Am J Physiol Gastrointest Liver Physiol 310: G228–G233, 2016.
First published December 10, 2015; doi:10.1152/ajpgi.00212.2015.

Redefining the functional roles of the gastrointestinal migrating motor complex and motilin in small bacterial overgrowth and hunger signaling

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Submitted 29 June 2015; accepted in final form 7 December 2015

Deloose E, Tack J. Redefining the functional roles of the gastrointestinal migrating motor complex and motilin in small bacterial overgrowth and hunger signaling. *Am J Physiol Gastrointest Liver Physiol* 310: G228–G233, 2016. First published December 10, 2015; doi:10.1152/ajpgi.00212.2015.—During the fasting state the upper gastrointestinal tract exhibits a specific periodic migrating contraction pattern that is known as the migrating motor complex (MMC). Three different phases can be distinguished during the MMC. Phase III of the MMC is the most active of the three and can start either in the stomach or small intestine. Historically this pattern was designated to be the housekeeper of the gut since disturbances in the pattern were associated with small intestinal bacterial overgrowth; however, its role in the involvement of hunger sensations was already hinted in the beginning of the 20th century by both Cannon (Cannon W, Washburn A. *Am J Physiol* 29: 441–454, 1912) and Carlson (Carlson A. The Control of Hunger in Health and Disease. Chicago, IL: Univ. of Chicago Press, 1916). The discovery of motilin in 1973 shed more light on the control mechanisms of the MMC. Motilin plasma levels fluctuate together with the phases of the MMC and induce phase III contractions with a gastric onset. Recent research suggests that these motilin-induced phase III contractions signal hunger in healthy subjects and that this system is disturbed in morbidly obese patients. This minireview describes the functions of the MMC in the gut and its regulatory role in controlling hunger sensations.

migrating motor complex; hunger; motilin; ghrelin; food intake disorders

DURING THE INTERDIGESTIVE state, the upper gastrointestinal tract displays a typical contractility pattern (18). The first measurement of this periodic activity was described by Boldyreff in 1902 (3). Carlson (13) further defined the different phases of contractility, and in 1969 Szurszewski (49) measured the electrical activity and found that it migrated over the entire length of the small bowel; the term "migrating motor complex" (MMC) was born.

Currently the MMC is considered as the intestinal housekeeper of the gastrointestinal tract and motilin as a gastroprokinetic hormone. Their functions, however, seem to go beyond these descriptions as both past and recent research have shown. This review highlights some of the important findings of the classical role of the MMC in the prevention of small intestinal bacterial overgrowth (SIBO) but also focuses on the regulatory role of the MMC and motilin in hunger signaling and their disturbed patterns in food intake disorders.

Control of the MMC and Its Role in Small Intestinal Bacterial Overgrowth

The migrating motor complex. The MMC can be divided into three phases of contractile activity as described by Code and Marlett (16). The antral region will be in phase I ~50% of the entire MMC cycle length, whereas more distal in the small intestine phase II constitutes ~80% of the MMC (22). Phase I is a phase when no contractions are present. Phase II is described as a phase when contractions are present but the interval between consecutive contractions is irregular. The frequency of these high-pressure, peristaltic contractions will increase over time until it reaches 2–3 contractions/min in the stomach and 11–12 contractions/min in the small intestine, which is known as phase III. The contractions propagate slowly as a band of high-amplitude peristaltic contractions down the entire length of the small intestine at a rate of ~6–10 cm/min (58). Phase III is the most characteristic phase of the MMC and can start either in the stomach or the small intestine. About 70% of measured spontaneous phase III contractions in healthy volunteers start in the stomach (22).

When phase III has ended, phase I will start again and this cycle will continue until the next meal is consumed. MMC cycle length varies significantly between subjects, ranging from 113 to 230 min. Measurements within the same subject on separate occasions showed high intravariability with a standard deviation ranging from 58 to 70 min (22). The duration of an MMC cycle is dependent on the origin of phase III. The MMC cycle length is significantly longer when phase III has its origin in the antrum compared with the duodenum (34). Moreover intragastric pH influences MMC cycle length with an increase in duration with a more acidic pH (6, 7). A complete MMC cycle is schematically represented in Fig. 1*A*.

Motilin. The MMC is controlled by both gastrointestinal hormones and the nervous system (18). The main hormonal

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regulator of the MMC is motilin. This hormone, produced by endocrine cells of the proximal small intestine, fluctuates in synchrony with the phases of the MMC and peaks just prior to the occurrence of a phase III with gastric but not with duodenal onset (Fig. 1*B*) (5, 20, 39, 58). Further evidence of the involvement of motilin in the regulation of the MMC became evident when exogenous administration of motilin or the motilin receptor agonist erythromycin induced gastric phase III contractions (32, 52, 58). The potential of motilin to induce a gastric phase III seems to be dependent on the intraduodenal pH. Woodtli and Owyang (60) described that intraduodenal infusion of hydrochloric acid suppressed the occurrence of a gastric phase III despite the presence of a motilin plasma peak. Prior administration of atropine abolishes the effect of erythromycin on the interdigestive motor complex, indicating that motilin induces contractions through a cholinergic pathway (52). In both dogs and humans this cholinergic pathway is probably regulated via the vagus nerve, since it has been reported that after vagotomy gastric phase III activity is either abolished or disturbed (25, 29, 30, 43, 54). Differences in outcomes are likely due to differences in the vagotomy procedures.

Small intestinal bacterial overgrowth. The MMC has been considered an "intestinal housekeeper" that prevents SIBO. SIBO is usually determined by glucose or lactulose breath test, or by aspirate cultures from the small intestine, and is defined by the presence of excessive ($>10^5$ colony forming units/ml) bacterial growth in the small intestine (33). Common symptoms associated with SIBO are abdominal bloating, diarrhea, and abdominal pain (45). One of the main contributors to the development of SIBO is small intestinal dysmotility. It has been shown repeatedly that an absent or disordered pattern of the MMC is associated with SIBO (27, 41, 57). Moreover, disruption of the MMC in rats has shown that an absent MMC predisposes to both bacterial growth and translocation, indicating that the MMC is an important mechanism in controlling bacterial flora in the small intestine (38). No direct involvement of motilin has been reported in the development of SIBO. One paper reported on increased motilin plasma levels in scleroderma patients with bacterial overgrowth, but the clinical significance thereof is unclear (48). The protective effect of the MMC against SIBO is probably due to the migrating band of small intestinal contractions that clear out the luminal content toward the lower intestines.

Although the MMC is necessary to control the growth of bacterial flora in the small intestine, the gut microbiome also plays a role in the functionality of the MMC. Germ-free rats have been reported to have longer cycle lengths and fewer activity fronts that reach the midpoint (28). It has been suggested that this decreased motility in germ-free animals is caused by reduced excitability of neurons in the myenteric plexus (36). It seems that a delicate balance needs to be maintained between the intestinal flora and the MMC to maintain a healthy gut.

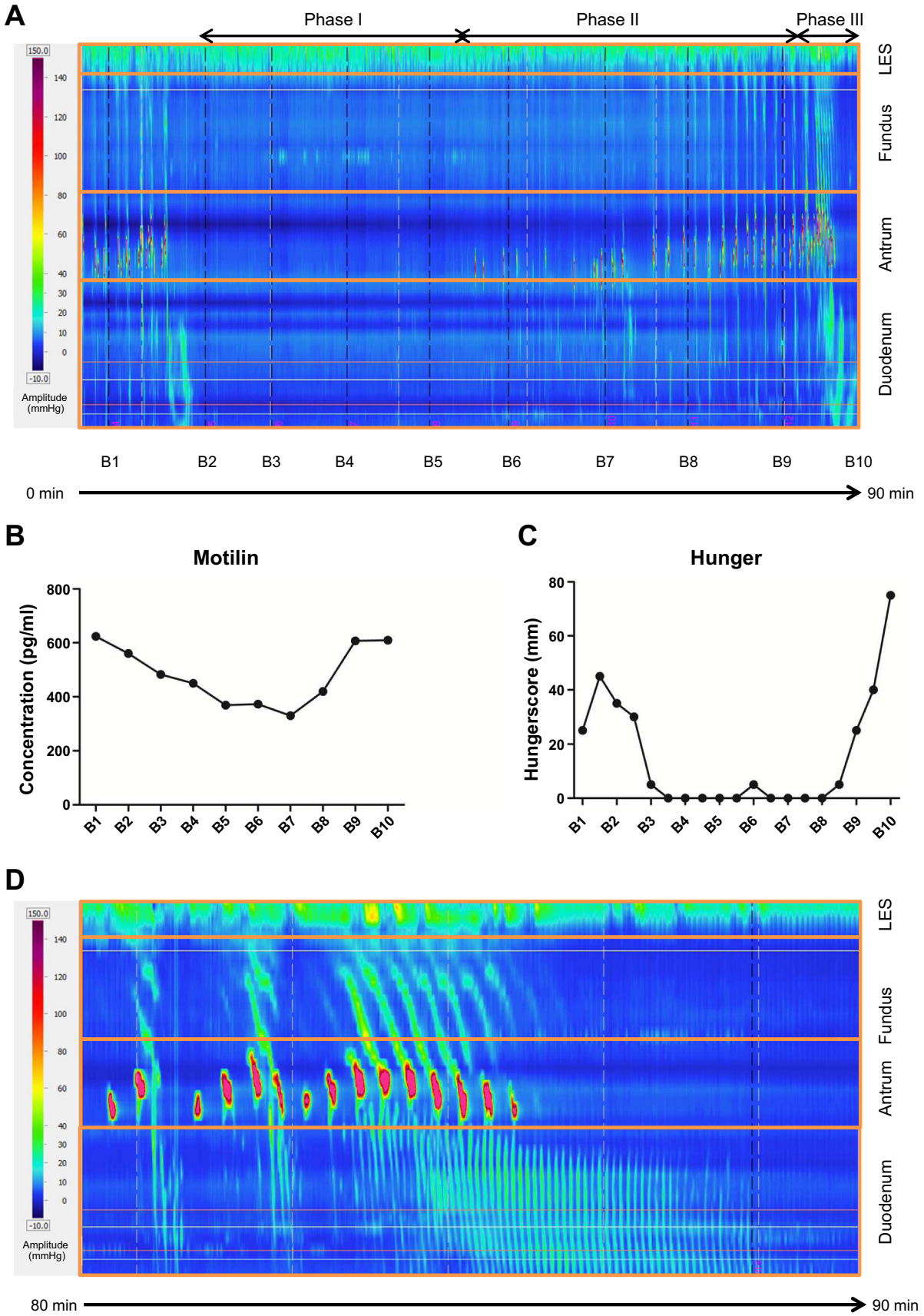
The Role of the MMC and Motilin in Hunger Signaling

The hungry stomach. In 1833 doctor William Beaumont (2) defined hunger as a buildup of gastric juice in vessels or glands of the stomach that emptied when food entered the stomach, causing a cessation of the hunger sensation. Later in the same century both Weber (1846) and Vierodt (1871) believed that strong stomach contractions during the fasting state could signal hunger (11). Hertz (1911) was probably the first to link the sensation of hunger to the gastric motor activity as described by Boldyreff (3). Nonetheless, Cannon and Washburn (11) and Carlson (12) are probably the most known representatives for the association between stomach contractions and hunger. Their research independently showed that hunger has a quick onset together with an intermittent periodic character that corresponds to the periodic activity of the fasted stomach. Moreover, the strength of the stomach contractions seems to determine the intensity of the hunger sensation. Causality between stomach contractions and hunger sensations was weakly shown by Carlson through the sudden inflation of a gastric balloon, which induced stomach contractions with hunger sensations (14); however, neither Cannon nor Carlson was able to propose a working theory for how a peripheral organ such as the stomach could regulate a central sensation as hunger.

Motilin: the missing link. In 1973 motilin was discovered and identified by Brown et al. (9). Further research by Itoh et al. in 1975 (31) showed that exogenous motilin administration was able to induce phase III contractions of the MMC or "hunger contractions" as described by Cannon and Carlson. Although further research identified motilin as a gastroprokinetic hormone and regulator of the MMC, its potential role in hunger signaling was not investigated. Two factors strongly slowed down motilin research: *1*) motilin and its receptor are not expressed in rodents and *2*) ghrelin was discovered in 1999 and identified as a hunger hormone (1, 26, 61).

Ghrelin and motilin share ~21% of their sequence identity, but ghrelin does not bind to the motilin receptor and vice versa (21). Ghrelin is mainly produced in the oxyntic mucosa of the stomach and is also able to induce gastric phase III contractions when administered exogenously in humans (17, 51). Moreover, in dogs plasma levels of ghrelin peak immediately after the motilin plasma peak (63). Based on these observations, ghrelin could be the candidate fulfilling the missing link in the hungry stomach theory.

However, we have reported recently that ghrelin plasma levels in humans do not fluctuate with the different phases of the MMC (20). We did confirm that motilin plasma levels peak before the occurrence of a phase III with gastric but not with duodenal onset (20). Intrigued by the findings of Cannon and Washburn (11) and Carlson (12) and the link between the MMC and motilin, we studied the association of motilin plasma levels with the hunger sensation identified during phase III of the MMC (50). The study revealed that hunger scores in healthy subjects fluctuate in synchrony with the activity of the MMC and peak during a phase III with gastric but not with duodenal onset (see Fig. 1*C*). Moreover, although administration of either motilin or ghrelin was able to induce premature gastric phase III contractions, only motilin-induced phase III contractions were associated with increased hunger ratings. Administration of the motilin receptor agonist erythromycin was also able to induce both gastric phase III contractions and hunger peaks, but induction of random gastric contractions through administration of the cholinesterase inhibitor neostigmine did not alter hunger ratings (50). These findings correspond with the studies of Cannon and Carlson and identify motilin as the missing link between the gastric motility in the periphery and the sensation of hunger generated by the central



nervous system, since only motilin-induced gastric contractions are able to inflict hunger increases. Further research, especially brain imaging during motilin infusion, is warranted to further unravel the underlying signaling pathways.

The Role of the MMC and Motilin in Food Intake Disorders

Obesity. In 1992 Pieramico et al. (40) reported that obese patients had significantly fewer phase III contractions that started in the stomach compared with healthy controls. This change in origin was associated with significantly lower motilin plasma levels in the obese patients compared with the lean controls. Unfortunately, hunger was not scored during the measurement.

We recently studied the association between gastric motility, motilin plasma levels, and hunger ratings in obese subjects and also found a shift in the origin of phase III contractions from stomach to duodenum in morbidly obese patients (19). Unlike the findings by Pieramico et al. (40), we found significantly elevated motilin plasma levels during all phases of the MMC and irrespective of the origin of phase III in obese patients compared with healthy controls. Although plasma levels were overall higher in the obese patients the fluctuation of motilin plasma levels was diminished (19). Our findings of elevated motilin levels are in agreement with two other studies reporting significantly higher motilin plasma levels in obesity (15, 40, 59). Hunger measurements showed lower hunger scores during phase III in the obese compared with the healthy controls, which is probably due to the shift in origin from gastric to duodenal, despite the higher motilin plasma levels (19). This shift in origin of phase III could be due to *1*) a lack of motilin fluctuation or *2*) a desensitization of the motilin receptor (8). Similarly, a shift toward more small intestinal phase III contractions has already been reported for elderly individuals, although their motilin plasma levels during all phases of the MMC were increased (4, 23). Differences in body mass index were, however, not evaluated between the controls and elderly, nor were their hunger scores measured and compared. In agreement with a changed MMC pattern, it has been reported that both obese and elderly subjects have a higher prevalence of SIBO (24, 35, 37, 42, 44).

After Roux-en-Y gastric bypass surgery we found that the pattern of the MMC is still present in the constructed Roux limb both 6 mo and 1 yr after surgery (19). Absence of this activity in the Roux limb can contribute to Roux-en-Y syndrome (56). Whether the stomach and bypassed duodenum still contribute to this bypassed MMC is unknown and difficult to measure manometrically. More interestingly, the motilin plasma levels both 6 mo and 1 yr after Roux-en-Y gastric bypass decreased significantly compared with the values preoperatively (19). Further research in both obese and elderly patients should be performed to clarify the clinical significance of the shift in the origin of phase III and the increased motilin plasma levels. Administration of the motilin receptor agonist, erythromycin still induced gastric phase III and increased hunger ratings in obese patients prior to bariatric surgery (19). Furthermore, our study suggests that "hedonic" rather than "physical" hunger drives food intake in obese patients. Hedonic hunger is defined as the drive to eat palatable food for pleasure in the absence of energy deficit and has been reported to be increased in obese individuals but decreases after Roux-en-Y gastric bypass surgery (46, 55). We have reported as well that hedonic hunger is decreased after Roux-en-Y gastric bypass surgery, together with a decrease in motilin plasma levels (19). The role of motilin in hedonic hunger sensations requires further attention.

Anorexia nervosa. Anorexia nervosa has been associated with antral hypomotility and duodenal dysmotility (10). These symptoms seem to be a consequence of the severe malnutrition associated with anorexia nervosa, but if these motility disorders are sustained they will in turn contribute to the symptoms that discourage eating such as early satiation, bloating, etc. It has been reported that ghrelin plasma levels are increased in patients with anorexia nervosa but normalize after weight gain (47, 53). No report has been made about motilin plasma levels in anorexia nervosa patients. One study, however, showed that increasing motilin plasma levels in anorectic children increased their body fat percentage (62). In patients with unexplained loss of appetite, gastric phase III occurrence is suppressed, and this is associated with lower hunger ratings. It is unclear whether this is also associated with altered motilin release (50). This recent concept of changed antroduodenal motility and motilin plasma levels in patients with anorexia (nervosa) deserves further attention.

Summary

Both the MMC and motilin have been intensely studied in the 1970s and 80s, but in the last three decades very little research has been performed on both topics. However, recent research has shown that both the MMC and motilin play a role in hunger signaling and changes in both occur in food intake disorders. These new findings should stimulate further research in signaling mechanisms and evaluate the pathophysiological and therapeutic potential of the MMC and motilin in obesity and anorexia nervosa.

GRANTS

This research was funded by a Methusalem Grant from the University of Leuven received by Prof. Jan Tack.

Fig. 1. Relationship between the migrating motor complex (MMC), motilin, and hunger scores in a healthy female volunteer. *A*: high-resolution manometry recording of a full MMC cycle in a healthy female volunteer (26 yr, 21 kg/m^2). The measurement was performed by using a solid-state catheter with 36 pressure channels spaced 1 cm apart (Manoscan 360, Sierra Scientific Instruments, Los Angeles, CA). The catheter was placed intranasally after an overnight fast of 12 h. The probe was positioned in such a way that measuring channels were located at the lower esophageal sphincter (LES), fundus, antrum, and proximal part of the duodenum. The position of the probe was checked by fluoroscopy. The measurement records a complete MMC cycle. The duration of the different phases is indicated on the recording together with the timing of blood samples (indicated by B1–B10). *B*: corresponding motilin plasma levels measured during the MMC cycle. Blood samples were taken every 10 min in a chilled LiHep tube containing aprotinin (500 kIU/ml). Samples were centrifuged at 4°C for 10 min at 3,000 *g* and plasma samples were analyzed by an in-house-developed radioimmunoassay for motilin (20). *C*: hunger scores were measured every 5 min on a visual analog scale of 100 mm with end points 0 mm = not at all hungry and 100 mm = as hungry as I have ever felt. *D*: enlarged view of the second phase III with a gastric origin.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

E.D. performed experiments; E.D. analyzed data; E.D. and J.F.T. interpreted results of experiments; E.D. prepared figures; E.D. and J.F.T. drafted manuscript; J.F.T. conception and design of research; J.F.T. edited and revised manuscript; J.F.T. approved final version of manuscript.

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