1). There was a corresponding significant reduction in $t_{1/2}$ with the addition of MSG (with MSG: 153.0 ± 34.6 min; without MSG: 212.7 ± 102.6 min). On the basis of these data, we concluded that MSG significantly accelerates gastric emptying of a protein-rich meal (Table 1).

**Effect of MSG on gastric emptying after a carbohydrate meal**

In contrast, no significant differences attributable to MSG were observed in %dose/h curves (Figure 2A). Cum-%dose/h during 180 min (36.4 ± 2.6 compared with 38.6 ± 3.2), or $t_{1/2}$ (197.6 ± 92.8 compared with 172.6 ± 38.2 min) after ingestion of a carbohydrate meal (Table 1). We concluded that MSG had no effect on gastric emptying after a carbohydrate meal.

**Effect of MSG on gastric emptying after a water meal**

There were no significant differences in $t_{1/2}$ (90.8 ± 9.0 compared with 97.4 ± 10.2 min) or in Cum-%dose/h during 180 min (42.7 ± 4.8 compared with 45.6 ± 1.7) in participants who ingested the water meal with or without MSG (Table 1). Although the %dose/h curves for water showed a significant interaction between time and treatment (P < 0.05), partial tests did not show any significant differences at single time points (Figure 3). We concluded that MSG does not significantly enhance gastric emptying after intake of water (Table 1).

**TABLE 1**

<table>
<thead>
<tr>
<th></th>
<th>Protein-rich meal (n = 10)</th>
<th>Carbohydrate-rich meal (n = 9)</th>
<th>Water (n = 9)</th>
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<tbody>
<tr>
<td>$t_{1/2}$ (min)$^2$</td>
<td></td>
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<tr>
<td>Without MSG</td>
<td>212.7 ± 102.6</td>
<td>172.6 ± 38.2</td>
<td>97.4 ± 10.2</td>
</tr>
<tr>
<td>With MSG</td>
<td>153.0 ± 34.6$^b$</td>
<td>197.6 ± 92.8</td>
<td>90.8 ± 9.0</td>
</tr>
<tr>
<td>AUC for total excretion of $^{13}$CO$_2$ (Cum-%dose/h)$^d$</td>
<td></td>
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<tr>
<td>Without MSG</td>
<td>24.7 ± 3.4</td>
<td>38.6 ± 3.2</td>
<td>42.7 ± 4.8</td>
</tr>
<tr>
<td>With MSG</td>
<td>28.6 ± 2.4$^b$</td>
<td>36.4 ± 2.6</td>
<td>45.6 ± 1.7</td>
</tr>
</tbody>
</table>

$^b$ All values are mean ± SD. A repeated-measures 3-factor ANOVA (time, treatment, and meal) with interaction detected significant differences in %dose/h curves between the 3 types of meals (P < 0.001). Post hoc paired comparisons of each meal showed that gastric emptying was significantly faster after ingestion of water than after a protein-rich or carbohydrate meal (P < 0.01), but that there were no significant differences in emptying time between a protein-rich meal and a carbohydrate meal. MSG reduced $t_{1/2}$ and increased the total excretion of $^{13}$CO$_2$ significantly during 180 min with intake of a protein-rich meal but not with intake of a carbohydrate or water meal, indicating that MSG can modulate digestive function after protein intake.

$^d$ Half the gastric excretion (emptying) time, ie, the time at which half of the total input of $^{13}$C is excreted when time is infinite.

$^b$ Significantly different from without MSG condition for the same meal type, P < 0.05.

$^d$ Area under the curve for the cumulative excretion of $^{13}$CO$_2$ from 0 to 180 min.

**Effects of liquid test meals**

A repeated-measures 3-factor ANOVA (time, treatment, and meal) with interaction detected significant differences in %dose/h curves between the 3 types of meals (P < 0.001). Post hoc paired comparisons of each meal showed that gastric emptying was significantly faster after ingestion of water (P < 0.01), but that there were no significant differences in emptying after a protein-rich meal or a carbohydrate meal.
DISCUSSION

In this study, enrichment of a high-energy liquid diet rich in casein (a major dairy protein in liquid meals) with MSG promoted gastric emptying in healthy men. We anticipate that the results of this study will be useful in designing treatments for the elderly, patients with dyspepsia and anorexia, and others for whom delayed gastric emptying is a significant problem. Delayed gastric emptying and subsequently prolonged antral distension result in reduced hunger, increased satiety, and, in some cases, stomach discomfort, which often prevents elders and patients from continuing proper nutrition intake (1).

Free L-glutamate binds to taste receptors on taste cells in the oral cavity and activates taste nerves to elicit the unique taste of umami (11, 12)—a pleasant taste sensation that differs qualitatively from sweet, salty, sour, and bitter. Glutamate monosodium salt is used widely as a flavor enhancer in Asian cuisine. Because typical dietary proteins are tasteless by themselves (with salt is used widely as a flavor enhancer in Asian cuisine), it has been suggested that the umami taste presented by glutamate monosodium (11, 12)—a pleasant taste sensation that differs qualitatively from sweet, salty, sour, and bitter—may contribute to taste perception (38). Our finding that free L-glutamate in aqueous solution (39) activates taste receptor cells in the circumvallate papillae (40—43). In general, noncaloric water leaves the stomach most quickly, carbohydrates and proteins leave the stomach at a similar intermediate speed, and lipids clear most slowly. Our findings in post hoc paired comparisons of the gastric emptying curves for 3 types of meals after repeated-measures 3-factor ANOVA support this generalization. The acceleration of gastric emptying observed only with the high-protein diet suggests that glutamate’s effects may vary depending on other nutritional factors or ingredients in ingested food.

According to several reports, oral intake of monosodium L-glutamate stimulates exocrine secretion (saliva and gastric, bile, and pancreatic juices) (5—9). Thus, the mechanism involved in the promotion of gastric emptying of a high-protein meal is likely to involve the digestive juice secretion. Several recent reports also suggest involvement of the gastric phase of digestion: mucosal receptors for L-glutamate (umami substances) have recently been identified in mice, rats, and the human GI tract (19, 20), and it has been suggested that luminal L-glutamate may activate these mucosal receptors or vagal nerve afferents (21). However, the primary mechanism of L-glutamate’s effect on gastric emptying remains to be determined.

Conclusions

This report provides evidence that enrichment of dietary free L-glutamate promotes gastric emptying of a high-energy, high-protein liquid diet in humans. Although further studies of gastric emptying, as well as postprandial sensations, are necessary, our findings suggest the potential for improvements in GI dysfunction involving delayed gastric emptying. The physiologic action promoted by various amino acids must be clarified further to apply this knowledge specifically in a clinical setting.

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The authors’ responsibilities were as follows—HZ: study design, subject recruitment, study setup, data collection, and manuscript writing; MM: study design, interpretation of data, and critical revision of the manuscript; HH, YS, AN, and MM: study setup, data collection, and OK and MM: interpretation of data and critical revision. None of the authors had any conflicts of interest.

REFERENCES