Title: Intragastric monosodium L-glutamate stimulates motility of the upper gut via the vagus nerve in conscious dogs

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Abbreviations:

MSG-Monosodium L-glutamate

MI-Motility index

5-HT3-5-hydroxytryptamine -3

5-HT -5-hydroxytryptamine

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RMCs - Retrograde migrating contractions

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Abstract

Background & Aims: Monosodium L-glutamate (MSG) is a substance known to produce the umami taste. Recent studies indicate that MSG also stimulates a variety of activities in the gastrointestinal tract through its receptor in the gut, but no study has reported the activity in conscious large experimental animals. The aim of our study is to investigate whether direct intragastric MSG stimulates gut motility and to identify the mechanism in conscious dogs.

Methods: Contractile response to intraluminal injection of MSG was studied in the fed and fasted state by means of chronically implanted force transducers. MSG (5, 15, 45, and 90 mM/kg) dissolved in water was injected into the stomach and duodenum in normal and vagotomized dogs. MSG solution was administered into the stomach before feeding and gastric emptying was evaluated. Several inhibitors of gastrointestinal motility (atropine, hexamethonium, and granisetron) were injected intravenously before MSG administration to the stomach. The effect of MSG was investigated in Pavlov (vagally innervated corpus pouch), Heidenhain (vagally denervated corpus pouch), and antral pouch (vagally innervated) dogs.

Results: Upper gut motility was significantly increased by intragastric MSG but not significantly stimulated by intraduodenal MSG. Intragastric MSG (45 mM/kg) stimulated postprandial motility and accelerated gastric emptying. The MSG-induced contractions were inhibited by truncal vagotomy, atropine, hexamethonium, and granisetron. The gut motility
was increased by intrapouch injection of MSG in Pavlov pouch, but it was not affected in
Heidenhain or antral pouch.

**Conclusions:** Intragastric MSG stimulates upper gut motility and accelerates gastric emptying.

The sensory structure of MSG is present in the gastric corpus, and the signal is mediated by the
vagus nerve.

**Key words:** monosodium L-glutamate, gut nutrient sensing, gastrointestinal motility, vagus
nerve
Introduction

L-glutamate is a multifunctional amino acid in the human body. In the brain, it acts as a major excitatory neurotransmitter. Monosodium L-glutamate (MSG) is known to bind to receptors on taste cells in the oral cavity and to elicit the umami taste and stimulate secretions from the gastrointestinal exocrine systems (22, 24) and release of insulin (8). Enhancement using MSG has been reported to accelerate gastric emptying of a protein-rich meals in humans (39).

On the other hand, recent studies have revealed the expression of various taste receptors in the gastrointestinal tract (6, 10, 15, 36). Genes encoding glutamate-sensing receptor molecules were recently identified in the oral cavity. It has been reported that the candidate of umami receptor are T1R1/T1R3, mGluR1, and mGluR4 (5, 19, 25, 32). Interestingly, several recent reports have shown that these receptors are also expressed in the upper gastrointestinal mucosa of humans, rats, and mice (1, 3, 11, 26).

The physiological studies have reported that intragastric administration of MSG increases the firing rate of afferent fibers in the gastric branch of the rat vagus nerve (34). Furthermore, intragastric administration of MSG has induced activation in forebrain regions via the vagus nerves (33). However, the effect of intraluminal administration of MSG on upper gut motility has not been investigated.
Thus, we hypothesized that intragastric MSG also stimulates upper gut motility through the MSG receptor and the vagus nerve. In relation to the expression profile of the receptor in the dog, it was found to be impossible to demonstrate by using materials used in the rat due to the species difference. Therefore, in the present study we concentrated our aim to investigate the effect of intraluminal administration of MSG on upper gut motility and the mechanism whereby the effects are mediate using various antagonists in conscious dogs with various types of gastric pouch.
Materials and Methods

Preparation of Animals

Twenty-nine healthy mongrel dogs of both sexes weighing 10-14kg were divided into 5 groups: normal (n = 8), truncal vagotomy (n = 6), vagally innervated corpus pouch (Pavlov; n = 5), denervated (Heidenhain; n = 5) corpus pouch, and vagally innervated antral pouch (n = 5). There were no statistical differences among the 5 groups in sex distribution and weight.

The overnight-fasted dogs were anesthetized, each with a single intravenous injection of thiopeptonal sodium (Ravonal, Tanabe Pharmaceutical Co., Ltd., Osaka, Japan; 20 mg/kg body weight), and general anesthesia was maintained by intratracheal inhalation of halothane (Fluothane, Takeda Chemical Industries, Ltd., Osaka, Japan) and oxygen. Under aseptic conditions, a silastic tube (Silastic 602-205; Dow Corning, Midland, MI, USA) was inserted into the superior vena cava through a branch of the right external jugular vein (jugular catheter). The jugular catheter was brought out through a skin incision on the neck and fixed to the adjacent skin with silk sutures. The abdominal cavity was opened by a middle incision.

In the normal group, force transducers (13) were implanted on the serosal surfaces of the gastric body at the level of the short gastric artery, the gastric antrum 3cm proximal to the pyloric ring, the mid-duodenum at the level of the main pancreatic duct, and the jejunum 1 and 2 (25cm and 35cm distal to the Treitz ligament, respectively) to detect circular muscle
contraction. A silastic tube was inserted in the gastric lumen so that the tip was positioned in the gastric body proximal to the first transducer (called the gastric catheter). Another silastic tube was placed in the duodenal lumen via the first position of the duodenum with the tip at the duodenal transducer (called the duodenal catheter) (Figure 1A).

In the truncal vagotomy group, the ventral and dorsal vagi were cut immediately below the diaphragm. Force transducers and a gastric catheter were then implanted similarity to the normal group. The completeness of a truncal vagotomy was confirmed by the 2-deoxy-D-glucose test (18).

In the Pavlov pouch group, the pouch was constructed at the greater curvature opposite the splenic hilus preserving myoneural continuity and drained at the distal end of the pouch with a metal cannula (17). A silastic tube was inserted into the pouch at the proximal end of the pouch. This tube (called the pouch catheter) was used as a route for intrapouch infusion of the test solution. Another silastic tube was positioned in the main gastric lumen via the gastric fundus (called the main stomach catheter). Force transducers were implanted on the serosal surface of the middle portion of the pouch, the gastric body opposite the pouch, the gastric antrum 3cm proximal to the pyloric ring, and the mid-duodenum at the level of the main pancreatic duct (Figure 1B).

In the Heidenhain pouch group, the pouch was created in the same region where the Pavlov
pouch was constructed according to the methods described previously (17). All the other procedures were similar to those for the Pavlov pouch group (Figure 1C).

In the vagally innervated antral pouch group, the antral portion was isolated from the corpus portion preserving the vagal trunk. The gastroduodenal junction was cut 5mm distal to the pyloric ring, and the oral end of the duodenum was closed. The gastric corpus was anastomosed to the jejunum 20cm distal to the Treitz ligament with side-to-side anastomosis. Gastric secretions from the pouch were allowed to drain spontaneously from the exteriorized metal cannula. A silastic tube was inserted into the pouch and fixed with a silk suture. This tube (called the pouch catheter) was used as a route for intrapouch infusion of the test solution. Another silastic tube was positioned in the main gastric lumen via the gastric fundus (called the main stomach catheter). Force transducers were implanted on the serosal surface of the middle portion of the pouch, the gastric body at the level of the short gastric artery, the mid-duodenum at the level of the main pancreatic duct, and the jejunum 1 and 2 (15cm and 25cm distal to the Treitz ligament, respectively) (Figure 1D).

The lead wires of the force transducers and silastic tubes were taken out of the abdominal cavity through a subcutaneous tunnel and brought out through a skin incision made between the right and left scapula. After closure of the abdominal cavity, a jacket-type protector was placed on each dog to protect the lead wires and tubes from being damaged in the event that the
dogs scratched themselves. The dogs were housed in individual experimental cages, maintained with intravenous drip infusions of a lactated Ringer’s solution containing vitamins and electrolytes for 5 postoperative days, and gradually returned to a normal diet (15g/kg body weight per day; Funabashi Farm Inc., Funabashi, Japan). All dogs recovered successfully, and they were fed at 5 PM and allowed free access to drinking water except during the experiment. The procedures used in this study were approved by the Review Committee on Animal Use of Gunma University, Maebashi, Japan (#07-198).

**Monitoring of Gastrointestinal Contractions**

The wires from the transducer were connected to a telemeter, and the data were transmitted to a recording system (Eight Star System, Star Medical, Tokyo, Japan). Recorded signals were used to determine each phase of the contraction and the motility index (MI). The MI was the integrated area between the baseline (zero level) and the contractile wave using the Eight Star System.

**Experimental Procedures**

*Intragastric or intraduodenal administration of MSG in the normal group*

These experiments were performed in phase I of the interdigestive state. Each dose of MSG was tested 3 times in each animal on different days and an experiment of administration of MSG was performed once a day.
Forty ml of distilled water containing MSG (5, 15, 45, and 90 mM/kg) was administered as a bolus into the upper gut lumen through the gastric or duodenal catheter 5-10 minutes after the end of interdigestive phase III contractions in the jejunum. The gastrointestinal motor response obtained by the intragastric or intraduodenal administration of 40 ml of 0.9% saline was used as a control. Moreover, to compare with other amino acids, glutamine with an equal concentration to that of MSG was administered into the gastric lumen. Intravenous 5-hydroxytryptamine (5-HT) stimulated the antral motor activity and the response was similar to the MSG-induced contractions. To measure the concentration of serum 5-HT, venous blood samples were obtained at the end of interdigestive phase III contractions and at intervals of 10 minutes after intragastric administration of MSG.

**Gastric emptying**

Each gastric emptying study was performed within 3 weeks of the surgery. Gastric emptying was evaluated by the acetaminophen method. Acetaminophen absorption was used as an indirect measure of gastric emptying. After 12 hours of fasting, the dogs were fed 300 g of dog food (Cainz Dog Meal; Cainz, Takasaki, Japan) including 500 mg of acetaminophen (Calonal, Showa Yakuhin Kako Co., Tokyo, Japan) 5 minutes after intragastric administration of MSG (15, 45, 90, and 135 mM/kg) or 0.9% saline as the control. A blood sample (2 ml) was withdrawn from the jugular catheter 0, 15, 30, 45, 60, 75, 90, 105, 120, 135,
and 150 minutes after the feeding. The serum was separated, frozen, and stored at -30\(^\circ\)C until assaying. The serum acetaminophen concentration was determined with an automatic fluorescence polarization immunoassay (TDx, Abbott Laboratories, IL) at the Department of Pharmacy, Gunma University Hospital. Areas under the contractile waves were measured for 90 minutes after feeding of each solution and expressed as the MI

_Intragastric administration of MSG in the truncal vagotomy group_

Forty ml of distilled water containing MSG (45 mM/kg) or 40ml of 0.9% saline as a control was administered as a bolus into the gastric lumen through the gastric catheter 5-10 minutes after the end of interdigestive phase III contractions in the jejunum 2.

_Intravenous administration of antagonists with intragastric administration of MSG in the normal group_

To study the mechanism of the MSG-induced contractions, the muscarinic receptor antagonist atropine (0.1 mg/kg bolus + 0.1 mg/kg/h for 30 minutes), the nicotinic receptor antagonist hexamethonium (5 mg/kg bolus + 10 mg/kg/h for 30 minutes), the 5-hydroxytryptamine -3 (5-HT3) receptor antagonist granisetron (100 \(\mu\)g/kg/ bolus) or 0.9% saline as the control was administered intravenously 5 minutes after the end of phase III contractions in the jejunum. Intragastric administration of 45 mM/kg MSG was performed 10 minutes after the start of the intravenous infusion of the antagonist.
Administration of MSG into the main stomach or pouch in Pavlov, Heidenhain and innervated antral pouch dogs

After the metal cannula was capped, 40 ml of 45 mM/kg MSG or 40 ml of 0.9% saline as a control was administered as a bolus into the pouch through the pouch catheter 5-10 minutes after the end of interdigestive phase III contractions. After the experiment was finished, the plastic cap was taken off to drain the pouch. Intragastric administration of 40 ml of 45 mM/kg MSG was performed through the main stomach catheter.

Measurement of Serum 5-Hydroxytryptamine

The samples (1 mL) were immediately placed into test tubes containing 100 μL of 10% EDTA and 5% L-ascorbic acid. Then, 2 mL trichloroacetic acid was added and centrifuged at 3,000 rpm for 5 minutes at room temperature. The supernatant was filtered through a 0.45-μm nylon filter, and the samples were subjected to high-performance liquid chromatography according to a previous study (9).

Drugs

MSG, which was purchased from Wako Pure Chemicals Co. (Osaka, Japan), was dissolved in distilled water to make each concentration. We used 40 ml of 0.9% saline (Otsuka Pharmaceutical Co. Ltd., Tokyo, Japan) as the control because the sodium ion contained in 0.9% saline is equivalent to 150 mM of MSG. Atropine sulfate (muscarinic receptor antagonist;
Tanabe Pharmaceutical Co. Ltd., Osaka, Japan), hexamethonium bromide (nicotinic receptor antagonist; Wako Pure Chemicals Co., Osaka, Japan), and granisetron (5-HT3 receptor antagonist; Chugai Pharmaceutical Co. Ltd., Tokyo, Japan) were purchased. The doses of atropine, hexamethonium, and granisetron used in this study were previously reported to inhibit phase III in the stomach in conscious dogs (12, 14, 29).

**Analysis of Data**

Areas under the contractile waves were measured for 20 minutes after intragastric administration of each solution and are expressed as the MI. A computer-assisted system (Eight Star System, version 6.0, Star Medical, Tokyo, Japan) was used for the calculation of the MI (31). We defined the initiation of the upper gut motor response as the start of consecutive non-propagated contractions after administration of MSG. Furthermore, we measured the lag time between MSG administration and the initiation of the motor response and the duration time of MSG-induced contractions at each site. The mean of three studies for each dog was calculated, and all data are expressed as the mean ± SEM. The data were subjected to detailed statistical analysis to obtain repeated measures of analysis of variance followed by Fisher’s protected least significant difference method. Differences at *P* values lower than 0.05 were considered to be significant. The statistical calculations were carried out using the Stat View® software (version 5.0; Abacus Concepts, Inc., Berkeley, CA).
Results

Effect of MSG on upper gastrointestinal motility and serum 5-hydroxytryptamine concentration in the normal group

Intragastric administration of 40 ml saline as a control did not induce any apparent motor effect at any site. Glutamine, which is similar to glutamate in its chemical structure, had little effect on the contractile activity in the stomach when given into the stomach (data not shown). In contrast, intragastric administration of MSG at doses of 5, 15, and 45 mM/kg induced phasic contractions in the gastric body, antrum, duodenum, and jejunum, as shown in Figure 2A and 2B. However, intraduodenal administration of MSG at the same doses did not induce any contractions in the upper gut, as shown in Figure 2C.

The overall pattern of these MSG-induced contractions was consecutive non-propagated contractions. The MI for the 20 minutes after 5, 15, 45 and 90 mM/kg MSG administration increased in a bell-shaped curve at all sites of the upper gut (Figure 3). The durations of MSG-induced contractions at each site increased gradually, except for 90 mM/kg (Figure 4). After the MSG-induced contractions finished, the spontaneous phase I was observed, and the next spontaneous phase III occurred about 100 minutes later. MSG-induced contractions did not affect the contractile pattern of the next phase III. The lag time between MSG administration and the initiation of the motor response was the shortest in the gastric body at all
sites. The times of response in both the jejunum 1 and 2 were significantly longer than that in the gastric body (the data of 45 mM/kg is only shown in Table 1) (P=0.012 and 0.002, respectively).

Serum 5-HT after intragastric MSG was within the range of 150-500 ng/ml regardless of the dose of MSG, and intragastric MSG did not induce a specific pattern such as an increase or decrease of serum 5-HT (data not shown).

Both intragastric and intraduodenal MSG at 90 mM/kg induced consecutive non-propagating contractions from each site of the administration. In addition, intragastric MSG at a dose of 90 mM/kg mostly induced retrograde migrating contractions (RMCs) in the jejunum (83.3%: 20/24 number of experiments), which propagated to the gastric body and were followed by vomiting within 50 minutes (Figure 5A and 5B). Furthermore, intraduodenal 90 mM/kg MSG always induced vomiting (100%: 24/24 Figure 5C). No dog vomited within 50 minutes after the administration of 5 and 15 mM/kg MSG and the control solution into the stomach.

*Postprandial contractions and gastric emptying with or without intragastric MSG*

The postprandial contractions after intragastric administration of MSG were stronger than those after intragastric administration of the control (Figure 6A and 6B). The MI for the 90 minutes after MSG administration was significantly larger than the control administration at all sites (Figure 7A). Gastric emptying was significantly accelerated by 45 mM/kg MSG
compared with the control (P < 0.05 at 45, 60, 75, and 90 min.) (Figure 7B). The area under the curve in 45 mM/kg was significantly larger than that in the control and 135 mM/kg (Figure 7C).

**Effect of intragastric MSG on upper gastrointestinal motility in the truncal vagotomy group**

After truncal vagotomy, phase III contractions of the stomach were observed in an immature form. However, intragastric administration of MSG (45 mM/kg) did not induce any contractions (Figure 8A). In comparison with the normal group, the MI for the 20 minutes after administration of both saline and 45 mM/kg MSG was significantly small (Figure 8B).

**Effect of antagonists on intragastric MSG-induced contractions in the normal group**

Atropine completely inhibited MSG (45 mM/kg)-induced contractions in the gastric body, antrum, duodenum, and jejunum. Pre-treatment with hexamethonium and granisetron significantly diminished MSG-induced contractions, although their inhibitory activity was not as strong as that of atropine, as shown in Figure 9.

**Effect of MSG administered into the pouch and main stomach in Pavlov and Heidenhain pouch dogs**

Administration of MSG (45 mM/kg) into a Pavlov pouch induced significantly stronger phasic contractions in the gastric body, pouch, antrum, and duodenum than the control (Figure 10A and 10B). However, administration of MSG into a Heidenhain pouch did not induce any
contractions (Figure 10C and 10D). In addition, administration of MSG into the main stomach in both Heidenhain and Pavlov pouch dogs significantly induced phasic contractions in the gastric body, pouch, antrum and duodenum (data not shown).

Effect of MSG administered into the pouch and main stomach in antral pouch dogs

Intrapouch administration of MSG (45 mM/kg) did not induce any contraction (Figure 10E and 10F). In contrast, administration of MSG into the main stomach significantly induced phasic contractions in the gastric body, pouch, duodenum, and jejunum (data not shown).
Discussion

In the present study, we showed that intragastric MSG stimulated upper gut motility via the vagus nerve and accelerated gastric emptying in conscious dogs. Furthermore, we indicated that the sensory structure of intragastric MSG was present in the gastric corpus.

In the fasted state, we first reported that intragastric administration of MSG induced consecutive non-propagated contractions at all sites and doses. Since MSG contains the sodium ion in addition to the glutamate ion, we used 0.9% saline as a control solution, because it contains the sodium ion in an equivalent amount to that in the 150mM MSG solution. As intragastric administration of the same volume of saline did not induce any apparent effect at any site, consecutive non-propagated contractions induced by MSG reflected solely the effect of the glutamate ion.

The MI and durations of intragastric MSG-induced contractions increased gradually, but the response to 90 mM/kg was not greater than that to 45 mM/kg. In contrast, the lag time between MSG administration and the initiation of the upper gut motor response at the oral side was shorter than that at the anal side regardless of the dose. Berthoud et al. reported that the vagal efferent neuron demonstrated a gradient of generally decreasing innervation at distal segments of the gut (2). If the MSG-induced contractions are mediated by the vagal efferent nerve, the different innervation of the efferent nerve of the gut may contribute to the difference
in the lag time.

The fact that intraduodenal MSG did not induce any contractions in the present study suggests that the sensory structure that caused MSG-induced contractions is present in the stomach. In this study, MSG-induced contractions occurred rapidly and lasted for several minutes. Generally, the vagus nerve rapidly responds to gastrointestinal chemical stimuli (21). A recent study by Tsurugizawa et al. has indicated that the vagus nerve is important for signaling the presence of intragastric glutamate in the rat forebrain (33). Our result that intragastric MSG did not induce any contractions in the truncal vagotomy strongly suggests that the vagus nerve plays a major role. Furthermore, the response induced by intravenous injection of 5-HT is similar to MSG-induced contractions (38). Since vagal activity increased by direct intragastric MSG has been shown to be related to 5-HT (34) and MSG-induced contractions in our study were inhibited by granisetron, we tried to determine whether or not intragastric MSG elevates the serum concentration of 5-HT. However, it was found that the serum 5-HT concentration was not affected by intragastric MSG, as shown in the present study. We have no direct data but we believe that the effect of MSG are mediated via 5-HT locally.

In our study, intrapouch administration of MSG in the Pavlov pouch stimulated the main stomach as well as the pouch motility, but intrapouch MSG did not induce any contractile response in the Heidenhain pouch. Although, we could not deny the effect was mediated
through intraluminal nerves, we speculated that the presence of intragastric MSG was sensed by
the vagal afferent nerve because the difference between the two pouches was whether the vagal
nerve had been preserved or removed. Uneyama et al. have reported that intragastric MSG
increased the firing rate of afferent fibers of the vagal gastric branch in the rat (34). This
report strongly supports our speculation.

Recently, it has been reported that mGluR1, which is known to be a specific receptor to MSG,
is located at the apical membrane of chief cells (26). In addition, 5-HT3 and nitric oxide
synthase-expressing cells, which are involved in glutamate signaling, have also been found in an
immunohistochemical study in the rat stomach (11). In the present study, we found that
intrapouch administration of MSG stimulated upper gut motility in Pavlov pouch dogs but did
not stimulate it in the vagally innervated antral pouch. These results strongly suggest that the
sensory structure of intragastric MSG is present in the gastric corpus. This suggestion is
compatible with those in previous studies, and supported by the fact that administration of MSG
into main stomach stimulated upper gut motility. We cannot deny the possible participation of
the sympathetic afferent nerve, but the present findings indicate that intragastric MSG is sensed
in the gastric corpus and the signal is transmitted to the vagal afferent nerve.

Intragastric MSG-induced contractions were abolished by atropine and inhibited by
hexamethonium at all sites. These findings are in line with our hypothesis that the
MSG-induced contractions were mediated through the vagal efferent nerve. Then intravenous administration of granisetron inhibited MSG-induced contractions. We could not specify the localization of the 5-HT3 receptor but speculate that intragastric MSG stimulates upper gut motility via 5-HT3 receptor in vagal afferent nerve. The presumed locations of 5-HT3 receptors in the enteric nervous systems are in the enteric neurons and vagal afferent nerve (4, 16, 20), and granisetron inhibited the activation of vagal afferent nerve by intragastric MSG (34). These reports support our speculation.

San Gabriel et al. and Iijima et al. reported the existence of mGluR1 in the mucosal membrane in the rat stomach; therefore, the most likely explanation for the present results in the dog is that the MSG is sensed in the gastric corpus and the signal is transmitted to the vagal afferent nerve via the 5-HT3 receptor. We have no direct evidence, but the signal may be transmitted to the brain. Then, the signal stimulated upper gut motility via the vagal efferent nerve.

The result that intragastric administration of glutamine at an equal concentration to that of MSG did not cause any contractions is in harmony with the findings of a previous report (34) and denies the possibility that the osmotic pressure is involved in MSG-induced contractions. Glutamine has a structure in which the hydroxyl basis of glutamate is replaced with the amino basis. Therefore, the hydroxyl basis may play an important role in the stimulation of upper gut
motility.

When MSG was given in the fed state, the MI was significantly larger than that of the control, and gastric emptying was also significantly accelerated. The past studies in dog (30, 35) reported that amino acids delay gastric emptying, but the delay in emptying seems to be caused by the smaller dose of MSG. We did not study the mechanism of the stimulatory effect of gastric emptying in any more detail; however, it is assumed that the strong contractile activity induced in the gastric antrum accelerated gastric emptying.

Meanwhile, it was reported that the oral ingestion of an excessive dose of MSG in human caused vomiting, redness, and headache, symptoms that are referred to as the Chinese restaurant syndrome (7, 28, 37). The mechanism of the Chinese restaurant syndrome is unknown, but the acceptable daily intake of MSG was not determined by the Joint Expert Committee on Food Additives (JECFA) in 1987. However, it is controversial whether MSG causes the Chinese restaurant syndrome in a double-blind, placebo-controlled study (7, 37). The daily intake of MSG in humans is reported to be about 2g and equivalent to 40ml of 25 mM/kg MSG. In our study, intragastric MSG at a dose of 90 mM/kg induced RMCs beginning in the jejunum and propagating to the gastric body with frequent vomiting within 50 minutes of administration. Our data, in which intraduodenal MSG at a dose of 90 mM/kg always induced RMCs with vomiting, strongly suggests that the mechanism of RMCs and vomiting induced by MSG is at
work in the distal part from the duodenum. Furthermore, both intragastric and intraduodenal
MSG at 90 mM/kg induced consecutive non-propagating contractions from each site of the
administration. Therefore, we speculate that the sensory structure of MSG of the body is
responsible for the consecutive non-propagated contractions via sensing the low-high dose of
MSG. In contrast, the sensory structure of MSG of the distal part from the duodenum is
responsible for the RMCs via sensing the high dose of MSG. The Chinese restaurant syndrome
is caused by oral intake of MSG, and therefore we cannot deny this syndrome is mediated the
receptors of MSG in the tongue. However, we believe that MSG of 90 mM/kg is an overdose
for a dog and this effect may be related to the Chinese restaurant syndrome.

It is well known that MSG is a cue signal of protein ingestion and stimulates secretions from
both the gastrointestinal exocrine and the endocrine systems through its receptor in the tongue
(22, 24). Our data and recent publications by others indicate that MSG is sensed in the gastric
corpus and causes a response. We believe that these findings contribute to the elucidation of
the gut nutrient sensing.

In conclusion, intragastric MSG stimulates upper gut motility through the vagus nerve, which
involves the 5-HT3 receptor and the cholinergic neuron, and this effect can accelerate gastric
emptying. The sensory structure of intragastric MSG is present in the gastric corpus.
Perspectives and Significance

To elucidate the mechanism of the effect of direct intragastric MSG, it is very important to investigate whether the receptors of MSG express in dog stomach and duodenum in vitro. The present study suggests the possibility that MSG might be useful as a prokinetic agent in the upper gut.

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References


**Figure legends**

Figure 1. Schematic diagram showing operative procedures in the following groups: normal (A), Pavlov pouch (B), Heidenhain pouch (C), and innervated antral pouch (D). A silastic tube was inserted as shown in this figure. The black squares denote the site of implantation of force transducers.

Figure 2. Representative effect of intragastric or intraduodenal monosodium L-glutamate (MSG) on upper gut motility in the normal group. (A) Intragastric MSG (15 mM/kg) induced phasic contractions in the gastric body, antrum, duodenum, and jejunum for about 50 minutes. (B) Intragastric MSG (45 mM/kg) induced phasic contractions in the gastric body, antrum, duodenum, and jejunum for a long time. (C) Intraduodenal MSG (45 mM/kg) did not show any response after administration.

Figure 3. Upper gut motility index for 20 minutes after intragastric administration of monosodium L-glutamate. *P < 0.05

Figure 4. Duration of contractile response to monosodium L-glutamate-induced contractions in the normal group. *P < 0.05

Figure 5. Representative effect of intragastric monosodium L-glutamate (MSG) at 90 mM/kg on upper gut motility in the normal group. (A) Intragastric MSG (90 mM/kg) induced retrograde migrating contractions following phasic contractions in the gastric body, antrum, duodenum, and jejunum. (B) The detailed response contractions at vomiting, demonstrating that they
migrated in a retrograde direction. (C) Intraduodenal MSG (90 mM/kg) induced retrograde migrating contractions following phasic contractions in the duodenum and jejunum.

Figure 6. Representative effect of intragastric monosodium L-glutamate (MSG) on upper gut motility in the postprandial period. The postprandial contractions after intragastric administration of MSG (45 mM/kg) (B) were stronger than those after the administration of a control solution (A).

Figure 7. Effect of monosodium L-glutamate (MSG) in the postprandial period. (A) The motility index after administration of 45 mM/kg MSG was significantly large compared with that of the control. (B) The serum acetaminophen concentrations of 45 mM/kg MSG were significantly high compared with those of the control at 45, 60, 75, and 90 min. *P < 0.05 compared with the control. (C) The area under the curve in 45 mM/kg was significantly larger than that in the control and 135 mM/kg. *P < 0.05.

Figure 8. Representative tracings (A) and the motility index (MI) for 20 minutes (B) after intragastric administration of monosodium L-glutamate (MSG) in the truncal vagotomy group. (A) Intragastric MSG did not show any response after administration. (B) The MI after administration of both control and MSG was significantly small compared with that of the normal. *P < 0.05 compared with the normal.

Figure 9. Effect of antagonists on the motility index (MI) for 20 minutes under conditions of
intragastric 45 mM/kg monosodium L-glutamate (MSG)–induced motor response. Atropine, granisetron, and hexamethonium significantly inhibited the upper gut MI of MSG-induced contractions at all sites. *P < 0.05 compared with the control.

Figure 10. Representative tracings showing the effect of intrapouch and motility index (MI) for 20 minutes after administration of monosodium L-glutamate (MSG) into a pouch. (A, B) Administration of MSG (45 mM/kg) into the Pavlov pouch induced phasic contractions and significantly increased the gut MI in the gastric body, pouch, antrum, and duodenum. *P < 0.05 compared with the control. (C, D) Administration of MSG (45 mM/kg) into the Heidenhain pouch did not induce any contractions. (E, F) Administration of MSG (45 mM/kg) into the antral pouch did not induce any contractions.
Table legends

Table 1. Values are expressed as mean ± SEM. *P < 0.05 compared with body.
Fig. 3

[Bar chart showing motility index (gr/min) across different regions of the stomach and small intestine (Body, Antrum, Duodenum, Jejunum1, Jejunum2) for different concentrations (control, 5mM/kg, 15mM/kg, 45mM/kg, 90mM/kg). Asterisks indicate significant differences.]
Fig. 8

A

Gastric body
Gastric antrum
Duodenum
Jejunum 1
Jejunum 2

MSG, 45 mM/kg, Intragastric administration

10 min.

B

Motility Index (gr.min)

Body | Antrum | Duodenum | Jejunum 1 | Jejunum 2

normal | control | vagotony

* * * * *
Fig. 9
Table 1

Lag time (min.) between administration of monosodium L-glutamate and the initiation of upper gut motor response in normal group

<table>
<thead>
<tr>
<th></th>
<th>45mM/kg</th>
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<tbody>
<tr>
<td>Body</td>
<td>2.73 ± 0.20</td>
</tr>
<tr>
<td>Antrum</td>
<td>2.80 ± 0.20</td>
</tr>
<tr>
<td>Duodenum</td>
<td>3.26 ± 0.32</td>
</tr>
<tr>
<td>Jejunum 1</td>
<td>4.75 ± 0.90*</td>
</tr>
<tr>
<td>Jejunum 2</td>
<td>5.39 ± 0.75*</td>
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