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

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Intragastric monosodium L-glutamate stimulates motility of the gut via vagus nerve in conscious dogs. Am J Physiol Regul Integr Comp Physiol 298: R1125–R1135, 2010. First published January 13, 2010; doi:10.1152/ajpregu.00691.2009.—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 was to investigate whether direct intragastric MSG stimulates gut motility and to identify the mechanism in conscious dogs. Contractile response to intraluminal injection of MSG was studied in the fed and fasted states 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). 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. MSG-induced contractions were inhibited by truncal vagotomy, atropine, hexamethonium, and granisetron. Gut motility was increased by intrapouch injection of MSG in the Pavlov pouch, but it was not affected in the Heidenhain or antral pouch dogs. We conclude that 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.

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 with MSG has been reported to accelerate gastric emptying of a protein-rich meal 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 candidates for 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).

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 because of the species difference. Therefore, in the present study we concentrated our efforts on investigating the effect of intraluminal administration of MSG on upper gut motility and the mechanism whereby the effects are mediated, 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 10–14 kg were divided into five groups: normal (n = 8), truncal vagotomy (n = 6), vagally innervated corpus pouch (Pavlov; n = 5), denervated corpus pouch (Heidenhain; n = 5), and vagally innervated antral pouch (n = 5). There were no statistical differences among the five groups in sex distribution and weight.

The overnight-fasted dogs were anesthetized, each with a single intravenous injection of thiopental sodium (Ravonal, Tanabe Pharmaceutical, Osaka, Japan; 20 mg/kg body wt), and general anesthesia was maintained by intratracheal inhalation of halothane (Fluothane, Takeda Chemical Industries, Osaka, Japan) and oxygen. Under aseptic conditions, a Silastic tube (Silastic 602-205; Dow Coming, Midland, MI) 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 3 cm proximal to the pyloric ring, the midduodenum at the level of the main pancreatic duct, and jejunal 1 and 2 (25 cm and 35 cm 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) (Fig. 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 similarly 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 3 cm proximal to the pyloric ring, and the midduodenum at the level of the main pancreatic duct (Fig. 1B).

In the Heidenhain pouch group, the pouch was created in the same region where the Pavlov pouch was constructed according to methods described previously (17). All other procedures were similar to those for the Pavlov pouch group (Fig. 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 5 mm distal to the pyloric ring, and the oral end of the duodenum was closed. The gastric corpus was anastomosed to the jejunum 20 cm 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 midduodenum at the level of the main pancreatic duct, and jejunum 1 and 2 (15 cm and 25 cm distal to the Treitz ligament, respectively) (Fig. 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 solution containing vitamins and electrolytes for 5 postoperative days, and gradually returned to a normal diet (15 g/kg body wt per day; Funabashi Farm, 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 (no. 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 with the Eight Star System.

**Experimental Procedures**

*Intragastric or intraduodenal administration of MSG in normal group.* These experiments were performed in phase I of the interdigestive state. Each dose of MSG was tested three times in each animal on different days, and an experiment of administration of MSG was performed once a day.

Forty milliliters 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 min after the end of interdigestive phase III contractions in jejunum 2. The gastrointestinal motor response obtained by the intragastric or intraduodenal administration of 40 ml of 0.9% saline was used as a control. Moreover, for comparison with other amino acids, glutamine with a concentration equal 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 (38). 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 min after intragastric administration of MSG.

**Gastric emptying.** Each gastric emptying study was performed within 3 wk of the surgery. Gastric emptying was evaluated by the acetaminophen method (23, 27). Acetaminophen absorption was used as an indirect measure of gastric emptying. After 12 h 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, Tokyo, Japan) 5 min 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 min after the feeding. The serum was separated, frozen, and stored at −30°C until assay. Serum acetaminophen concentration was determined with an automatic fluorescence polarization immunoassay (TDx, Abbott Laboratories) at the Department of Pharmacy, Gunma University Hospital. Areas under the contractile waves were measured for 90 min after feeding of each solution and expressed as the MI.

*Intragastric administration of MSG in truncal vagotomy group.* Forty milliliters of distilled water containing MSG (45 mM/kg) or 40 ml of 0.9% saline as a control was administered as a bolus into the gastric lumen through the gastric catheter 5–10 min after the end of interdigestive phase III contractions in jejunum 2.

*Intravenous administration of antagonists with intragastric administration of MSG in normal group.* To study the mechanism of MSG-induced contractions, the muscarinic receptor antagonist atropine (0.1 mg/kg bolus + 0.1 mg·kg⁻¹·h⁻¹ for 30 min), the nicotinic receptor antagonist hexamethonium (5 mg/kg bolus + 10 mg·kg⁻¹·h⁻¹ for 30 min), the 5-HT type 3 (5-HT₃) receptor antagonist granisetron (100 µg/kg bolus), or 0.9% saline as the control was administered intravenously 5 min after the end of phase III contractions in the jejunum. Intragastric administration of 45 mM/kg MSG was performed 10 min after the start of the intravenous infusion of the antagonist.

*Administration of MSG into 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 min 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

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

Drugs

MSG, which was purchased from Wako Pure Chemicals (Osaka, Japan), was dissolved in distilled water to make each concentration. We used 40 ml of 0.9% saline (Otsuka Pharmaceutical, 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), hexamethonium bromide (nicotinic receptor antagonist; Wako Pure Chemicals), and granisetron (5-HT3 receptor antagonist; Chugai Pharmaceutical, 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 min after intragastric administration of each solution and are expressed as the MI. A computer-assisted system (Eight Star System version 6.0) was used for the calculation of the MI (31). We defined the initiation of the upper gut motor response as the start of consecutive nonpropagated 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 means ± SE. 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 with Stat View software (version 5.0; Abacus Concepts, Berkeley, CA).

RESULTS

Effect of MSG on Upper Gastrointestinal Motility and Serum 5-Hydroxytryptamine Concentration in Normal Group

Intragastric administration of 40 ml of 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 contractile activity in the stomach when administered 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 Fig. 2, A and B. However, intraduodenal administration of MSG at the same doses did not induce any contractions in the upper gut, as shown in Fig. 2C.

The overall pattern of these MSG-induced contractions was consecutive nonpropagated contractions. The MI for the 20 min after 5, 15, 45, and 90 mM/kg MSG administration increased in a bell-shaped curve at all sites of the upper gut (Fig. 3). The durations of MSG-induced contractions at each site increased gradually, except for 90 mM/kg (Fig. 4). After the MSG-induced contractions finished, a spontaneous phase I was observed, and the next spontaneous phase III occurred ~100 min 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 jejunum 1 and 2 were significantly longer than that in the gastric body (data for 45 mM/kg only are shown in Table 1) (P = 0.012 and 0.002, respectively).

Table 1. Lag time between administration of monosodium L-glutamate and initiation of upper gut motor response in normal group

<table>
<thead>
<tr>
<th>Lag Time, min</th>
<th>Body</th>
<th>Antrum</th>
<th>Duodenum</th>
<th>Jejunum 1</th>
<th>Jejunum 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body</td>
<td>2.73 ± 0.20</td>
<td>2.80 ± 0.20</td>
<td>3.26 ± 0.32</td>
<td>4.75 ± 0.90*</td>
<td>5.39 ± 0.75*</td>
</tr>
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</table>

Values are mean ± SE lag times between administration of 45 mM/kg monosodium L-glutamate and motor response. *P < 0.05 compared with body.
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 nonpropagating 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 experiments), which propagated to the gastric body and were followed by vomiting within 50 min (Fig. 5, A and B). Furthermore, intraduodenal 90 mM/kg MSG always induced vomiting (100%, 24/24 experiments, Fig. 5C). No dog vomited within 50 min after the administration of 5 and 15 mM/kg MSG and the control solution into the stomach.

Fig. 5. Representative effect of intragastric 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: detailed response of 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.
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 (Fig. 6). The MI for the 90 min after MSG administration was significantly larger than that for the control administration at all sites (Fig. 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) (Fig. 7B). The area under the curve for 45 mM/kg was significantly larger than that for the control and 135 mM/kg (Fig. 7C).

Effect of Intragastric MSG on Upper Gastrointestinal Motility in 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 (Fig. 8A). Compared with the normal group, the MI for the 20 min after administration of both saline and 45 mM/kg MSG was significantly small (Fig. 8B).

Fig. 6. Representative effect of intragastric MSG on upper gut motility in the postprandial period. Postprandial contractions after intragastric administration of MSG (45 mM/kg; B) were stronger than those after the administration of a control solution (A).
Effect of Antagonists on Intragastric MSG-Induced Contractions in Normal Group

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

Effect of MSG Administered into 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 (Fig. 10, A and B). However, administration of MSG into a Heidenhain pouch did not induce any contractions (Fig. 10, C and D). 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 Pouch and Main Stomach in Antral Pouch Dogs

Intrapouch administration of MSG (45 mM/kg) did not induce any contraction (Fig. 10, E and F). 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 nonpropagated 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 amount equivalent to that in the 150 mM MSG solution. Because intragastric administration of the same volume of saline did not induce any apparent effect at any site, consecutive nonpropagated 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 antral side regardless of the dose. Berthoud et al. (2) reported that the vagal efferent neuron demonstrated a gradient of generally decreasing innervation at distal segments of the gut. 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 responds rapidly to gastrointestinal chemical stimuli (21). A recent study by Tsurugizawa et al. (33) indicated that the vagus nerve is important for signaling the presence of intragastric glutamate in the rat forebrain. Our finding that intragastric
MSG did not induce any contractions in the truncal vagotomy group 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 effects 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 that 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. (34) have reported that intragastric MSG increased the firing rate of afferent fibers of the vagal gastric branch in the rat. 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

Fig. 8. Representative tracings (A) and MI for 20 min (B) after intragastric administration of MSG in the truncal vagotomy group. A: intragastric MSG did not show any response after administration. B: MI after administration of both control and MSG was significantly small compared with that of the normal group. *P < 0.05 compared with normal.
Fig. 9. Effect of antagonists on MI for 20 min under conditions of intragastric 45 mM/kg 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.

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. 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 has been reported that oral ingestion of an excessive dose of MSG in humans causes 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 caused the Chinese restaurant syndrome in a double-blind, placebo-controlled study (7, 37). The daily intake of MSG in humans is reported to be ~2 g and equivalent to 40 ml 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 min of administration. Our data, in which intraduodenal MSG at a dose of 90 mM/kg always induced RMCs with vomiting, strongly suggest 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 nonpropagating contractions from each site of administration. Therefore, we speculate that the sensory structure for MSG of the body is responsible for the consecutive nonpropagated contractions by sensing the low-high dose of MSG. In contrast, the sensory structure for 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 that this syndrome is mediated by the receptors of MSG in the tongue. However, we believe that 90 mM/kg MSG 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 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 for 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.
Fig. 10. Representative tracings showing the effect of intrapouch administration and MI for 20 min after administration of MSG into a pouch. A and 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 and D: administration of MSG (45 mM/kg) into the Heidenhain pouch did not induce any contractions. E and F: administration of MSG (45 mM/kg) into the antral pouch did not induce any contractions.
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DISCLOSURES

The authors have no conflicts of interest to disclose.

REFERENCES