Neuronal Control of Motility Changes in the Canine Lower Esophageal Sphincter and Stomach in Response to Meal Ingestion

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Abstract

Background & Aims: Neuronal control of motility changes in the lower esophageal sphincter (LES), gastric body (GB) and gastric antrum (GA) in response to meal ingestion is not fully understood. The aim of this study was to investigate the neuronal mechanism of the LES and gastric motility response to meal ingestion in conscious dogs. Methods: Dogs fitted with force transducers in the LES, GB and GA were given neuronal antagonists before a meal. Motility was assessed for 10 min after feeding and was compared to results without antagonists. Results: In the LES, atropine inhibited tonic contractions, whereas Nω-nitro-L-arginine (L-NAME) significantly enhanced tonic contractions initiated by meal ingestion. In the GB, atropine, hexamethonium or L-NAME inhibited receptive relaxation, and the effect of hexamethonium was significantly greater than that of atropine or L-NAME. In the GA, atropine, hexamethonium or naloxone inhibited postprandial phasic contractions, whereas L-NAME tended to enhance phasic contractions. Conclusions: Neuronal control of postprandial motility was clearly different in each region: (1) LES tonic contractions are mainly regulated by muscarinic receptors, (2) nicotinic transmission plays an essential role in receptive relaxation, which also involves muscarinic receptors and nitric oxide, (3) cholinergic nerves and opiate receptors are involved in the occurrence of antral phasic contractions, and (4) endogenous nitric oxide may inhibit postprandial contractions in the LES and GA.

Key words: dog, gastrointestinal motility, lower esophageal sphincter, neuronal mechanism, stomach

Introduction

In the interdigestive state in humans and dogs, the cyclic occurrence of phase III contractions is observed in the stomach and small intestine. Phase III contractions are usually
initiated in the stomach, including the lower esophageal sphincter (LES) (Itoh et al., 1978; Dent et al., 1983), and migrate through the entire small intestine. Ingestion of a meal causes remarkable changes in gastrointestinal motility. An increase in LES pressure, which is observed in association with feeding in humans and dogs (Itoh et al., 1978; Nebel and Castell, 1972; Maher et al., 1978), is thought to prevent gastroesophageal reflux of the ingested meal. Muscarinic cholinergic pathways are involved in postprandial and acid-stimulated rises in LES pressure (Maher et al., 1978). On the other hand, the muscle tone of the gastric body decreases with ingestion of a meal, called receptive relaxation (Cannon and Lieb, 1911), which allows a large meal to be accommodated without a significant increase in gastric pressure. It has been suggested that nonadrenergic and noncholinergic inhibitory neurotransmitters such as vasoactive intestinal polypeptide (Grider et al., 1985) and nitric oxide (NO) (Desai et al., 1991) are involved in the initiation of receptive relaxation. In the gastric antrum, phasic contractions occur almost at a constant frequency, and these contractions work to grind, sieve and empty food particles. It is well known that the phasic contractions in the gastric antrum are mainly regulated by cholinergic pathways.

Nonetheless, neuronal control of the changes in upper gastrointestinal motility after meal ingestion is not fully understood, and comparison of the mechanisms involved in the regulation of postprandial motility changes in the LES, gastric body and gastric antrum have not been studied. The aim of this study was to investigate the neuronal mechanisms of immediate postprandial motility changes in the LES, gastric body and gastric antrum in conscious dogs.

Materials and methods

Animal preparations

Six mongrel dogs were used in this study. They were anesthetized by intravenous thiopental sodium (Ravonal, Tanabe Pharmaceutical Co., Osaka, Japan) and intubated intratracheally. The general anesthesia was maintained by halothane (Fluothane, Takeda Pharmaceutical Co., Osaka, Japan). After celiotomy, strain gauge force transducers (Itoh et al., 1977) were implanted on the serosal surface in the LES, in the gastric body opposite the splenic hilum and in the gastric antrum 3 cm proximal to the pyloric ring, to monitor gastrointestinal contractions. The lead wires of the transducers were taken out of the abdominal cavity and brought out through a skin incision made between the scapulae. The outer ends of the lead wires were attached to a small connector. A silicone tube (Silascon Medical Tube SH No. 1, Kaneka Medix Co., Osaka, Japan) was implanted in the superior vena cava via a branch of the right external jugular vein for the injection of test materials. After the operation, the dog was fitted with a canvas jacket to protect the connector and tube. The dogs were housed in individual cages and fed dry-pellet type dog food (Gaines Meal, Ajinomoto-General Foods Co., Tokyo, Japan; 20 g/kg body weight; 72 kcal/20 g; 20% protein, 7% fat, and 48% carbohydrate) once a day with free access to water.

Motor Activity Recordings

The connector was joined to cable leads from an amplifier (UG-5, Nihon Kohden Kohgyo
Co., Tokyo, Japan). Signals from the amplifier were recorded on a multichannel penwriting recorder (WI-681G, Nihon Kohden Kohgyo), and were fed into a personal computer (PC-9801VX, NEC Inc., Tokyo, Japan) for further analysis of the motility at each site.

**Experimental Procedure**

Experiments were started two weeks after the operation. Dogs were fed 20 g/kg body weight (72 kcal/kg) of the dog meal 10–20 min after the termination of spontaneously occurring phase III contractions in the stomach, with or without neuronal antagonists. The drugs used in the present study were atropine (a muscarinic receptor antagonist, 0.01+0.01, 0.03+0.03 and 0.1 mg/kg+0.1 mg/kg-h), hexamethonium (a nicotinic receptor antagonist, 0.3+0.6, 1.0+2.0 and 3 mg/kg+6 mg/kg-h), phentolamine (an α receptor antagonist, 1.0 mg/kg), propranolol (a β receptor antagonist, 1.0 mg/kg), naloxone (an opiate receptor antagonist, 0.3, 1.0 and 3.0 mg/kg), devazepide (formerly L-364718, a CCK-A receptor antagonist, 0.1, 0.3 and 1.0 mg/kg), and Nω-nitro-L-arginine methyl ester (L-NAME, an inhibitor of NO synthase, 1.0, 3.0 and 10.0 mg/kg-h). In the case of atropine and hexamethonium, they were given as a single injection followed by a continuous infusion. L-NAME was infused over 1 hour starting 10–20 min after the end of spontaneously occurring phase III contractions in the stomach, before feeding. Other drugs or normal saline, as a control, was given intravenously 5 min before feeding. Each drug was tested twice in each of six dogs.

**Materials**

Devazepide was a kind gift from Merck Sharp and Dohme (Rahway, NJ). The following materials were purchased: atropine sulfate (Tanabe Pharmaceutical Co. Ltd., Osaka, Japan), hexamethonium bromide (Wako Pure Chemical Industries Ltd., Osaka, Japan), phentolamine mesylate (Ciba-Geigy, Hyogo, Japan), propranolol hydrochloride (Sumitomo Pharmaceutical Co. Ltd., Osaka, Japan), naloxone hydrochloride and L-NAME (Sigma Chemical Co., St. Louis, MO). All drugs except for devazepide were dissolved or diluted in normal saline. Devazepide was dissolved by 1.0 ml of dimethyl sulfoxide (Wako Pure Chemical Industries Ltd., Osaka, Japan). A preliminary study showed that intravenous administration of normal saline or 1.0 ml of dimethyl sulfoxide did not affect gastrointestinal motility.

**Data Analysis**

The tonic contractions in the LES, relaxation in the gastric body and phasic contractions in the gastric antrum were analyzed quantitatively for 10 min after feeding using our own computer system (KC-9801VX, NEC Inc., Tokyo, Japan). Analog signals from the transducers were converted to digital signals through an analog to digital converter every 500 ms with a resolution of 12 bits. The motor index (MI) was calculated using the same computer by integrating the area surrounded by the baseline and the contractile waves for a given period, and was expressed in motor units. One motor unit is equivalent to a 50-g load on a strain gauge force transducer for 1 min. The MIs for the LES and gastric antrum after administration of saline alone were taken as 100% and that for the gastric body as -100%. The amplitude of the maximum contraction from the baseline in the LES and gastric antrum and that of the
maximum relaxation in the gastric body after administration of saline were also taken as 100% and -100%, respectively. The MI and the maximum amplitude for each drug were expressed as percentages of the control values.

All results are expressed as the mean ±SE, and were compared by an analysis of variance followed by Fisher’s protected least-squares difference test. Differences between groups were considered significant at P<0.05.

Results

Figure 1 shows typical contractile patterns in the LES, gastric body and gastric antrum before and after a meal in a conscious dog. In the interdigestive state, periodic phase III contractions were observed at each site. With the start of ingestion of a meal, the LES and gastric body showed a tonic increase and a tonic decrease from the baseline, respectively, and phasic contractions began in the gastric antrum. These contractile patterns were observed in all six dogs. Treatment with each of the antagonists used in the study did not affect the eating behavior of the dogs.

LES

Atropine dose-dependently inhibited the occurrence of tonic contractions in the LES after meal ingestion began, and doses of 0.03 mg/kg+0.03 mg/kg-h or more significantly decreased both the MI and the maximum amplitude of the tonic contractions (Figure 2, Table 1). Nevertheless, the MI did not fall below 22±8% and the maximum amplitude of the contractions did not fall below 50±13% even at a dose of 0.1 mg/kg+0.1 mg/kg-h atropine (Figure 2, Table 1), a dose which completely abolished bethanechol (30 µg/kg)-induced LES-contractions (data not shown). By contrast, hexamethonium did not inhibit the occurrence of tonic contractions in the LES, and it did not significantly affect either the MI or the amplitude of the maximum

Fig. 1. Typical example showing normal contractile patterns in the LES, gastric body and antrum before and after a meal in a conscious dog. During the interdigestive state, the periodic occurrence of phase III contractions was observed in each site. Just after feeding, a tonic increase and a decrease from the baseline were observed in the LES and the gastric body, respectively, and phasic contractions were observed in the gastric antrum.
Atropine dose-dependently reduced the MIs of the LES, gastric body and gastric antrum. Hexamethonium did not inhibit the occurrence of tonic contractions in the LES, but it dose-dependently reduced the MI of the relaxation in the gastric body, and of phasic contractions in the gastric antrum. *P<0.05, **P<0.01 and ***P<0.001 compared to the control.

Fig. 2. Effects of atropine and hexamethonium on the MIs of tonic contractions in the LES, receptive relaxation in the gastric body (GB) and phasic contractions in the gastric antrum (GA).

Fig. 3 shows a typical example of the effects of the highest dose of atropine and hexamethonium on the tonic contractions in the LES; atropine, but not hexamethonium, inhibited the occurrence of tonic contractions after meal ingestion. Neither
Table 1. Effects of antagonists on the percentage maximum amplitude of contractions in the LES and gastric antrum, and of relaxation in the gastric body

<table>
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<th>Gastric Body</th>
<th>Gastric Antrum</th>
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<tr>
<td>Control</td>
<td>100±4</td>
<td>-100±4</td>
<td>100±6</td>
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<td>Atropine, mg/kg + mg/kg-h</td>
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<td>113±20</td>
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<td>50±13*</td>
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n=6, *P<0.05, **P<0.01 and ***P<0.001 compared to the control.

Fig. 3. A typical example showing the effects of atropine, hexamethonium and L-NAME on meal-induced motility changes in the LES, gastric body (GB) and gastric antrum (GA). Atropine (0.10 mg/kg + 0.10 mg/kg-h), but not hexamethonium (3 mg/kg + 6 mg/kg-h), inhibited the occurrence of tonic contractions in the LES. Both drugs inhibited receptive relaxation in the gastric body. Atropine and hexamethonium each noticeably inhibited phasic contractions in the gastric antrum. Treatment with L-NAME (3.0 mg/kg-h) increased tonic contractions in the LES and phasic contractions in the gastric antrum. Receptive relaxation of the gastric body was inhibited by treatment with L-NAME.
Naloxone at 1.0 mg/kg, but not at 3.0 mg/kg, significantly inhibited the MI of phasic contractions in the gastric antrum. *P < 0.05 compared to the control.

phenolamine, propranolol nor naloxone affected meal-induced tonic contractions in the LES, based on the MI and the maximum amplitude (Figure 4, Table 1). Devazepide tended to increase the MI and maximum amplitude of the contractions in the LES, but the effect was not significantly different from the control (Figure 4, Table 1). Treatment with L-NAME at doses of 3.0 mg/kg-h or more significantly increased the MI and the maximum amplitude of tonic contractions in the LES (Figure 5, Table 1). A typical example with L-NAME at a dose of 3.0 mg/kg-h is shown in Figure 3; treatment with L-NAME enhanced the tonic contractions in the
Fig. 5. Effect of treatment with L-NAME on the MIs of tonic contractions in the LES, receptive relaxation in the gastric body (GB) and phasic contractions in the gastric antrum (GA). Treatment with L-NAME at doses of 3.0 mg/kg-h or more significantly increased the MI of the tonic contractions in the LES, and reduced the MI of the relaxation in the gastric body, but 10.0 mg/kg-h L-NAME failed to inhibit receptive relaxation significantly. L-NAME at a dose of 3.0 mg/kg-h tended to increase the MI of the phasic contractions in the gastric antrum. *P<0.05 and **P<0.01 compared to the control.

LES after meal ingestion.

**Gastric Body**

Atropine significantly inhibited the receptive relaxation in the gastric body at a dose of 0.10 mg/kg+0.10 mg/kg-h based on the MI, and at doses of 0.03 mg/kg+0.03 mg/kg-h or more based on the maximum amplitude (Figure 2, Table 1). Nevertheless, the MI of the receptive relaxation did not fall below 52±10% of the control even at a dose of 0.10 mg/kg+0.10 mg/kg-h atropine (Figure 2). Hexamethonium dose-dependently inhibited the MI and the maximum amplitude of the relaxation, and 3.0 mg/kg+6.0 mg/kg-h hexamethonium significantly inhibited the MI of relaxation in the gastric body by 75±5% (Figure 2, Table 1). Figure 3 shows a typical example of the effects of the highest doses of atropine and hexamethonium on receptive relaxation in the gastric body; both drugs inhibited meal-induced relaxation in the gastric body. Neither of the adrenoceptor antagonists, naloxone or devazepide affected the relaxation in the gastric body (Figure 4, Table 1). Treatment with L-NAME at a dose of 3.0 mg/kg-h significantly inhibited the MI of the relaxation in the gastric body by 32±14% compared to the control (Figures 3 and 5), but 10.0 mg/kg L-NAME failed to significantly inhibit the occurrence of receptive relaxation (Figure 5).

**Gastric Antrum**

Atropine and hexamethonium dose-dependently and significantly inhibited phasic contractions in the gastric antrum as shown by both its MI and maximum amplitude (Figure 2, Table 1). Phasic contractions in the gastric antrum were almost completely inhibited by the highest
dose of atropine and were markedly reduced by the highest dose of hexamethonium (Figure 3). Adrenoceptor antagonists and devazepide had little effects on the phasic contractions in the gastric antrum (Figure 4, Table 1). Naloxone at 1.0 mg/kg significantly inhibited the MI of the phasic contractions in the gastric antrum, but its effect at 3.0 mg/kg was not significant (Figure 4). Naloxone did not affect the maximum amplitude of phasic contractions (Table 1). The effect of L-NAME showed variability between dogs. L-NAME at a dose of 3.0 mg/kg-h markedly enhanced the phasic contractions in three out of six dogs as shown in Figure 3, but it had no effect in the remaining three dogs. Therefore, although it tended to increase the phasic contractions, the effect was not significant (Figures 5, Table 1). L-NAME at a dose of 10.0 mg/kg-h did not affect phasic contractions.

Discussion

The present study showed that neuronal control of postprandial motility changes immediately after food ingestion in the LES, gastric body and gastric antrum is clearly different in each region. Excitation of muscarinic cholinergic receptors is the main regulator of the occurrence of tonic contractions in the LES, and nicotinic transmission plays an essential role in the occurrence of receptive relaxation in the gastric body. Cholinergic pathways and opiate receptors regulate phasic contractions in the gastric antrum.

Tonic contractions in the LES in association with feeding have been believed to prevent gastroesophageal reflux. The results of this study show that the occurrence of tonic contractions in the LES is mainly regulated by the activation of muscarinic receptors, because only atropine significantly inhibited the occurrence of these contractions in association with feeding. This finding is in agreement with previous studies which showed that postprandial and acid-stimulated rises in LES pressure are inhibited by atropine (Maher et al., 1978), that muscarinic agents cause contractions of the LES (Roling et al., 1972), that the LES has muscarinic cholinergic receptors (Rimele et al., 1979), and that intramural cholinergic neurons are present in the LES (Seelig et al., 1984). Nevertheless, atropine did not completely abolish the occurrence of tonic contractions in the LES, suggesting that atropine-insensitive excitatory pathway(s) exist. Previous reports have suggested that substance P may play a role in atropine-resistant contractions in the LES (Reynolds et al., 1984; Aggestrup 1985; Aggestrup et al., 1986). Another possibility is that the increase in abdominal pressure after meal ingestion may cause noncholinergic contractions in the LES. In fact, Lind et al. (Lind et al., 1968) and Cohen and Harris (Cohen and Harris, 1972) showed that a rise in intra-abdominal pressure results in a rise in LES pressure. The increase in LES pressure in response to increased intra-abdominal pressure appears to be atropine-resistant (Landers and Jamieson, 1987; Mittal et al., 1990).

By contrast to atropine, hexamethonium did not affect the occurrence of tonic contractions in the LES, suggesting that nicotinic transmission does not play a major role in regulating these contractions. Coruzzi et al. (Coruzzi et al., 1985) also reported that contractions in the isolated LES of the rat are associated mainly with the stimulation of post-synaptic muscarinic receptors, and that nicotinic receptors seem to play a minor role, if any. This regulation of LES
contractions differs from the case in the interdigestive state in which motilin-induced phase III contractions are abolished by intravenous administration of hexamethonium (Holloway et al., 1985).

The gastric body acts as a reservoir to accommodate food without significant increase in intragastric pressure. The results of the present study show that nicotinic cholinergic transmission plays an essential role in regulating receptive relaxation in conscious dogs. Furthermore, muscarinic transmission and NO are also involved in the occurrence of receptive relaxation in the gastric body. Gastric relaxation has been postulated to be regulated by nonadrenergic noncholinergic neurotransmitters, and recent studies suggest that NO is the most important factor of this type which relaxes smooth muscles in the gastric body (Detai et al., 1991), however, in the present study NO synthase inhibitor only partly inhibited the occurrence of gastric relaxation, and the effect of L-NAME was less than that of atropine or hexamethonium. If NO is a final mediator which governs receptive relaxation in the stomach, L-NAME would have more markedly affected the occurrence of receptive relaxation. Therefore, our results suggest that cholinergic pathways are more important than NO in initiating meal-induced gastric relaxation in conscious dogs. Recently, Krowicki and Hornby (Krowicki and Hornby, 1996) demonstrated that cholinergic pathways play an important role in regulating CNS-evoked gastric relaxation in conscious rats.

Gue et al. (Gue et al., 1989) reported that selective opioid agonists affect the occurrence of gastric relaxation in conscious dogs, but that naloxone had no effect. Our observation of the lack of effect of naloxone on gastric relaxation is in accordance with their report, suggesting that endogenous opioids are not involved in the regulation of meal-induced receptive relaxation in conscious dogs.

The occurrence of phasic contractions in the gastric antrum in association with feeding was almost completely inhibited by either atropine or hexamethonium, suggesting that muscarinic and nicotinic cholinergic transmissions play essential roles in the mediation of antral contractions. These results confirm the findings of previous studies in the rat and dog (Bojo et al., 1994; Shiba et al., 1995). Furthermore, it is suggested that opiate receptors are partly involved in the regulation of phasic contractions in the gastric antrum. This finding is in accordance with our previous report, in which we showed that cholinergic pathways and opiate receptors are involved in the regulation of gastric antral contractions during the first 2–5 hours after feeding (Shiba et al., 1995), however, the effect of naloxone was not dose dependent, and 3.0 mg/kg naloxone failed to significantly inhibit phasic contractions in the gastric antrum. This result may depend on the non-specific antagonism of opiate receptors by naloxone.

Adrenoceptor antagonists, phentolamine and propranolol, did not affect the immediate postprandial motility changes in the LES, gastric body and gastric antrum. Although previous studies have shown that adrenoceptor antagonists affect LES pressure (Reynolds et al., 1984) and gastric phasic motility (Bojo et al., 1994), we did not observe any significant effects of adrenoceptor antagonists on postprandial motility changes in the upper gastrointestinal tract. Furthermore, it has long been suggested that CCK is involved in the regulation of LES relaxation and gastric emptying, but in the present study the effect of devazepide on immediate postprandial motility changes was not significant, although it tended to enhance the tonic
contractions of the LES. Therefore, endogenous CCK–A receptors do not play an important role in the occurrence of meal-induced immediate motility changes in the LES and stomach in conscious dogs.

L-NAME significantly enhanced meal-induced contractions in the LES and tended to increase phasic contractions in the gastric antrum. Although the effect of L-NAME on antral motility was not significant in the present study, we recently reported that Nω-L-arginine significantly enhances postprandial antral motility in conscious dogs (Tanaka et al., 1997). These results suggest that endogenous NO inhibits the release of excitatory cholinergic or noncholinergic neurotransmitters, or of inhibitory neurotransmitters, both in the LES and gastric antrum.

We conclude that (1) post-ganglionic cholinergic nerves are the main regulators of tonic contractions in the LES, (2) nicotinic transmission plays an essential role, and muscarinic receptors and NO are also involved, in the occurrence of receptive relaxation in the gastric body, (3) cholinergic nerves and opiate receptors are involved in the occurrence of phasic contractions in the gastric antrum, and (4) endogenous NO pathways may inhibit postprandial contractions in the LES and gastric antrum.

References


(Received February 2nd, 1998: Accepted March 3rd, 1998)