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ORIGINAL ARTICLE—ALIMENTARY TRACT

Mechanism of interdigestive migrating motor complex in conscious dogs

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Abstract
Background The migrating motor complex (MMC) is well characterized by the appearance of gastrointestinal contractions in the interdigestive state. This study was designed to clarify the mechanisms of gastric MMC (G-MMC) and intestinal MMC (I-MMC) in conscious dogs.
Methods Five strain gauge transducers were implanted on the stomach and intestine. To investigate the correlation between luminal 5-HT and phase III contractions, gastric and duodenal juices were collected during the MMC cycle. The 5-HT concentrations in gastric and duodenal juice were measured by HPLC. To investigate whether luminal 5-HT initiates MMC, 5-HT (10^{-8}–10^{-6} M, 10 ml) was administered into the duodenum 20 min after gastric phase III. To investigate the involvement of 5-HT_3 or 5-HT_4 receptors in mediating G-MMC and I-MMC, 5-HT_3 antagonists (ondansetron) or 5-HT_4 antagonists (GR 125,487) were infused for 120 min.
Results Luminal administration of 5-HT (10^{-6} M) initiated duodenal phase II followed by G-MMC and I-MMC with a concomitant increased release of plasma motilin. The duodenal 5-HT concentration was significantly increased during phase II (59 ± 9 ng/ml) and phase III (251 ± 21 ng/ml) compared to that of phase I (29 ± 5 ng/ml). On the other hand, the 5-HT content in the stomach was not significantly changed throughout the MMC cycle. Intravenous infusion of motilin (0.3 μg/kg/h) increased the luminal 5-HT content and induced G-MMC and I-MMC. 5-HT_4 antagonists significantly inhibited both G-MMC and I-MMC, while 5-HT_3 antagonists inhibited only G-MMC.
Conclusion It is suggested that the MMC cycle is mediated by a positive feedback mechanism via the interaction between motilin and 5-HT.

Keywords 5-HT · Motilin · Gastric MMC · Intestinal MMC

Abbreviations

EC cell	Enterochromaffin cell
HPLC	High-performance liquid chromatography
IPAN	Intrinsic primary afferent neurons
MMC	Migrating motor complex
MI	Motility index
RIA	Radioimmunoassay

Introduction

The migrating motor complex (MMC) is well characterized by the appearance of gastrointestinal contractions in the interdigestive state in dogs and humans. The MMC consists of three phases: phase I (period of motor quiescence), phase II (period of irregular low-amplitude contractions) and phase III (period of regular high-amplitude contractions). The physiological importance of gastric MMC pertains to the mechanical and chemical cleansing of the

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empty stomach in preparation for the next meal [1]. The duodenum, which stores motilin, plays an important role in initiating gastric MMC. Intravenous (iv) infusion of motilin induces premature gastric phase III in dogs [2] and humans [3].

Although plasma motilin levels are closely associated with the appearance of gastric phase III in dogs [2] and humans [3], the peak plasma motilin level is observed during the late phase of gastric phase III or after finishing gastric phase III. Exogenous motilin can stimulate endogenous motilin release [4]. Therefore, Sarna et al. [5] proposed the possibility that endogenous motilin does not initiate spontaneous phase III. Instead, phase III contractions release motilin. Is the release of motilin the cause or an effect of gastric phase III?

Gastric MMC (G-MMC) and intestinal MMC (I-MMC) are thought to be controlled by different mechanisms. Although plasma motilin levels are highly associated with the appearance of gastric phase III in dogs [2], phase III contractions in the small intestine sometimes occur without a concomitant increase in plasma motilin concentration [6]. Motilin antiserum inhibits the occurrence of phase III contractions only in the stomach, not in the intestine [7]. After duodenectomy, no obvious phase III contractions were seen in the gastric antrum, but migrating phase III contractions were seen in the upper jejunum [8]. These suggest that motilin regulates G-MMC, but not I-MMC.

Gastric phase III, but not intestinal phase III, is abolished by a cooling blockade of the cervical vagosympathetic nerve trunk in dogs [9]. Sympathetic receptor blockers do not affect the inhibitory effect of vagal blockade [10], suggesting that gastric phase III is regulated by vagus nerve. Chronic vagotomy reduces the motor activity of gastric phase III contractions without affecting the cycle of G-MMC and I-MMC [11]. These suggest that vagal innervation regulates G-MMC but not I-MMC. If so, how is I-MMC regulated?

When we carefully examined the previous studies of gastrointestinal MMC recordings in dogs, it became obvious that duodenal phase II is frequently antecedent to gastric phase II and gastric phase III [2]. However, no reasonable explanation for this has been provided. What is the relationship between duodenal phase II/III and gastric phase II/III?

5-Hydroxytryptamine (5-HT) in the gastrointestinal tract is involved in regulating gastrointestinal motility. 5-HT stimulates phase II-like contractions when administered during phase I of the canine small intestine [12]. In humans, 5-HT re-uptake inhibitor (paroxetine) shortened the MMC cycle and increased the propagation velocity of intestinal phase III [13]. Motilin-induced phase III of the stomach is antagonized by systemic treatment with 5-HT_3 receptor antagonists in dogs [14] and humans [15]. Spontaneous gastric phase III, but not intestinal phase III, is also antagonized by 5-HT_3 antagonists [14]. These suggest that gastric phase III is mediated via an endogenous release of 5-HT as well as motilin. How does motilin interact with 5-HT to mediate gastric MMC?

To answer these questions, we studied the mechanism of interaction between motilin and 5-HT in regulating gastrointestinal MMC in conscious dogs.

Methods

Animals

Protocols describing the use of dogs were approved by the Institutional Animal Care and Use Committee of Duke University (Durham) and Zablocki VA Medical Center (Milwaukee) and carried out in accordance with the National Institutes of Health *Guide for the Care and Use of Laboratory Animals*. All efforts were made to minimize animal suffering and to reduce the number of animals used in the experiments.

Animal preparation

Seven female hound dogs (BW 20–25 kg) were used. Under general anesthesia, five strain gauge transducers (Star Medical, Japan) were implanted at gastric body, antrum, duodenum, proximal jejunum (jejunum-1) and distal jejunum (jejunum-2) to record circular muscle motor activity, as previously reported [16]. Jejunum-1 was located 5 cm distal from the Treitz ligament. The distance between jejunum-1 and jejunum-2 was 15 cm. In order to measure luminal pH, 5-HT content and pressure of the duodenum, a cannula (ID 8 mm) was inserted into the proximal duodenum. The duodenal transducer was implanted 5 cm distal from the duodenal cannula. To collect the gastric juice for 5-HT assay, a catheter (ID 3 mm) was inserted into the gastric lumen of the midbody. The dogs were allowed to recover from the surgery for 2 weeks.

Recording of GI motility, duodenal pH and duodenal pressure

After a 16 h fast, gastrointestinal MMC was recorded in a conscious state. To investigate the relationship between luminal pH and luminal pressure of the duodenum during the MMC cycle, a catheter (ID 3 mm) and a pH electrode (SA-100; Star Medical, Japan, ID 2.1 mm) were inserted into the duodenal lumen through the duodenal cannula. The

catheter was connected to a pressure transducer (MLT-844; AD Instruments, Colorado Springs, CO, USA).

Luminal 5-HT content and plasma motilin levels during the MMC cycle

To investigate the relationship between duodenal 5-HT content and plasma motilin levels, the plasma motilin concentration was measured before and after the intraluminal administration of 5-HT. The plasma motilin level was measured using a radioimmunoassay (RIA) kit (Peninsula Lab Inc., San Carlos, CA, USA). Twenty minutes after finishing the spontaneous phase III of the stomach, 5-HT (10^{-8}–10^{-6} M; 10 ml) was administered into the duodenal lumen via the duodenal cannula. Saline infusion (10 ml) was used as the control.

To investigate the relationship between duodenal 5-HT content and gastrointestinal MMC, the luminal contents of 5-HT of the stomach and duodenum were measured by high-performance liquid chromatography (HPLC). During the various phases of gastrointestinal MMC, gastric juice (20 μl) and duodenal juice (20 μl) were collected via the gastric cannula and duodenal cannula, respectively. The samples were filtered with a 0.45 μm centrifuge tube filter (Coster, Corning Inc., NY, USA) by centrifuging for 30 min at 4°C. Ten microliter aliquots of filtrate were injected into an HPLC (HTEC-500, Eicom, Japan).

Effect of 5-HT antagonists on spontaneous MMC in the interdigestive state

Twenty minutes after finishing gastric phase III, a 5-HT_3 antagonist (Ondansetron 10–100 μg/kg/h) or a 5-HT_4 antagonist (GR 125,487; 3–80 μg/kg/h) was infused intravenously for 120 min. Saline, used as a control, was infused at the rate of 1 ml/min.

The area under the curve of the motility recording was taken as the motility index (MI) and analyzed using a computer-assisted system (Power Lab/8sp, AD Instruments), as previously reported [16]. The MIs of gastric phase II/III and duodenal phase II/III were calculated, and the gastric and duodenal phases II/III that occurred after 5-HT antagonist infusion were compared to those that followed saline injection in each animal.

Chemicals

Motilin was purchased from Peninsula (Belmont, CA, USA). 5-HT was purchased from Sigma (St. Louis, MO, USA). GR 125,487 was purchased form Tocris (Ellisville, MO, USA). Ondansetron was purchased from Hospira (Lake Forest, IL, USA).

Statistical analysis

Results are shown as mean ± SE. Statistical data analysis was performed using a one-way analysis of variance (ANOVA) followed by Dunnett's post hoc test. A p value of <0.05 was considered to be statistically significant.

Results

Intraluminal pressure and pH recording during the MMC cycle

As shown in Fig. 1a, b, changes in duodenal pressure were observed during the silent phase (phase I). The luminal pressure of the duodenum increased by 20.1 ± 5.3 H_2O ($n = 7$), just before the occurrence of duodenal phase II. Duodenal phase II was followed by gastric phase III (Fig. 1a). The spontaneous duodenal phase II was always antecedent to the spontaneous gastric phase II (Figs. 1, 2, 3, 4 and 5). The pressure changes were highly correlated with the changes in duodenal pH in 4 out of 7 dogs.

In the other 3 dogs, luminal pH was not altered even though there was an increase in duodenal pressure during duodenal phase I (Fig. 1b).

Effects of intraluminal administration of 5-HT on the MMC cycle and motilin release

Intraluminal administration of saline or 5-HT (10^{-8} M; 10 ml) did not affect duodenal contractions. Three to four minutes (3.5 ± 0.4 min, $n = 7$) after the intraluminal administration of 5-HT (10^{-7} M; 10 ml), phasic contractions were observed at the duodenum that migrated to the jejunum (Fig. 2a). Intraluminal administration of 5-HT (10^{-7} M) did not induce any gastric phase III-like contractions. The plasma motilin level during phase I was 10.4 ± 3.2 pg/ml ($n = 7$), which was not affected by the intraluminal administration of 5-HT (10^{-7} M) (Fig. 2a).

In contrast, intraluminal administration of 5-HT (10^{-6} M; 10 ml) induced phasic contractions of the duodenum followed by gastric contractions (phase III-like contractions). The latent time before the occurrence of gastric phase III-like contractions following 5-HT (10^{-6} M) administration was 8.6 ± 1.2 min ($n = 7$). The interval of gastric phase III was significantly shortened by intraluminal administration of 5-HT (10^{-6} M), from 95 ± 15 min (saline infusion) to 65 ± 12 min ($n = 7$, $P < 0.01$). Intraluminal administration of 5-HT (10^{-6} M) significantly increased the plasma motilin level to 31.6 ± 5.7 pg/ml ($n = 7$, $P < 0.05$). Intraluminal administration of 5-HT (10^{-6} M) increased the plasma motilin level (from 10.6 ± 2.6 to 31.6 ± 5.7 pg/ml, $n = 7$) to a

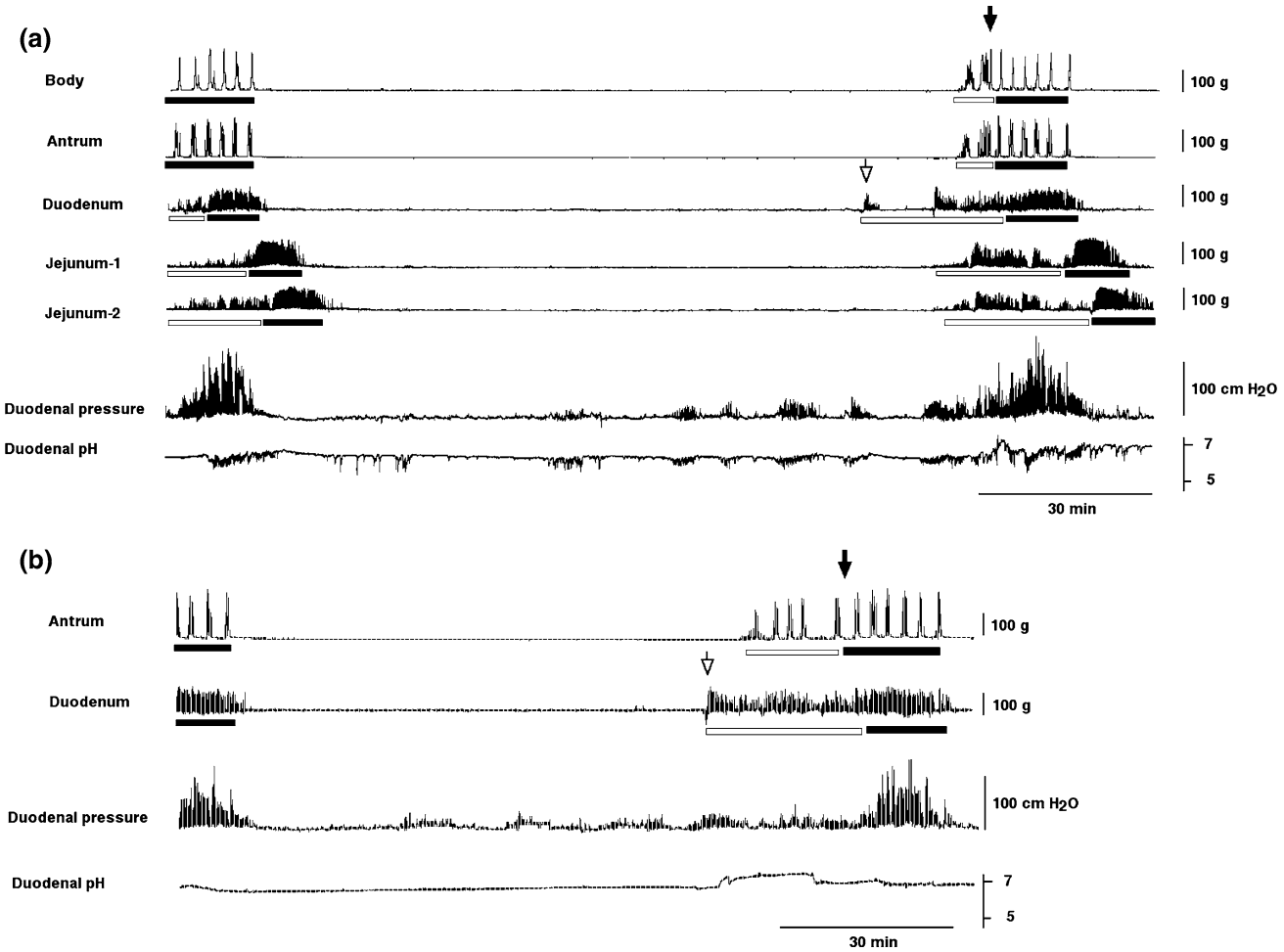

Fig. 1 Simultaneous recording of gastrointestinal MMC, duodenal pH and duodenal pressure. During phase I, duodenal pressure changes were observed. The luminal pressure of the duodenum increased by 20–30 H_2O just before the occurrence of duodenal phase II (*open arrow*). Duodenal phase II (*open arrow*) was followed by gastric phase III (*solid arrow*). The pressure changes were highly correlated with the changes in duodenal pH in 4 out of 7 dogs (**a**). In the other 3 dogs, luminal pH did not alter even though the duodenal pressure increased (**b**; *open squares* indicate phase II contractions and *closed squares* indicate phase III contractions)

similar level to that observed during spontaneous gastric phase III (from 10.2 ± 2.4 to 34.1 ± 6.7 pg/ml, $n = 7$) (Fig. 2b).

Luminal 5-HT content during the MMC cycle

During duodenal phase I, the luminal concentration of 5-HT in the duodenum was 28.5 ± 5.1 ng/ml ($n = 7$), which significantly increased to 58.7 ± 8.6 ng/ml ($n = 7$, $P < 0.05$) during the duodenal phase II. The luminal concentration of 5-HT in the duodenum further increased to 250.6 ± 21.3 ng/ml ($n = 7$, $P < 0.05$) during phase III (Fig. 4a, b). Thus, it is estimated that the peak 5-HT concentrations observed during duodenal phases II and III were equivalent to 1.5×10^{-7} and 6.5×10^{-7} mol/L, respectively (Fig. 3a).

During gastric phase I, the luminal concentration of 5-HT of the stomach was 30.5 ± 4.6 ng/ml ($n = 7$). In contrast to the duodenum, the luminal concentration of 5-HT in the stomach did not significantly change during phases I, II and III (Fig. 3b).

Motilin infusion (0.3 μg/kg/h for 20 min; iv) produced phase III-like contractions of the stomach and duodenum. The luminal concentration of 5-HT in the duodenum was significantly increased by motilin infusion from 21.7 ± 3.1 to 232.7 ± 42.8 ng/ml ($n = 5$, $P < 0.01$) (Fig. 4).

Effects of 5-HT receptor antagonist on the MMC cycle

Saline infusion did not cause any significant changes in gastric phase II/III and intestinal phase II/III (data not shown). Pretreatment with a 5-HT_3 antagonist (ondansetron

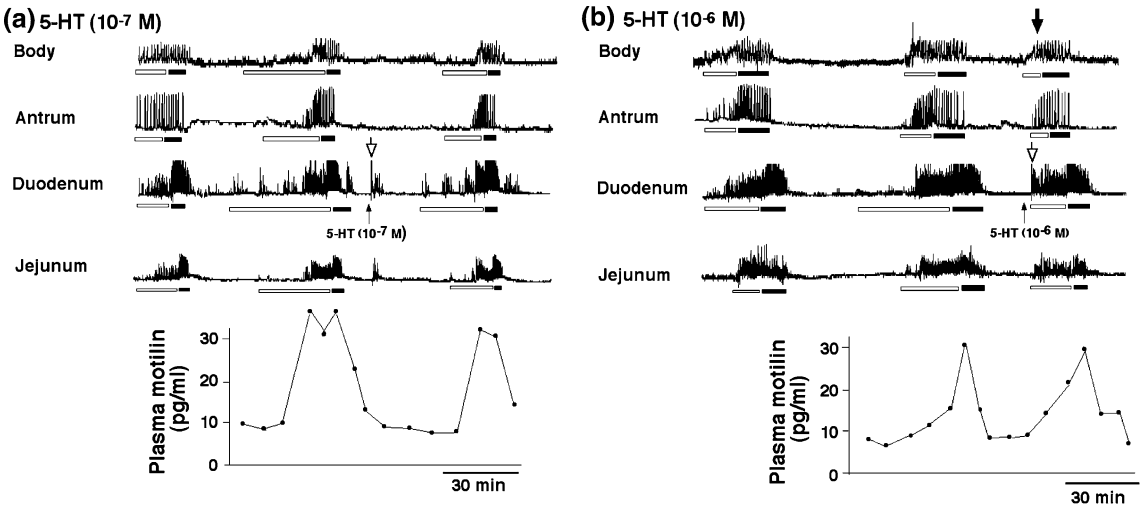

Fig. 2 Effects of intraduodenal administration of 10^{-7} M (**a**) and 10^{-6} M (**b**) of 5-HT on gastrointestinal MMC and motilin release. Intraluminal administration of 5-HT (10^{-7} M; 10 ml) caused phasic contractions (phase II-like contractions) of the duodenum (*open arrow*), which migrated to the jejunum. However, intraluminal administration of 5-HT (10^{-7} M) did not induce any gastric phase III-like contractions. The plasma motilin level was not changed by intraluminal administration of 5-HT (10^{-7} M) (**a**). In contrast, intraluminal administration of 5-HT (10^{-6} M; 10 ml) induced phasic contractions of the duodenum (an *open arrow*) followed by gastric contractions (phase III-like contractions; *solid arrow*). Intraluminal administration of 5-HT (10^{-6} M) increased the plasma motilin to a level similar to that observed during spontaneous gastric phase III. The interval of gastric phase III was significantly shortened by the intraluminal administration of 5-HT (10^{-6} M) (**b**; *open squares* indicate phase II contractions and *closed squares* indicate phase III contractions)

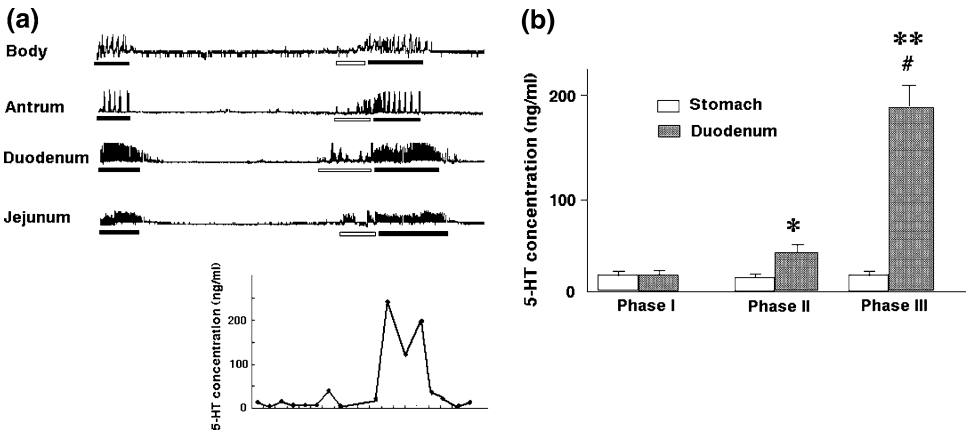

Fig. 3 Luminal concentration of 5-HT in the duodenum during the MMC cycle (**a**). Luminal concentrations of 5-HT in the stomach and duodenum during phases I, II and III (**b**). During duodenal phase I, the luminal concentration of 5-HT in the duodenum was 28.5 ± 5.1 ng/ml, which increased significantly to 58.7 ± 8.6 ng/ml during duodenal phase II. The luminal concentration of 5-HT in the duodenum was further increased to 250.6 ± 21.3 ng/ml during phase III (**a**, **b**). It is estimated that the peak 5-HT concentrations observed at duodenal phase II and phase III were equivalent to 1.5×10^{-7} and 6.5×10^{-7} mol/L, respectively (**a**). In contrast to the duodenum, the luminal concentration of 5-HT in the stomach was not significantly changed during phases I, II and III (**b**; *open squares* indicate phase II contractions and *closed squares* indicate phase III contractions; $n = 7$; $^{*}P < 0.05$, $^{**}P < 0.01$ versus phase I, $\#P < 0.05$ versus phase II)

10–100 μg/kg/h) significantly attenuated the magnitude of gastric phase II/III contractions in a dose-dependent manner without affecting the intestinal phase II/III contractions (Fig. 5a, c). In contrast, both gastric phase II/III and intestinal phase II/III contractions were significantly attenuated by the 5-HT_4 antagonist (GR 125,487; 3–80 μg/kg/h) in a dose-dependent manner (Fig. 5b, d).

Discussion

While 5-HT acts as a neurotransmitter of the enteric nervous system, the majority of the 5-HT is stored in the enterochromaffin (EC) cells of epithelial cells [17]. 5-HT released from EC cells plays an important role in regulating the peristalsis of the gastrointestinal tract. EC cells can

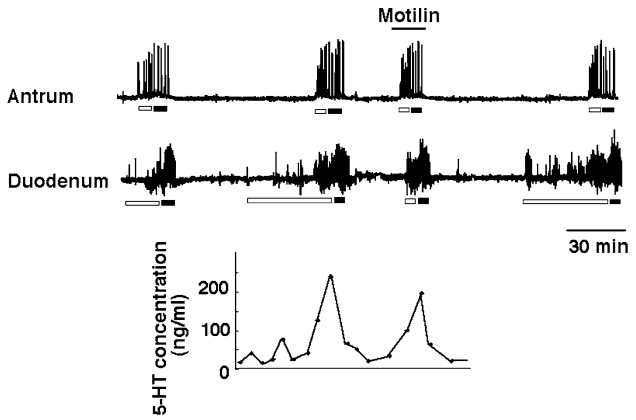

Fig. 4 Luminal concentration of 5-HT in the duodenum in response to motilin infusion. Motilin infusion causes an increase in the 5-HT content of the duodenum from 21.7 ± 3.1 to 232.7 ± 42.8 ng/ml ($n = 5$, $P < 0.01$). Antecedent duodenal phase II contractions were observed prior to the spontaneous gastric phase II and III contractions. However, antecedent duodenal phase II contractions were not observed prior to the gastric phase II and III contractions in response to motilin infusion. (*Open squares* indicate phase II contractions and *closed squares* indicate phase III contractions)

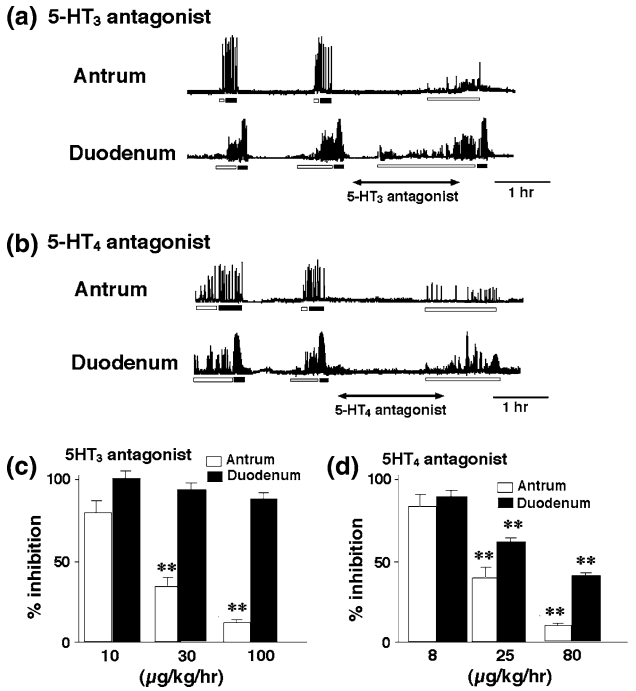

Fig. 5 Effect of a 5-HT_3 (**a**, **c**) and 5-HT_4 (**b**, **d**) receptor antagonists on gastric MMC and duodenal MMC. The 5-HT_3 antagonist significantly attenuated the magnitude of gastric phase II/III contractions (*solid arrow*) without affecting the duodenal phase II/III contractions (**a**). In contrast, the 5-HT_4 antagonist significantly reduced duodenal phase II/III as well as gastric phase II/III contractions (**b**). (*Open squares* indicate phase II contractions and *closed squares* indicate phase III contractions; $n = 5$, $^{*}P < 0.05$, $^{**}P < 0.01$)

release 5-HT into the blood vessels and intrinsic nerve terminals via a basolateral border [18]. An increased 5-HT concentration in the intestinal lumen is observed in response to various stimuli [19–22]. An immunoelectron microscopic study showed that 5-HT is stored in the secretory granules of EC cells and released into the cytoplasmic matrix. 5-HT particles diffuse or are transported into the intestinal lumen in response to intraluminal pressure increases in rat duodenum [23]. Luminally applied 5-HT can move by passive diffusion across the intestinal wall of the guinea pig ileum [24]. A recent study also showed that 5-HT can cross the intestinal wall from the mucosa to the serosa [25]. Thus, the 5-HT of the intestinal lumen can reach the synaptic circuitry, resulting in the stimulation of 5-HT receptors located on the lamina propria.

5-HT activates enteric afferent neurons to stimulate intestinal motor function [17]. Luminal administration of 5-HT into the proximal colon increases the fecal pellet output and accelerates colonic transit [26] in rats. 5-HT_3 and 5-HT_4 receptors are located on the nerve endings of the sensory neurons in the intestinal mucosa. These nerve endings may well be the targets for the 5-HT released from EC cells. Exogenously applied motilin increases the luminal concentration of 5-HT in the duodenum in conscious dogs [27]. An in vitro study also showed that the luminal concentration of 5-HT is increased by motilin of the canine jejunum [28]. These findings raise the possibility that motilin initiates gastrointestinal phase III through the release of 5-HT from the duodenal mucosa.

During duodenal phase II, the luminal content of 5-HT in the duodenum increased from 29 to 59 ng/ml. The luminal content of 5-HT in the duodenum further increased to 250 ng/ml during gastric phase III. In contrast, the luminal concentration of 5-HT in the stomach did not change significantly during phases I, II and III. This suggests that the luminal concentration of 5-HT in the duodenum, but not the stomach, may play an important role in regulating gastrointestinal MMC. We also showed that motilin infusion significantly increased the luminal content of 5-HT in the duodenum.

A previous study showed that intraluminal administration of 5-HT (10^{-5} M; 1 ml/min) in the duodenum causes phasic contractions in dogs [29]. Our current study showed that intraduodenal administration of 5-HT (10^{-7} M) initiated duodenal phase II in conscious dogs. These 5-HT (10^{-7} M)-induced duodenal phase II contractions migrated to the jejunum. In contrast, increasing the concentration of 5-HT tenfold (to 10^{-6} M) initiated duodenal phase II followed by gastric phase II/III and plasma motilin release.

Gastric MMC, but not intestinal MMC, is antagonized by 5-HT_3 antagonists [14]. We confirmed that gastric phase II/III was inhibited by a 5-HT_3 receptor antagonist (ondansetron 3–100 μg/kg/h) in a dose-dependent manner.

However, duodenal phase II/III was not inhibited by ondansetron. On the other hand, duodenal phase II/III as well as gastric phase II/III were significantly attenuated by a 5-HT_4 receptor antagonist (GR 125,487; 3–80 μg/kg/h) in a dose-dependent manner. This suggests that intestinal MMC is regulated by 5-HT_4 receptors, while gastric MMC is regulated by 5-HT_3 receptors and 5-HT_4 receptors.

It is generally accepted that the physiological function of motilin is mediated by vagal cholinergic pathways [30]. Gastric phase III contractions are attenuated after vagotomy in dogs [11]. Gastric phase III, but not intestinal phase III, is abolished by bilateral vagal blockade in dogs [9]. These suggest that gastric MMC is vagus dependent, while intestinal MMC is vagus independent. 5-HT_3 receptors and 5-HT_4 receptors are located on the cholinergic neurons of the myenteric plexus as well as the sensory neurons of the intestinal mucosa. In addition, 5-HT_3 receptors are also located on the nerve terminals of vagal afferents of the duodenal mucosa [31]. As gastric MMC was inhibited by a 5-HT_3 receptor antagonist, it is suggested that gastric MMC is regulated by 5-HT_3 receptors located on the vagal afferents.

In contrast to 5-HT_3 receptors, there is no evidence of the presence of 5-HT_4 receptors on vagal afferents or the nodose ganglion. 5-HT released by mucosal stimuli initiates peristalsis by activating 5-HT_4 receptors on sensory CGRP neurons of the rat colon in vitro [32]. Ascending contractions and descending relaxations were inhibited by selective 5-HT_4 but not by selective 5-HT_3 antagonists in human jejunum in vitro [33]. Therefore, 5-HT_4 receptors located at IPAN play a major role in mediating an intrinsic neural reflex.

Our current study showed that intestinal MMC was attenuated by a 5-HT_4 receptor antagonist. This suggests that intestinal MMC is regulated by intrinsic 5-HT_4 receptors.

We showed that the luminal pressure of the duodenum gradually increased, even during the silent phase of gastrointestinal motility (phase I). Gastric, pancreatic and biliary juices are spontaneously secreted, even though gastrointestinal motility is silent during the phase I period. Pancreatic and biliary secretion into the duodenum is observed during the period of duodenal phase I in conscious dogs [34]. The basal secretion of gastric, pancreatic and biliary juices gradually increases the luminal pressure of the duodenum during phase I, which can stimulate 5-HT release from EC cells [23]. This 5-HT release initiates duodenal phase II via the 5-HT_4 receptors of IPAN. Thus, the initiation of duodenal phase II is not due to the increased release of plasma motilin.

The pressure changes in the duodenum during phase I were highly correlated with the changes in duodenal pH in 4 out of 7 dogs. It is suggested that secreted gastric juice enters the duodenum to reduce duodenal pH and increase duodenal pressure in these dogs. In the other 3 dogs, luminal pH did not alter even though there was an increase in duodenal pressure (Fig. 1a). Duodenal pH may depend on the balance between secreted gastric juice (acid) and pancreatic and biliary juice (alkali).

Duodenal phase II causes an increase in duodenal pressure, which further stimulates the release of 5-HT. This positive circuit (pressure increase and 5-HT release) may gradually enhance the amplitude of duodenal phase II, leading to duodenal phase III. Finally, the maximally increased duodenal pressure stimulates motilin release from the duodenal mucosa. The released motilin further stimulates 5-HT release by a positive feedback mechanism. This large amount of 5-HT acts on 5-HT_3 receptors of the duodenal vagal afferent, in addition to the 5-HT_4 receptors of duodenal IPAN.

Therefore, it is likely that the released motilin induces gastric phase II and III via vagus-dependent mechanisms (probably via a vagovagal reflex). This may be the reason why duodenal phase II contractions are antecedent to gastric phase II contractions. In contrast, motilin infusion did not elicit antecedent duodenal phase II contractions prior to the gastric phase II contractions. This suggests that motilin initiates gastric phase II contractions but not duodenal phase II contractions.

Our current study suggests that duodenal phases II and III are mediated by 5-HT release and 5-HT_4 receptors of the duodenum. We showed that a tenfold higher concentration of 5-HT is needed to initiate gastric phase II/III and plasma motilin release than that to initiate duodenal phase II. We cannot, however, exclude the possibility that the 5-HT_4 receptors of IPAN are 10 times more sensitive than 5-HT_3 receptors of the vagal afferent in the canine duodenum.

How gastrointestinal MMC is regulated periodically every 90–120 min has been a mystery. A positive feedback mechanism is likely to operate when the plasma motilin concentration increases during the interdigestive state. Accordingly, an inhibitory mechanism should be present to break the positive feedback system; otherwise, endogenous release of motilin will continue. How gastrointestinal MMC is terminated remains a mystery.

Perspectives

The physiological importance of gastric MMC is the mechanical and chemical cleansing of the empty stomach in preparation for the next meal [1, 30]. When gastric phase III activity is impaired, the gastric contents may remain for a longer period. Impaired gastric phase III activity may cause retention of the gastric contents and bacterial overgrowth, resulting in various symptoms. Over 30 years ago, Vantrappen et al. [1] proposed the possibility that bacterial

overgrowth may be due to a specific motility disorder, namely a complete or almost complete absence of interdigestive MMC.

Abnormal motility patterns of gastric MMC have been demonstrated in the clinical setting [35]. The incidence of gastric phase III activity of the antrum was significantly reduced in patients with functional dyspepsia (FD) compared to that in healthy controls [36]. As mentioned above, gastric MMC in the interdigestive state plays a major role in preparing for the next meal. The impaired and/or irregular gastric MMC may aggravate dyspeptic symptoms following food ingestion. Thus, it is highly possible that dyspeptic symptoms of the postprandial state will be reduced when impaired gastric MMC in the interdigestive state is improved.

Patients with FD sometimes show reduced activity of the vagus [37]. As the vagus plays an important role in mediating gastric MMC, impaired activity of the vagus may contribute to the impaired gastric MMC in FD patients. We believe that maintaining gastric MMC in the interdigestive state is an important factor in preventing postprandial dyspeptic symptoms.

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