

# Mechanism of Interdigestive Migrating Motor Complex

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Migrating motor complex (MMC) is well characterized by the appearance of gastrointestinal contractions in the interdigestive state. This review article discussed the mechanism of gastrointestinal MMC. Luminal administration of 5-hydroxytryptamine (5-HT) initiates duodenal phase II followed by gastrointestinal phase III with a concomitant increase of plasma motilin release in conscious dogs. Duodenal 5-HT concentration is increased during gastric phase II and phase III. Intravenous infusion of motilin increases luminal 5-HT content and induces gastrointestinal phase III. 5-HT<sub>4</sub> antagonists significantly inhibits both of gastric and intestinal phase III, while 5-HT<sub>3</sub> antagonists inhibited only gastric phase III. These suggest that gastrointestinal MMC cycle is mediated via the interaction between motilin and 5-HT by the positive feedback mechanism. Gastric MMC is regulated via vagus, 5-HT<sub>3/4</sub> receptors and motilin, while intestinal MMC is regulated via intrinsic primary afferent neurons and 5-HT<sub>4</sub> receptors. Stress is highly associated with the pathogenesis of functional dyspepsia. Acoustic stress attenuates gastric phase III without affecting intestinal phase III in conscious dogs, via reduced vagal activity and increased sympathetic activity. It has been shown that subset of functional dyspepsia patients show reduced vagal activity and impaired gastric phase III. The physiological importance of gastric MMC is a mechanical and chemical cleansing of the empty stomach in preparation for the next meal. The impaired gastric MMC may aggravate dyspeptic symptoms following a food ingestion. Thus, maintaining gastric MMC in the interdigestive state is an important factor to prevent the postprandial dyspeptic symptoms.

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## Key Words

Autonomic pathways; Enterochromaffin cell; Motilin; Serotonin

## Introduction

Gastric motility in the fasted state is a cyclical phenomenon called the migrating motor complex (MMC). In a normal MMC cycle in humans and dogs, there are four phases. Phase I is a quiescent period with virtually no contractions. Phase II consists of intermittent, irregular low-amplitude contractions. Phase

III consists of short burst of regular high-amplitude contractions. Phase IV represents a short transition period back to the quiescence of phase I.<sup>1</sup> Phase III contractions periodically occur every 90-120 minutes in humans and dogs.

Plasma motilin level is highly associated with the appearance of gastric phase III in humans and dogs. Plasma motilin levels vary in a cyclic fashion and its peaks regularly occur every 90-100 minutes during the period of gastric phase III in dogs<sup>2,3</sup> and

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humans.<sup>4,5</sup> Motilin administration causes gastric phase III contractions in dogs<sup>2,6</sup> and humans.<sup>5</sup>

In 1999, ghrelin was discovered as the endogenous ligand for the growth hormone secretagogue receptor (GHS-R) from rat stomach.<sup>7</sup> Because of a structural resemblance to motilin, ghrelin is known as a motilin-related peptide.<sup>8,9</sup> Phase III-like contractions are observed every 12-15 minutes in rats<sup>10,11</sup> and mice.<sup>12</sup> As it is rather difficult to distinguish 3 phases in rats and mice, these phases are called as phase I-like contractions and phase III-like contractions in rats and mice.<sup>10,12</sup> Ghrelin administration elicits phase III-like contractions of the stomach in rats<sup>10,13</sup> and mice.<sup>12</sup> Plasma ghrelin levels were highly associated with the occurrence of phase III-like contractions of the rat stomach. Spontaneous phase III-like contractions of the antrum were abolished by a GHS-R antagonist.<sup>13</sup> These suggest that the spontaneous phase III-like contractions of the antrum are mediated via endogenously released ghrelin in rats.<sup>13</sup>

In contrast, ghrelin failed to cause any phase III contractions of the dog stomach.<sup>14</sup> Although ghrelin has a structural resemblance to motilin, motilin administration failed to affect gastric emptying and GI transit in rats.<sup>15</sup> Moreover, motilin and motilin receptor have not been found in rats.<sup>15</sup> It seems that action of ghrelin and motilin in mediating interdigestive gastric contractions are different to some extent among humans, dogs and rodents. It is well established that motilin regulates gastric phase III contractions in dogs and humans, while ghrelin regulates gastric phase III-like contractions in rats and mice.

This review article focused on the mechanism of gastrointestinal MMC associated with motilin in humans and dogs. The mechanism of MMC still remains unclear and several serious questions have been raised.

## Questions About the Mechanism of Gastrointestinal Migrating Motor Complex —

### Mechanism of Motilin Release

The duodenum, which stores motilin, plays an important role to initiate gastric MMC in dogs and humans. Motilin-immunoreactive cells are concentrated in the deeper portion of the crypt of the human and dog intestine. They are most frequent in the duodenal and jejunal mucosa; a few of them are also seen in the ileal mucosa. No motilin cells are found in the stomach, colon, and rectum.<sup>16</sup>

After duodenectomy, no obvious phase III contractions are

seen in the gastric antrum. The plasma motilin concentration does not fluctuate as it does in normal dogs, and remains low after duodenectomy. The contractile response of the stomach to exogenous motilin after duodenectomy is similar to that of intact dogs.<sup>17</sup> These indicate that released motilin from the duodenal mucosa and upper jejunum mediate gastric phase III.

The presence of nutrient in the duodenum strongly suppresses the endogenous release of motilin in a digestive state. In an interdigestive state, luminal acidification and bile are important factors in regulating motilin release from the duodenal mucosa.<sup>18</sup> Atropine or hexamethonium blocks a cyclic increase in the plasma motilin concentration. Carbachol-induced motilin release is blocked by atropine, but not by hexamethonium.<sup>19</sup> The existence of muscarinic receptors is demonstrated in motilin producing cells.<sup>20</sup> Muscarinic type 3 receptors are responsible for motilin release from motilin-producing cells in perfusion system of the canine duodenum.<sup>21</sup>

It has been shown that the cyclical increments of pancreatic polypeptide and gastrin are both dependent on excitatory vagal innervation. However, participation of vagal control in the release of motilin has been controversial. Electrical stimulation of the vagus results in a significant increase in the plasma motilin concentration in anesthetized dogs.<sup>19,22,23</sup> On the other hand, others demonstrated that truncal vagotomy did not influence the intermittent fluctuation or concentration of plasma motilin in the fasting state.<sup>24</sup> This is further supported by an acute experiment showing that the spontaneous fluctuations in the plasma motilin concentration were not influenced by vago-sympathetic nerve blockade.<sup>3</sup> Although the precise mechanism of motilin release still remains unclear, the release of motilin is likely to be controlled by non-vagal cholinergic innervation in normal conditions.<sup>3,25</sup>

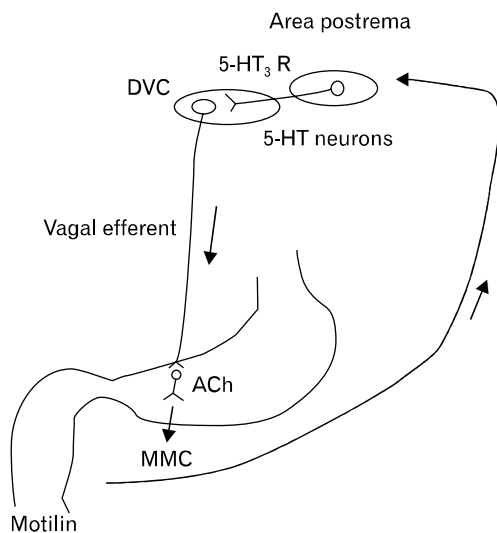
It is well known that intravenous-infusion of motilin induces gastric phase III.<sup>1</sup> It is also known that exogenous motilin can stimulate the endogenous motilin release.<sup>26</sup> The peak of plasma motilin level is observed during the late phase of gastric phase III or after finishing gastric phase III.<sup>27</sup> Thus, Sarna et al<sup>28</sup> proposed the possibility that endogenous motilin did not initiate spontaneous phase III. Instead, phase III contractions released motilin. They suggested that a positive feedback mechanism might exist because phase III contractions released motilin and that motilin, in turn, potentiated contractions.<sup>28</sup>

## Question No.1: Is Released Motilin Cause or Effect of Gastric Phase III?

### Site of action of motilin

Motilin receptors are present in the myenteric plexus, mucosa and muscle cells of gastrointestinal tract.<sup>29</sup> These receptors may mediate its pharmacological as well as physiological actions. However, it has not been well established whether motilin acts through intrinsic neurons,<sup>30</sup> extrinsic neurons<sup>25</sup> or smooth muscles.<sup>31</sup> Motilin induced contractions were not inhibited by tetrodotoxin of the rabbit antrum *in vitro*,<sup>31</sup> suggesting the direct action on the smooth muscle cells. In contrast, others demonstrated that atropine and hexamethonium attenuate motilin-induced contractions of the isolated stomach.<sup>30</sup> This suggests that intramural cholinergic pathway is involved in mediating motilin-induced contractions of the dog stomach *in vitro*.

*Ex vivo* isolated stomach does not show cyclic MMC pattern and motilin-induced contractions are much less potent than that of *in vivo*.<sup>30</sup> Gastric phase III, but not intestinal phase III, is abolished by blockade of the cervical vago-sympathetic nerve trunk in conscious dogs *in vivo*.<sup>3</sup> As sympathetic receptor blockers do not affect the inhibitory effect of vagal blockade,<sup>32</sup> gastric phase III seems to be regulated by vagus nerve. Spontaneous phase III contractions after vagotomy are also less potent than that of be-



**Figure 1.** Suggested mechanism of motilin-induced gastric migrating motor complex by Dr. Itoh.<sup>25</sup> Released motilin from the duodenal mucosa reaches at the area postrema and activates 5-hydroxytryptamine (5-HT) neurons at the dorsal vagal complex. Stimulation of 5-HT neurons activates vagal efferents through 5-HT<sub>3</sub> receptors. DVC, dorsal vagal complex; ACh, acetylcholine; MMC, migrating motor complex.

fore vagotomy.<sup>33</sup> Therefore, it is generally accepted that motilin-induced gastric phase III is vagal dependent in a physiological condition.<sup>25</sup>

Motilin-induced phase III of the stomach is antagonized by the systemic treatment with 5-hydroxytryptamine 3 (5-HT<sub>3</sub>) receptor antagonists in dogs<sup>34,35</sup> and humans.<sup>36</sup> Spontaneous gastric phase III, but not intestinal phase III, is also antagonized by 5-HT<sub>3</sub> antagonists.<sup>34,35</sup> These suggest that gastric phase III is mediated via an endogenous release of 5-HT.

The area postrema is very rich in fenestrated capillaries, and also supplied with numerous neurons including 5-HT neurons in the perivascular spaces around the capillaries and linked to the dorsal vagal complex.<sup>37</sup> Based on this evidence, Itoh<sup>25</sup> previously proposed the possibility that motilin may stimulate motilin receptors of 5-HT neurons in the area postrema. Stimulation of 5-HT neurons by motilin activates vagal efferents through 5-HT<sub>3</sub> receptors, resulting in gastric phase III (Fig. 1). However, the existence of motilin receptors has not been demonstrated in the area postrema.

## Question No.2: Where Are Motilin Receptors Located Which Mediate Gastric Phase III?

## Question No.3: What Is the Relationship Between Motilin and 5-Hydroxytryptamine?

## Question No.4: Where Are 5-Hydroxytryptamine 3 Receptors Located Which Mediate Motilin-induced Gastric Phase III?

### Different mechanism between gastric migrating motor complex and intestinal migrating motor complex

Gastric MMC and intestinal MMC are thought to be controlled by different mechanisms. Although plasma motilin level is highly associated with the appearance of gastric phase III,<sup>1</sup> phase III contractions in the small intestine sometimes occur without a concomitant increase in plasma motilin concentration.<sup>38</sup> Motilin antiserum inhibits the occurrence of phase III contractions only in the stomach, and not in the intestine.<sup>39</sup> After duodenectomy, no obvious phase III contractions are seen in the gastric antrum, but migrating phase III contractions are seen in the upper jejunum.<sup>17</sup> Chronic vagotomy reduces gastric phase III contractions without affecting the intestinal phase III contractions.<sup>33</sup> These suggest that vagal innervation regulates gastric MMC, but not intestinal MMC.

As mentioned above, it seems that gastric MMC is mediated

via motilin, vagal pathway and 5-HT<sub>3</sub> receptors. In contrast, intestinal MMC is not antagonized by 5-HT<sub>3</sub> antagonists.<sup>34,35</sup>

### Question No.5: What Is the Mediator of Intestinal Migrating Motor Complex?

When we carefully check gastrointestinal MMC recordings in dogs, it is obvious that duodenal phase III is frequently antecedent to gastric phase III.<sup>1,40-42</sup> However, no reasonable explanation has been shown.

### Question No.6: What Is the Relationship Between Duodenal Phase III and Gastric Phase III?

#### Mystery of gastrointestinal migrating motor complex

It has been a mystery how gastrointestinal MMC is regulated periodically every 90-120 minutes. It has been demonstrated that exogenous motilin stimulates endogenous release of motilin.<sup>26</sup> This suggests 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.

### Question No.7: What Is the Initial Stimulator and Terminator of Gastric Phase III?

## Possible Mechanisms of Mediating Gastrointestinal Migrating Motor Complex

### Luminal Release of 5-Hydroxytryptamine

A 5-HT in the gastrointestinal tract is involved in regulating its motility. A 5-HT stimulates phase II-like contractions when administered during phase I of the canine small intestine.<sup>43</sup> In humans, 5-HT re-uptake inhibitor (paroxetine) shortens MMC cycle and increases the propagation velocity of intestinal phase III.<sup>44</sup> This suggests that endogenous 5-HT plays an important role to regulate intestinal MMC in humans.

While 5-HT acts as a neurotransmitter of the enteric nervous system,<sup>45</sup> the majority of 5-HT is stored in enterochromaffin (EC) cells of epithelial cells. EC cells have been considered to release 5-HT mainly into the blood vessels and/or intrinsic nerve terminal via a basolateral border.<sup>46</sup> In contrast, others showed that 5-HT was also released into the intestinal lumen.<sup>47-50</sup> Electrical stimulation of the vagus nerves or duodenal acidification evokes 5-HT release from EC cells into the intestinal lumen in concen-

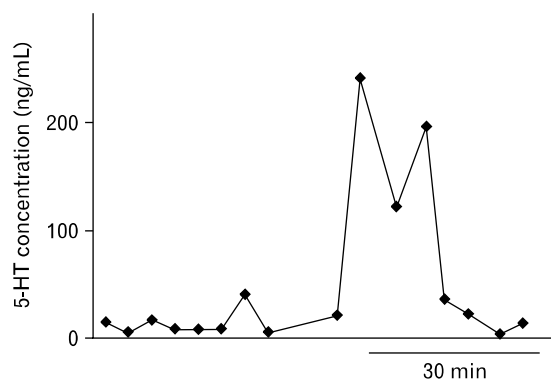
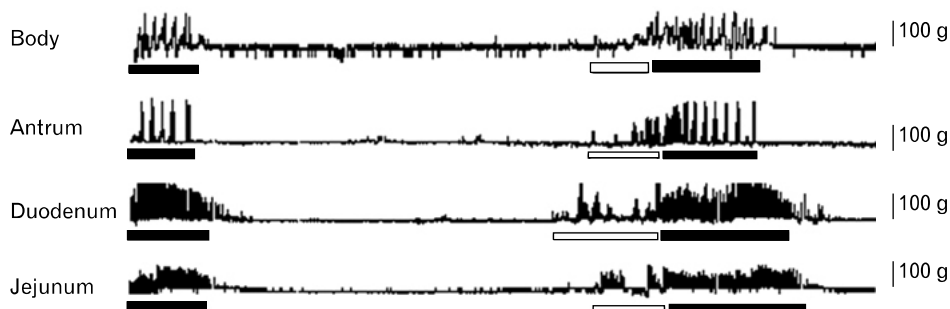
trations as high as 1.9  $\mu\text{M}$ <sup>49,51,52</sup> A 5-HT is released into the lumen, but not into the portal circulation, in response to luminal pressure increase of the rat colon.<sup>53</sup>

Immunoelectron microscopic study showed the anatomical evidence that 5-HT is released from EC cells in response to increase of luminal pressure of the rat duodenum.<sup>54</sup> Aggregation of secretory granules of 5-HT is located in the apical as well as basolateral cytoplasm of EC cells in basal conditions. After the increase of intraluminal pressure, an increase of empty 5-HT granules and swelling of secretory 5-HT granules are observed at the apical cytoplasm. Many secretory 5-HT granules are no longer dense and 5-HT particles are scattered over the apical cytoplasmic matrix and microvilli.<sup>54</sup> This indicates that 5-HT is primarily stored in the secretory granules of EC cells. In response to intraluminal pressure increase, 5-HT particles are released into the extra-granular cytoplasmic matrix. Thus, 5-HT particles diffuse or are transported into the duodenal lumen through the apical cell membrane.<sup>54</sup>

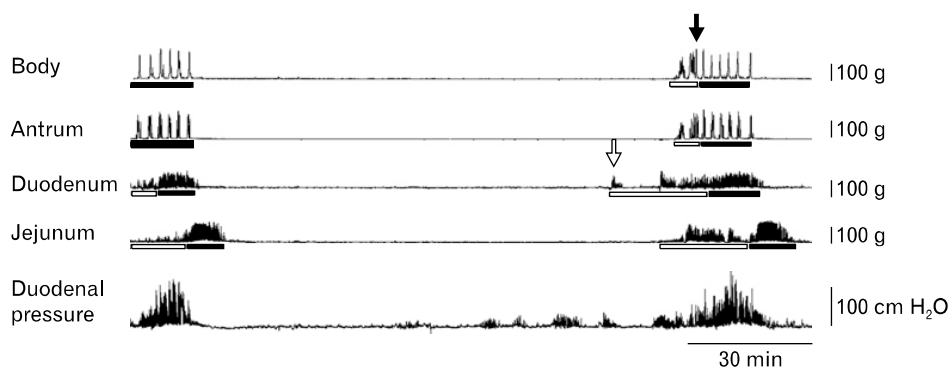
Luminally applied 5-HT can move by passive diffusion across the intestinal wall of the guinea pig ileum.<sup>55</sup> A 5-HT can cross the intestinal wall from the mucosa to the serosa (apical-to-basolateral direction).<sup>56</sup> Thus, 5-HT into the intestinal lumen could reach the synaptic circuitry resulting in stimulation of 5-HT receptors located on the lamina propria and/or enteric nervous system. Luminally released 5-HT from EC cells stimulates 5-HT<sub>3</sub> receptors located on the vagal sensory fibers. Through the brain stem (nucleus tractus solitarius and dorsal motor nucleus of the vagus [DMV]), the sensory information is transferred and the vagal efferent stimulates the release of acetylcholine from the myenteric plexus, resulting in muscle contraction.<sup>57</sup> A 5-HT also activates enteric afferent neurons to stimulate intestinal motor function.<sup>58-60</sup>

Luminally administered 5-HT initiates duodenal phase II followed by gastric phase III with the concomitant increase of plasma motilin levels in conscious dogs.<sup>61</sup> During duodenal phase II, luminal content of 5-HT of the duodenum is increased from 29 to 59 ng/mL. Luminal content of 5-HT of the duodenum is further increased to 250 ng/mL during gastric phase III. In contrast, the luminal concentration of 5-HT of the stomach does not significantly change during phase I, II and III (Fig. 2). This suggests that luminal concentration of 5-HT of the duodenum, but not the stomach, may play an important role to regulate gastrointestinal MMC.

The changes of the duodenal pressure are observed during gastrointestinal phase I. Luminal pressure of the duodenum in-



**Figure 2.** Luminal concentration of 5-hydroxytryptamine (5-HT) of the duodenum during migrating motor complex cycle. During duodenal phase I, the luminal concentration of 5-HT of the duodenum is 29 ng/mL, which is significantly increased to 59 ng/mL during the duodenal phase II. Luminal concentration of 5-HT of the duodenum is further increased to 250 ng/mL during phase III. In contrast to the duodenum, luminal concentration of 5-HT of the stomach is not significantly changed during phase I, II and III. Open squares indicate phase II contractions and closed squares indicate phase III contractions. Adapted from Nakajima et al.<sup>61</sup>



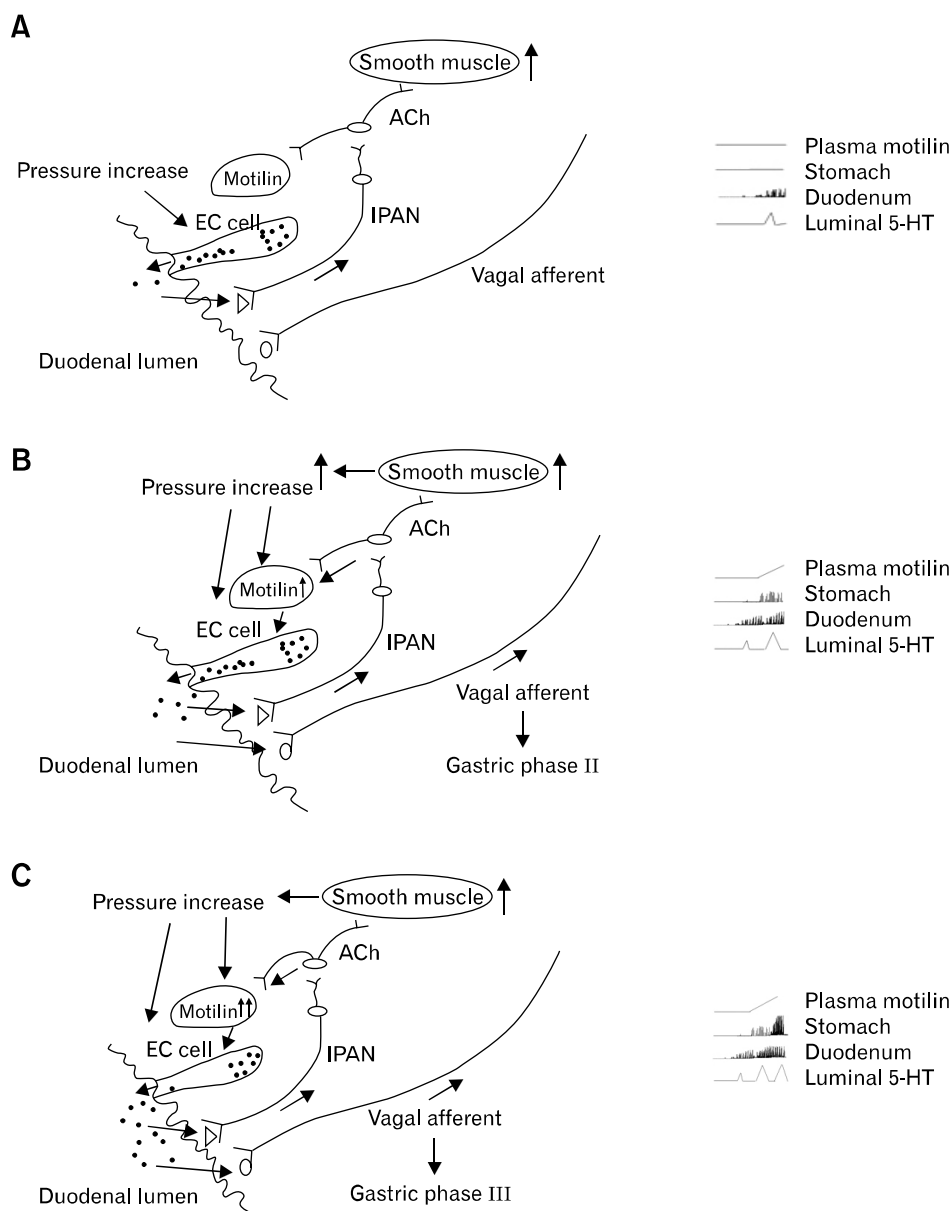
**Figure 3.** Simultaneous recording of gastrointestinal migrating motor complex and duodenal pressure. During phase I, duodenal pressure changes are observed. Luminal pressure of the duodenum increases by 20–30 H<sub>2</sub>O, just before the occurrence of duodenal phase II and III (an open arrow). Duodenal phase II (an open arrow) is followed by gastric phase III (a solid arrow). Open squares indicate phase II contractions and closed squares indicate phase III contractions. Adapted from Nakajima et al.<sup>61</sup>

creases by 20–30 cm H<sub>2</sub>O, just before the occurrence of duodenal phase II. Duodenal phase II is followed by gastric phase II and III. The spontaneous duodenal phase II is always antecedent to the spontaneous gastric phase II (Fig. 3).<sup>61</sup>

### Site of Action of Motilin

As mentioned above, it is highly likely that motilin-induced gastric phase III is mediated via vagal cholinergic pathways and 5-HT<sub>3</sub> receptors. Motilin released in the villi of the duodenum

enters the capillaries on the one hand, and may possibly stimulate nerve terminals in the villi on the other. However, no motilin receptors have been documented in the vagus nerve or nodose ganglion. In contrast, 5-HT<sub>3</sub> receptors are located on the nerve terminal of vagal afferent of the duodenal mucosa. Fibers immunoreactive for 5-HT<sub>3</sub> receptors in the duodenal mucosa are markedly reduced by subdiaphragmatic vagotomy or chemical denervation of vagal afferents.<sup>62</sup> Thus, nerve endings may well be the targets for the 5-HT released from EC cells.<sup>63</sup>



**Figure 4.** Possible mechanism of gastro-intestinal migrating motor complex during gastric phase I (A), phase II (B) and phase III (C). During gastric phase I, the basal secretion of gastric, pancreatic and biliary juices gradually increases the luminal pressure of the duodenum (A), resulting in 5-hydroxytryptamine (5-HT) release from enterochromaffin cells. Released 5-HT initiates duodenal phase II via 5-HT<sub>4</sub> receptors of intrinsic primary afferent neurons (IPAN) (A). Duodenal phase II causes further increase of duodenal pressure, which stimulates more 5-HT release. This positive circuit (pressure increase and 5-HT release) gradually enhances the amplitude of duodenal phase II, leading to duodenal phase III. Finally, maximally increased duodenal pressure stimulates motilin release (B). Released motilin stimulates large amounts of 5-HT release which acts on 5-HT<sub>3</sub> receptors of vagal afferent, in addition to 5-HT<sub>4</sub> receptors of IPAN. Released motilin induces gastric phase III via vago-vagal reflex<sup>61</sup> (C). Black dots indicate 5-HT granules/particles. Open triangle indicates 5-HT<sub>4</sub> receptors and open circle indicates 5-HT<sub>3</sub> receptors. ACh, acetylcholine; EC cell, enterochromaffin cell.

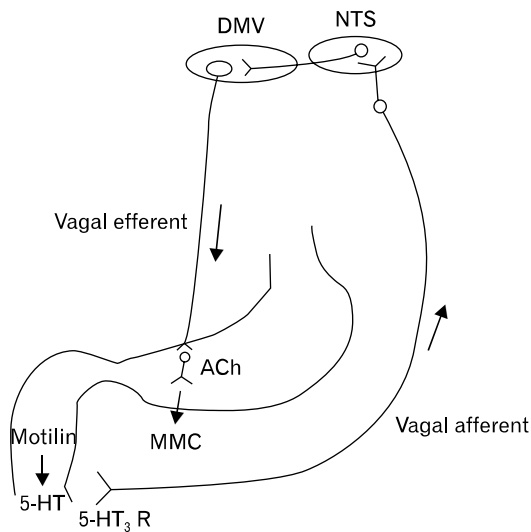
Motilin receptors are expressed in the muscle and mucosa of the human gastrointestinal tract.<sup>29</sup> Exogenously applied motilin stimulates 5-HT release into the lumen of the duodenum in conscious dogs.<sup>61,64</sup> In vitro study also showed that motilin stimulated 5-HT release into the lumen of the canine jejunum.<sup>65</sup> These findings raise the possibility that motilin initiates gastrointestinal phase III through the release of mucosal 5-HT from the duodenum.

It is conceivable that released motilin from the duodenal mucosa stimulates the release of 5-HT from the duodenal EC cells. Released 5-HT activates 5-HT<sub>3</sub> receptors of the vagal afferent

(Fig. 4). The sensory information is carried to the brain stem (nucleus tractus solitarius and DMV) and activates vagal efferent. Finally, motilin initiates gastric phase III via vago-vagal reflex (Fig. 5).<sup>61</sup>

### Relationship Between Gastric Migrating Motor Complex and Intestinal Migrating Motor Complex

A 5-HT stimulates phase II-like contractions when administered during phase I of the canine small intestine. Endogenous 5-HT affects motor activity during phase II and III and appears to be a candidate regulator of the intrinsic mechanisms gov-



**Figure 5.** Possible mechanism of gastric migrating motor complex. Released motilin from the duodenal mucosa stimulates the release of 5-hydroxytryptamine (5-HT) from the duodenal enterochromaffin cells. Released 5-HT activates 5-HT<sub>3</sub> receptors of the vagal afferent. The sensory information is carried to the brain stem (nucleus tractus solitarius and dorsal motor nucleus of the vagus) and activates vagal efferent. Finally, motilin initiates gastric phase III via vago-vagal reflex. DMV, dorsal motor nucleus of the vagus; NTS, nucleus tractus solitarius; ACh, acetylcholine; MMC, migrating motor complex.

erning the initiation and propagation of the intestinal MMC.<sup>43</sup>

Previous study showed that intraluminal administration of 5-HT ( $10^{-5}$  M) into the duodenum caused phasic contractions in dogs.<sup>66</sup> Intra-duodenal administration of 5-HT ( $10^{-7}$  M) initiated duodenal phase II in conscious dogs. 5-HT ( $10^{-7}$  M)-induced duodenal phase II contractions migrated to the jejunum. In contrast, 10 times higher concentration of 5-HT ( $10^{-6}$  M) initiated duodenal phase II followed by gastric phase II/III and plasma motilin release.<sup>61</sup> This raises the possibility that 5-HT<sub>4</sub> receptors of intrinsic primary afferent neurons (IPAN) are 10 times more sensitive than 5-HT<sub>3</sub> receptors of the vagal afferent in the canine duodenum.

Gastric MMC is inhibited by a 5-HT<sub>3</sub> receptor antagonist (ondansetron), while intestinal MMC is not affected by ondansetron. On the other hand, intestinal MMC as well as gastric MMC is significantly attenuated by a 5-HT<sub>4</sub> receptor antagonist (GR 125,487).<sup>61</sup> This suggests that intestinal MMC is regulated by 5-HT<sub>4</sub> receptors, while gastric MMC is regulated by 5-HT<sub>3</sub> receptors and 5-HT<sub>4</sub> receptors.

Pancreatic and biliary secretion into the duodenum is observed in the period of duodenal phase I in conscious dogs.<sup>67,68</sup> It

is conceivable that the basal secretion of gastric, pancreatic and biliary juices gradually increases the luminal pressure of the duodenum during phase I, which may stimulate 5-HT release from EC cells. Released 5-HT initiates duodenal phase II via 5-HT<sub>4</sub> receptors of IPAN. Thus, the initiation of duodenal phase II is not due to the increase of plasma motilin release.

Duodenal phase II causes increase of duodenal pressure, which further stimulates the release of 5-HT. This positive circuit (pressure increase and 5-HT release) gradually enhances the amplitude of duodenal phase II, leading to duodenal phase III. Finally, maximally increased duodenal pressure stimulates motilin release (Fig. 4).

## Possible Answers to Question No.1-7

### Question No.1: Is Released Motilin Cause or Effect of Gastric Phase III?

Answer is both. Motilin stimulates gastric phase III. Released 5-HT induced by duodenal contractions stimulates motilin release.

### Question No.2: Where Are Motilin Receptors Located Which Mediate Gastric Phase III?

It is likely that motilin receptors are located at EC cells of the duodenal mucosa, which mediate gastric phase III.

### Question No.3: What Is the Relationship Between Motilin and 5-Hydroxytryptamine?

Luminal 5-HT stimulates duodenal contractions, resulting in luminal pressure increase. Increased luminal pressure initiates motilin release. Released motilin stimulates 5-HT release by a positive feedback mechanism, as previously suggested by Sarna et al.<sup>28</sup>

### Question No.4: Where Are 5-Hydroxytryptamine 3 Receptors Located Which Mediate Motilin-induced Gastric Migrating Motor Complex?

5-HT<sub>3</sub> receptors are located on vagal afferents, which indirectly mediate motilin-induced gastric MMC.

### Question No.5: What Is the Mediator of Intestinal Migrating Motor Complex?

Intestinal MMC is regulated by 5-HT<sub>4</sub> receptors of IPAN.

### Question No.6: What Is the Relationship Between Duodenal Phase III and Gastric Phase III?

Duodenal phase II and III can stimulate motilin release via increasing intraluminal pressure of duodenum. Released motilin can stimulate gastric phase II and III.

### Question No.7: What Is the Initial Stimulator and Terminator of Gastric Phase III?

Initial stimulator is released 5-HT in response to intraluminal pressure increase during duodenal phase II. Maximally increased duodenal pressure stimulates motilin release from the duodenal mucosa. Released motilin further stimulates 5-HT release by a positive feedback mechanism. A large amount of 5-HT release stimulated by motilin acts on 5-HT<sub>3</sub> receptors of the duodenal vagal afferent, in addition to 5-HT<sub>4</sub> receptors of duodenal IPAN (Fig. 4).

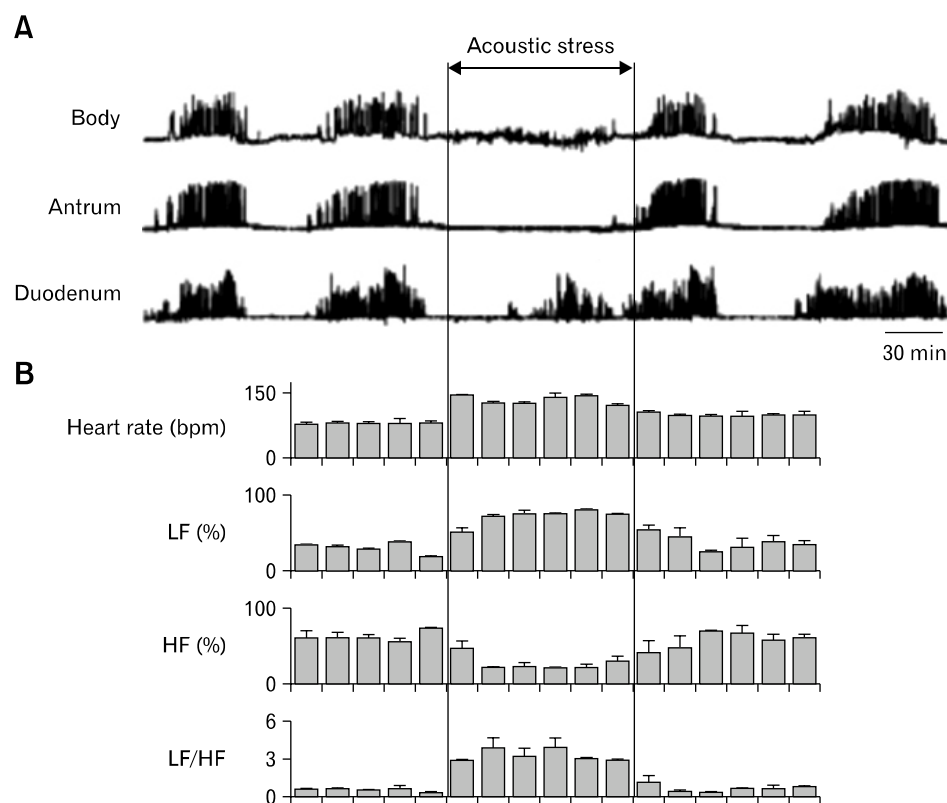
Therefore, released motilin induces gastric phase II and III via vagal dependent mechanisms. This may be the reason why duodenal phase II contractions are antecedent to gastric phase II contractions. In contrast, motilin infusion did not elicit antecedent duodenal phase II contractions prior to the gastric phase

II contractions.<sup>61</sup> This suggests that motilin initiates gastric phase II contractions, but not duodenal phase II contractions.

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. It still remains unknown how gastrointestinal MMC is terminated. As the luminal release of 5-HT is the key factor to initiate gastrointestinal MMC, the terminator should be involved in mediating the inhibition of 5-HT release.

### Effects of Stress on Gastrointestinal Migrating Motor Complex

Psychological stress plays a major role in functional gastrointestinal disorders, such as irritable bowel syndrome<sup>69</sup> and functional dyspepsia (FD).<sup>70,71</sup> Experimental studies demonstrated that colonic motility was stimulated,<sup>72-74</sup> while gastric emptying was delayed by stress<sup>75,76</sup> in rodents. The inhibitory effects of stress on gastric emptying were mediated via reduced parasympathetic pathways<sup>77,78</sup> or increased sympathetic pathways<sup>76,79</sup> in rodents.



**Figure 6.** Effects of acoustic stress on gastrointestinal migrating motor complex (MMC) (A) and heart rate variability (B) in conscious dogs. Acoustic stress almost completely abolishes gastric MMC (body and antrum) without affecting intestinal MMC (duodenum). During acoustic stress loading, heart rate and sympathetic tone (low frequency component; LF) are increased, while parasympathetic tone (high frequency component; HF) is reduced. As a result, the ratio between sympathetic tone and parasympathetic tone (LF/HF) is increased by acoustic stress. Adapted from Taniguchi et al.<sup>83</sup>



Acoustic stress forced to hear loud noise through earpieces in conscious dogs. Previous studies demonstrated that acoustic stress delayed the occurrence of the next gastric MMC.<sup>80-82</sup> Acoustic stress attenuates gastric phase III without affecting intestinal phase III.<sup>83</sup> In order to evaluate the function of autonomic nervous system in a conscious state, heart rate variability analysis has been widely used. During acoustic stress, heart rate and sympathetic tone (low frequency component) are increased, while parasympathetic tone (high frequency component) is reduced (Fig. 6). As gastric phase III, but not intestinal phase III, is regulated by vagal efferent, it is likely that the impaired gastric phase III induced by acoustic stress is mainly due to reduced vagal activity.<sup>83</sup> Therefore, if we can improve reduced vagal activity associated stress, impaired gastric phase III would be treatable. It has been shown that somatosensory nerve stimulation restores impaired gastric phase III induced by acoustic stress in conscious dogs.<sup>83</sup>

### Clinical Relevance of Gastrointestinal Migrating Motor Complex

The physiological importance of gastric MMC is a mechanical and chemical cleansing of the empty stomach in preparation for the next meal.<sup>25</sup> When gastric phase III activity is impaired, the gastric content may stay 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. proposed the possibility that bacterial overgrowth might be due to specific motility disorder, with namely a complete or almost complete absence of interdigestive MMC.<sup>84</sup>

Absence of phase III activity has been found in dyspeptic *Helicobacter pylori*-positive patients more frequently than in those without the infection. After *H. pylori* eradication, the incidence of gastrointestinal phase III was not altered.<sup>85,86</sup> Thus, it is assumed that this abnormal motility might be a predisposing condition for bacterial colonization of the gastric mucosa rather than its consequence.

FD is a symptom complex characterized by postprandial upper abdominal discomfort or pain, early satiety, nausea, vomiting, abdominal distension, bloating, and anorexia in the absence of organic disease. Approximately 50% of patients with FD have motor disorders, such as antral hypomotility, impaired accommodation reflex and gastric dysrhythmias. Studies using questionnaires showed that more than 75% of FD patients reported

relationship between aggravation of symptoms and ingestion of meal.<sup>87</sup>

In the clinical setting, abnormal motility patterns of gastric MMC have been demonstrated.<sup>88</sup> The incidence of gastric phase III activity of the antrum is significantly reduced in patients with FD, compared to that of healthy controls.<sup>89-91</sup> The impaired and/or irregular gastric MMC may aggravate dyspeptic symptoms following food ingestion. Dyspeptic symptoms in the postprandial state would be reduced when impaired gastric MMC in the interdigestive state is improved. Subsets of FD patients show the reduced activity of the vagus.<sup>92,93</sup> As vagus plays an important role to mediate gastric MMC, impaired activity of the vagus may contribute to the impaired gastric MMC in FD patients.

### Conclusion

Luminal administration of 5-HT initiates duodenal phase II followed by gastric phase III and intestinal phase III with a concomitant increase of plasma motilin release. Duodenal 5-HT concentration is significantly increased during phase II and phase III, compared to that of phase I. On the other hand, 5-HT content in the stomach is not significantly altered throughout the MMC cycle. Intravenous infusion of motilin increases luminal 5-HT content and induces gastric phase III and intestinal phase III. A 5-HT<sub>4</sub> receptor antagonists inhibit both of gastric and intestinal phase III, while 5-HT<sub>3</sub> receptor antagonists inhibit only gastric phase III. These suggest that MMC cycle is mediated via the interaction between motilin and 5-HT by the positive feedback mechanism.

Acoustic stress attenuates gastric phase III without affecting intestinal phase III in conscious dogs.

The impaired gastric phase III induced by stress is mediated via reduced vagal activity and increased sympathetic activity. Stress is highly associated with the pathogenesis of FD. It has been shown that subset of FD patients shows reduced activity of the vagus and that the incidence of gastric phase III is reduced in these patients. The impaired gastric MMC may aggravate dyspeptic symptoms following food ingestion. Thus, it is proposed that maintaining gastric MMC in the interdigestive state is an important factor to prevent the postprandial dyspeptic symptoms.

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