Motilin: from gastric motility stimulation to hunger signalling

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Abstract | After the discovery of motilin in 1972, motilin and the motilin receptor were studied intensely for their role in the control of gastrointestinal motility and as targets for treating hypomotility disorders. The genetic revolution — with the use of knockout models — sparked novel insights into the role of multiple peptides but contributed to a decline in interest in motilin, as this peptide and its receptor exist only as pseudogenes in rodents. The past 5 years have seen a major surge in interest in motilin, as a series of studies have shown its relevance in the control of hunger and regulation of food intake in humans in both health and disease. Luminal stimuli, such as bitter tastants, have been identified as modulators of motilin release, with effects on hunger and food intake. The current state of knowledge and potential implications for therapy are summarized in this Review.

The discovery of motilin in 1972 heralded a new era in gastrointestinal motility research¹. The involvement of motilin in the regulation of the migrating motor complex (MMC) was identified in dogs in 1975 (REF.²) and in humans in 1979 (REFS^{3,4}). Further studies showed that motilin had stimulatory effects on gastric and gallbladder emptying^{5,6}. Altered motilin release had been reported in a number of gastrointestinal disorders, but the importance of these changes remains unclear. In 1984, similarities in the motility patterns induced by motilin and by the 14-membered macrolide antibiotic erythromycin A were reported⁷. In 1989, erythromycin A was identified⁸ as a motilin receptor agonist. Erythromycin A belongs to the class of macrolides, a group of molecules consisting of different lactone ring sizes containing one or more deoxy sugars. Subsequent studies showed that many other erythromycin A derivatives⁹ (including 12-membered but not 16-membered macrolides) act as motilin receptor agonists. In the 1990s, several motilin receptor agonists were developed and studied for the treatment of gastrointestinal hypomotility disorders, but disappointing outcomes emerged from clinical trials with the motilide ABT-229. These results were attributed to receptor desensitization owing to the long half-life of the drug, wrong dose selection (which might have decreased the selectivity profile of the macrolide for the neural motilin receptor) or suboptimal patient selection¹⁰. These negative outcomes, as well as the lack of a functional motilin receptor in rodents (which is important for studies in knockout models), have hampered the further development of motilin ligands for therapeutic applications in humans.

In 2016, motilin was identified as a key hunger signal from the gastrointestinal tract¹¹. This discovery has redefined the potential physiological roles of this peptide and has opened a broad new range of applications for motilin receptor ligands or modulators of motilin secretion, including tastants. This Review provides a comprehensive overview of the current state of knowledge regarding the gastrointestinal hormone motilin, its receptor and motilin receptor agonists together with the role of motilin in normal physiology and pathophysiology.

Motilin

In 1967, duodenal alkalinization was discovered to stimulate the motility of denervated transplanted pouches of the gastric corpus in dogs¹². This effect was suspected to be the result of the release of a hormone, which was subsequently isolated in 1972 and named motilin^{1,13}. Porcine and human motilin share the same 22-amino acid sequence^{13,14}. Meanwhile, the peptide has been isolated from many species, with the exception of rats and mice, in which motilin exists only as a pseudogene^{15,16}. Indeed, in general, the rodent gastrointestinal tract has proved to be refractory to motilin and erythromycin A both in vitro and in vivo^{8,17}. Nevertheless, some studies have reported an excitatory effect of motilin on gastric motility, brain neurons and food intake in rodents¹⁶. Rodent-specific differences in gastrointestinal regulation might explain these different effects of motilin, but given that high concentrations of motilin were used in these studies, nonspecific effects cannot be excluded. On the basis of this divergence in evolution, we speculate that ghrelin might be the surrogate of motilin in rodents.

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Key points

- Motilin is a gastrointestinal hormone produced in the small intestine; during the fasting state, plasma levels of motilin fluctuate and induce gastric contractions to signal hunger via a cholinergic pathway.
- The cyclic release of endogenous motilin in the fasting state is mainly regulated by duodenal acidification and bile acids.
- Postprandially, the secretion of motilin is modulated by the presence of macronutrients and the release of other gut hormones (insulin, somatostatin, pancreatic polypeptide and secretin).
- Exogenously administered motilin or motilin agonists accelerate gastric emptying via high-sensitivity neural receptors and low-sensitivity muscular receptors and increase lower oesophageal sphincter pressure but have no effect on colonic motility.
- Stimulatory effects of motilin have been observed on hunger ratings, gallbladder emptying and glucose-induced insulin secretion.
- Targeting the motilin receptor has therapeutic potential to treat hypomotility disorders, modulate hunger and affect glucose metabolism.

The human motilin gene (9 kb) is localized on chromosome 6 and is encoded by 5 exons, of which exon I and exon V encode only the 5' untranslated region and the 3' untranslated region, respectively¹⁸. The motilin precursor is composed of a signal peptide (25 amino acids in length), motilin itself and so-called motilin-related peptide (65 amino acids in length)¹⁹. The plasma half-life of motilin is approximately 4 min²⁰. Motilin belongs to the ghrelin–motilin-related peptide family and shares 36% sequence similarity with ghrelin²¹.

Motilin is mainly produced by the enteroendocrine cells of the duodenum. Evidence suggests that motilin is co-stored with ghrelin in the same secretory granules of human and pig duodenal cells²². Motilin has also been identified in neurons in the myenteric plexus²³.

The NH₂ terminus has been identified as an essential region for the biological activity of motilin, while the COOH-terminal part stabilizes the NH₂ terminus^{24,25}. Moreover, the C-terminus of motilin is involved in desensitization and internalization of its receptor²⁶.

Regulation of motilin release

No cell line has been created to study the secretion of motilin at a cellular level; thus, the mechanisms underlying the control of its release remain obscure. A dose-dependent stimulatory effect of carbachol on motilin release from isolated canine intestinal cells, inhibited by atropine, implies the presence of muscarinic receptors on the motilin cell membrane²⁷. TABLE 1 summarizes the physiological factors influencing motilin secretion in humans.

Fluctuations in motilin levels

During the interdigestive state. In the fasting state, plasma levels of motilin fluctuate in parallel with phase III contractions of the MMC (see subsequent section)^{4,28–31}. The MMC is an aborally propagating contractility complex of the upper gastrointestinal tract during the fasting state, characterized by three different phases: phase I is a period of motor quiescence, phase II displays progressively increasing motor activity and phase III has the highest contractile activity and can start in either the stomach or small intestine. Findings in dogs that both spontaneous and induced phase III contractions were

associated with a peak in plasma levels of motilin, often occurring at the time of duodenal phase III, led researchers to believe that the increase in endogenous motilin was a consequence of the strong phase III contractions squeezing motilin out of its enteroendocrine cells³². However, this theory was refuted by results showing that the motilin plasma peak occurred before the start of phase III contractions and only if phase III started from the stomach but not with a duodenal origin^{30,31}. Moreover, in humans, phase III contractions induced by either erythromycin A or ghrelin are not associated with an increase in plasma levels of motilin^{33,34}. Thus, how fluctuations of endogenous motilin release are regulated remains unclear to date.

Because the gastric response to duodenal alkalization led to the discovery of motilin¹², the effect of manipulation of duodenal pH on motilin release has been of prime interest. Although several authors^{28,35,36} confirmed that intraduodenal alkalization produced an increase in plasma levels of motilin in dogs, studies in humans failed to show a similar phenomenon^{37,38}. Instead, acidification of the duodenum increases motilin release both in vivo and in vitro in humans^{38–41}. During the MMC, duodenal pH fluctuates, which is considered to reflect the secretory component of the MMC, as it has been shown that phase III coincides with peak duodenal, pancreatic and gastric secretions^{42,43}. During phase I, duodenal pH remains stable and is alkaline. A drop in pH occurs during phase II as a result of an increase in gastric output, with fluctuations between pH 2.0 and pH 7.5. Duodenal pH remains stable and alkaline during phase III owing to stimulation of bicarbonate release in the duodenum^{42,43}. Patients with duodenal peptic ulcers have a long MMC cycle despite increased plasma levels of motilin⁴⁴.

The presence of bile in the duodenum is another factor that influences motilin release during the fasting state. Gallbladder emptying during the interdigestive state occurs in synchrony with phase III contractions of the MMC and increases the release of motilin^{45–49}. Administration of taurocholate, a bile acid, stimulated the release of motilin in an ex vivo perfusion study⁵⁰. Future research is needed to evaluate how gastric acid and bile acids, resulting from gastric emptying and gallbladder contraction, interact to regulate motilin release from the duodenum.

During the postprandial state. The release of motilin after a meal depends on the nutrient composition of the meal. Equicaloric oral administration of protein, fat, carbohydrates and a mixed meal showed diverse effects on the release of motilin in humans³⁸. A small reduction occurred after the administration of glucose, but lipids markedly increased the release of motilin, with levels remaining elevated for 60 min after administration³⁸. The inhibitory effect of glucose and the stimulatory effect of lipids on motilin release have been confirmed by several other studies^{37,50–52}. When glucose or lipids were administered intravenously, the same response occurred as when these nutrients were given orally⁵². One study reported that intragastric, but not intraduodenal, administration of lipids increased plasma levels of

Table 1 | Factors influencing motilin release in humans

Factors influencing motilin	Plasma concentration of motilin	Refs
Acidification of the duodenum	↑	37–41,53
Alkalization of the duodenum	↓	37–40
Bile	↑	47–50,53
Protein	↑ and no effect	38,50
Fat	↑	37–39,50,52,53
Glucose	↓	38,50–52,54,165,166
Bitter compounds	↓	55–57
Insulin	↓	50,53,54,164
Somatostatin	↓	66,67
Ghrelin	No effect	33
Gastrin	No effect	50
Cholecystokinin	No effect	27,67
Pancreatic polypeptide	↓	78
Secretin	↓	67,79
Glucagon-like peptide 1	No effect	81

motilin³⁷. However, in another study, administration of a high dose of lipids directly into the duodenum did stimulate motilin release⁵³. Ingestion of a protein meal has been reported to increase or have no effect on plasma levels of motilin^{38,50}. Mixed meals have been reported to increase, decrease or have no effect on plasma levels of motilin^{37,38,50–52,54}.

As well as the macronutrient composition of the meal, non-nutrients also influence motilin release. Intragastric administration of the bitter compounds denatonium benzoate or quinine-hydrochloride substantially decreased endogenous plasma levels of motilin in healthy female volunteers^{55–57}. The presence of bitter taste receptors on enteroendocrine cells and the effect of bitter compounds on the release of gastrointestinal hormones have been shown by several groups^{58–61}. It is therefore likely that bitter taste receptors are also expressed on the motilin-producing cell or that the release of other peptides from enteroendocrine cells expressing bitter taste receptors alters motilin release. To date, no data are available on the receptor expression profile of motilin-producing cells, but many other gut peptides are able to affect motilin secretion.

In conclusion, food components have a complex effect on motilin release. The finding that a water load alone also induced a profound effect on motilin release further complicates the interpretation of the findings, as it suggests that gastric distension or lowering of the osmolarity in the duodenum might affect motilin release as well⁶².

Effect of endogenous hormones

Somatostatin. Somatostatin is secreted by D cells located in the gastric antrum and to a lesser extent in the duodenum⁶³. Somatostatin inhibits acid secretion and the release of several peptide hormones⁶⁴. Intravenous administration of somatostatin in humans and dogs inhibited motilin release^{20,65–67}. Moreover, the plasma concentration of somatostatin peaks before

the occurrence of a duodenal phase III contraction, when no motilin peaks occur⁶⁶. Administration of the somatostatin analogue octreotide inhibited the release of motilin in an ex vivo perfused model of the canine jejunum pretreated and denervated with tetrodotoxin, suggesting a direct inhibitory effect of somatostatin on motilin release⁶⁸.

Ghrelin. The gastrointestinal hormone ghrelin was discovered in 1999 (REF²¹). Although motilin and ghrelin show considerable amino acid sequence similarity, ghrelin does not bind to the motilin receptor⁶⁹. Ghrelin requires a post-translational esterification of the third serine residue with octanoic acid by ghrelin O-acyltransferase for its activation⁷⁰. Ghrelin is produced by P/D1 cells in the oxyntic mucosa and stimulates food intake, adipogenesis and gastric emptying⁷¹. In humans, endogenous levels of ghrelin neither fluctuate together with the phases of the MMC nor correlate with motilin levels^{72,73}. Indeed, exogenous administration of ghrelin in healthy volunteers does not alter plasma concentrations of motilin³³.

Gastrin. Gastrin, which is produced by G cells located in the gastric antrum and duodenum, stimulates the production of gastric acid by parietal cells⁷⁴. Intravenous administration of gastrin in humans and dogs had no effect on motilin release^{50,75}.

Cholecystokinin. Cholecystokinin is produced by the I cells in the small intestine and is involved in the stimulation of gallbladder emptying, pancreatic secretion, delay of gastric emptying and inhibition of food intake⁷⁴. Intravenous administration of cholecystokinin in dogs and humans did not alter the release of motilin^{67,75}. Stimulation of canine isolated intestinal cells with cholecystokinin did not increase motilin release in vitro²⁷.

Pancreatic polypeptide. Pancreatic polypeptide is produced by pancreatic polypeptide cells in the endocrine pancreas and inhibits pancreatic secretion and gastrointestinal motility⁷⁶. Administration of exogenous pancreatic polypeptide in a dosage corresponding to postprandial levels decreased plasma levels of motilin in both dogs and humans^{29,77,78}.

Secretin. Secretin is produced by S cells located in the duodenum and jejunum and inhibits the release of gastric acid while stimulating the production of bicarbonate and secretion of bile⁷⁴. Exogenous administration of secretin decreased the release of motilin in humans, which might be mediated via the concomitant release of somatostatin or the stimulation of pancreatic bicarbonate secretion^{67,79}. Secretin administration had no effect on motilin release in dogs⁷⁵.

Glucagon-like peptide 1. Glucagon-like peptide 1 is an incretin hormone produced by the L cells of the intestine. Glucagon-like peptide 1 is released after food intake and inhibits gastric emptying⁸⁰. Intravenous administration of glucagon-like peptide 1 in both healthy individuals and patients with irritable bowel syndrome did not affect plasma concentrations of motilin⁸¹.

Motilin receptor

The orphan G protein-coupled receptor GPR38, originally isolated from the thyroid gland, was identified as the motilin receptor in 1999 (REF.⁸²). Two alternatively spliced forms of this receptor exist: GPR38A is the typical (seven transmembrane domains) biologically active form; GPR38B is a truncated (five transmembrane domains) biologically inactive form. The motilin receptor is structurally related to the ghrelin receptor (overall amino acid identity 51.6%), neurotensin receptor 1 (32.7%), neurotensin receptor 2 (34.1%) and the orphan GPR39 receptor (28.7%)⁸³.

Motilin receptor density in humans is highest in the gastroduodenal region and decreases distally⁸⁴. By contrast, the highest motilin receptor density in rabbits is found in the colon⁸⁵. Receptor-binding studies show that motilin receptors are present on smooth muscle cell membranes but also in neural synaptosomes of the rabbit and human antrums^{86–89}. Immunofluorescence studies confirmed the expression of the motilin receptor in longitudinal muscle myenteric plexus preparations and cultured myenteric neurons of the guinea pig ileum²³.

Both ends of the second extracellular loop of the motilin receptor contain binding sites for motilin, which are not critical for erythromycin A^{90,91}. A common binding site for motilin and erythromycin A is located in the third transmembrane region of the motilin receptor⁹². The motilin receptor is susceptible to desensitization^{26,93,94}. The phosphorylated motilin receptor recruits β -arrestin 2 with greater affinity than β -arrestin 1. These multifunctional adaptor proteins bind to the phosphorylated receptor and disrupt the interaction between the receptor and G proteins to target the receptor to clathrin-coated pits⁹⁵. The ligand-receptor complex is subsequently sorted to recycling endosomes that traffic the motilin receptor back to the plasma membrane. Internalization and resensitization of the motilin receptor are agonist dependent. A higher degree of internalization and less recycling of the motilin receptor were observed with ABT-229 than with erythromycin A⁹⁶. The strong desensitization properties

of the motilide ABT-229 might have contributed to its failure in clinical trials¹⁰.

Motilin and gastrointestinal physiology

In the 1980s and 1990s, motilin was studied intensively for its effects on gastrointestinal motility^{3–5,29,30,32,34,46,97–105}. Since 2016, the implication of motilin in the control of hunger and food reward has generated a renewed interest in motilin and its receptor^{11,106,107}. FIGURE 1 provides an overview of the biological functions of motilin.

Mechanism of action on contractility

Functional in vitro contractility studies using rabbit and human antral smooth muscle strips showed that motilin enhanced post-ganglionic cholinergic neurotransmission at low doses and activated a smooth muscle receptor at high doses^{108–110}. In isolated rabbit gastric and intestinal smooth muscle cells, motilin initiated a transient contraction involving Gq-mediated inositol-1,4,5-trisphosphate (Ins(1,4,5)P₃)-dependent Ca²⁺ release and a sustained Gq-mediated and G α_{13} -mediated cascade involving RHO kinase and protein kinase C-dependent inhibition of myosin light chain phosphatase¹¹¹.

The motilin receptor is also expressed in the nodose ganglion of the Japanese house musk shrew (*Suncus murinus*)¹¹². In vitro, motilin increased the gastric but not the jejunal afferent nerve firing rate in these animals¹¹³. These findings substantiate the observations in some studies of reduced effects of motilin after vagotomy¹¹⁴.

The presence of motilin receptors in the brain^{112,115,116}, thyroid and bone marrow⁸² indicates that motilin is a multifunctional hormone, although its role in these regions remains to be explored.

The migrating motor complex

Motilin received its name from the initial observation that it stimulates motor activity of fundic pouches in dogs¹². The whole motilin molecule was first synthesized in 1975 (REF.¹¹⁷). In 1976, intravenous administration of motilin in fasted dogs was found to induce phase III of the MMC^{2,118}. This finding was later confirmed in humans³. The interdigestive motility pattern in the upper gastrointestinal tract was first observed by Boldyreff in 1905, who found that the stomach of starving dogs exhibited alternating periods of strong contractions and absolute quiescence¹¹⁹. These periods of activity were further described and classified as phase I, phase II and phase III¹²⁰. In 1969, electrical activity during these periods of gastrointestinal motility was identified and found to migrate caudally over the entire length of the small bowel¹²¹. Further studies showed that the MMC moves from the stomach to the terminal ileum over a period of 1.5–2.0 hours and is interrupted by nutrient intake^{122,123}.

Endogenous plasma levels of motilin fluctuate during the different phases of the MMC in dogs, with a peak in plasma concentration of motilin before phase III²⁸. After duodenectomy in the same species, plasma levels of motilin no longer fluctuate, and no antral phase III contractions occur¹²⁴. In 1980, plasma levels of motilin were reported to fluctuate in humans in accordance with MMC activity⁴. FIGURE 2 illustrates the relationship

Fig. 1 | Main biological functions of motilin. The main production site of motilin is the small intestine. In the gastrointestinal tract, motilin increases the pressure of the lower oesophageal sphincter (LES), initiates gastric phase III contractions of the migrating motor complex, stimulates gastric emptying, inhibits gastric accommodation and increases rectal compliance. Insulin secretion and gallbladder emptying are both increased by motilin. Finally, motilin also activates regions in the brain involved in the homeostatic and hedonic regulation of food intake.

between plasma levels of motilin and MMC activity in a healthy human individual. Interestingly, only phase III contractions that start in the stomach are motilin-dependent²⁹. This finding has been confirmed by other researchers^{30,31}, although motilin peaks before duodenal phase III contractions have been reported when these were preceded by strong gastric contractions not qualifying as gastric phase III³⁰. Plasma levels of motilin increase by 35% from phase I to phase III if phase III has a gastric origin⁷².

In contrast to motilin, endogenous ghrelin does not fluctuate with the phases of the MMC, although exogenous ghrelin administration can induce premature gastric phase III contractions in humans³³. In *S. murinus*, a synergistic effect was observed between ghrelin and motilin for the coordination of the MMC¹²⁵. Evaluating whether a similar relationship between ghrelin and motilin exists in humans would be interesting.

Lower oesophageal sphincter

The lower oesophageal sphincter (LES) is a high-pressure zone located between the stomach and the oesophagus to prevent regurgitation of stomach content to the oesophagus. Both the LES and the oesophagus show contractility patterns that are related to the MMC^{126,127}. Maximum pressures of the LES occur during late phase II and phase III, whereas minimum values are present during phase I of the MMC. These changes in LES contractility might contribute to preventing gastro-oesophageal reflux episodes in healthy individuals during strong gastric contractions¹²⁶. The oesophagus shows bursts of non-deglutitive contractions during the 15 min before the onset of phase III¹²⁷. In humans, intraduodenal acidification increased both endogenous motilin levels and LES pressure¹²⁸. Administration of motilin or motilin receptor agonists increased LES pressure in both healthy volunteers and patients with gastro-oesophageal

Fig. 2 | Fluctuation of plasma levels of motilin during the different phases of the migrating motor complex.

a | Antroduodenal motility was measured using a high-resolution manometry catheter (ManoScan 360, Sierra Scientific Instruments) in a healthy female volunteer (21 years old with a BMI of 22 kg/m²). The catheter was positioned with measuring channels in the fundus, antrum and proximal part of the duodenum after an overnight fast. The measurement continued for the duration of one complete migrating motor complex (MMC) cycle. Duration of the different phases is indicated above the pressure plot tracing. Two gastric phase III contractions were measured. B values on the y axis represent times of blood sample collection over the full MMC cycle. **b** | Blood samples were collected every 10 min in ice-chilled LiHep tubes containing aprotinin (500 kIU/ml) between two consecutive phase III contractions. Samples were centrifuged at 4 °C for 10 min at 3,000 g and analysed by a radioimmunoassay for motilin⁷². Plasma levels of motilin decrease during phase I and phase II and increase during phase III contractions.

reflux disease (GERD)^{129–134}. The therapeutic potential of motilin receptor agonists in GERD treatment is largely unexplored.

Gastric accommodation

After consumption of a meal, the fundic region of the stomach relaxes to accommodate the increase in volume without an increase in pressure¹³⁵. Administration of motilin or erythromycin A substantially reduces the accommodation reflex in humans by increasing the proximal gastric tone^{103,136}. Decreased gastric accommodation leads to early satiation and decreased nutrient volume intake, which suggests motilin and its receptor could be targets for controlling satiation and food intake^{136,137}. Patients with functional dyspepsia have impaired gastric accommodation to a meal, which is associated with symptoms of early satiety¹³⁸. However, baseline plasma levels of motilin and the effect on gastric compliance after motilin administration have been reported to be similar among patients with functional dyspepsia and healthy control individuals¹³⁹, although detailed studies with simultaneous measurement of interdigestive motility are lacking. By contrast, patients with functional dyspepsia, but not healthy volunteers, experienced an increased sensation of nausea after the administration of motilin, possibly reflecting hypersensitivity to tension generated by gastric contractions¹³⁹. However, these measurements were performed during the fasting state. Evaluating the role of motilin on gastric compliance after food consumption in patients with functional dyspepsia would be an interesting area of research.

Gastric emptying

After digestion of a meal, food remnants are emptied into the duodenum, where nutrient absorption occurs. One of the first studies on the effect of motilin on gastric emptying reported that administration of the motilin analogue 13-norleucine-motilin delayed the rate of gastric emptying of a liquid meal in humans¹⁴⁰. A later study⁹⁷, with the endogenous form of motilin in a higher dosage, reported an increase in the rate of gastric emptying of a solid meal. The effect of both motilin forms on human fundic muscle strips was similar, however, as both increased contractile responses *in vitro*¹⁴¹. Other studies have confirmed the stimulatory effect of motilin and erythromycin A on gastric emptying rate in healthy volunteers and in patients with idiopathic and diabetic gastroparesis, scleroderma, anorexia nervosa and intestinal pseudoobstruction^{5,99,142–150}. The effect of high doses of erythromycin A (200–250 mg) on gastric emptying seems to be independent of the vagus nerve, as erythromycin A accelerated gastric emptying in patients who had undergone a vagotomy^{98,151}.

Notably, the relationship between acceleration of gastric emptying and symptom improvement is weak in patients with gastroparesis¹⁵². Given that high doses of erythromycin A have even been reported to induce nausea in patients with dyspepsia and gastroparesis^{139,153}, low doses of motilin receptor agonists should be used that selectively activate neural instead of smooth muscle receptors in the stomach to stimulate gastric

emptying and in the vagus to promote appetite and reduce nausea¹⁵⁴.

Colonic motility

Motilin receptors are expressed in the colon of humans, but their density in the colon is substantially lower than that in the antroduodenal region^{82,84,110,155}. Motilin receptor agonists had no effect on contractility of human isolated colonic tissue nor did they increase colonic motility in healthy volunteers or patients with chronic obstipation (severe or complete constipation)^{110,156,157}. Administration of motilin in healthy volunteers increased rectal compliance without influencing rectal sensations¹⁵⁸.

Gallbladder emptying

Administration of erythromycin A increased gallbladder emptying in both healthy individuals and patients with gallstones¹⁵⁹. Moreover, gallbladder motility was normalized after erythromycin A administration in patients with impaired gallbladder emptying¹⁵⁹. Exogenous administration of motilin increased gallbladder emptying in a dose-dependent manner^{5,160}.

Role of motilin in glucose metabolism

Motilin not only regulates gastrointestinal motility but also influences plasma levels of insulin. During the interdigestive state in dogs, plasma levels of insulin fluctuate together with plasma levels of motilin without altering glucose levels¹⁶¹. Administration of exogenous motilin substantially increased insulin levels through a vagal cholinergic muscarinic pathway but did not affect glucose levels^{161,162}. A similar effect (that is, an increase) of basal and glucose-induced insulin secretion was observed in healthy volunteers and in patients with type 2 diabetes mellitus treated orally with erythromycin A for 1 or 4 weeks, accompanied by a decrease in glucose levels¹⁶³. Further research on the anti-diabetic effect and mechanism of action of motilin agonists in type 2 diabetes mellitus seems warranted.

While motilin influences insulin secretion, insulin also alters motilin secretion. In humans, an inverse correlation has been shown between motilin and glucose and motilin and insulin during the postprandial state^{50,54,164}. However, neither glucose nor insulin affects motilin secretion from human duodenal mucosa biopsy samples, indicating that their effect on motilin release is indirect. The inhibitory effect of insulin on motilin release in humans seems to be glucose-independent, as shown by using an euglycaemic glucose clamp¹⁶⁴. Administration of xylitol, a low-caloric sweetener with minimal effects on insulin secretion, increased rather than decreased plasma levels of motilin¹⁶⁵. Our group has also shown that administration of acesulfame K, a non-caloric sweetener with no effect on insulin secretion, did not alter plasma levels of motilin^{166,167}. Elevated plasma levels of motilin have been reported in patients with diabetes mellitus compared with healthy controls^{51,101}. Future research should explore the mechanisms behind the inhibitory effect of insulin on motilin secretion and how this relationship is disturbed in patients with diabetes mellitus^{51,101}.

Regulation of food intake and hunger

By 1833, the sensation of hunger was associated with the physiology of the stomach¹⁶⁸. In the same century, strong contractions of the stomach were postulated to be responsible for the sensation of hunger¹⁶⁹. This idea was further confirmed early in the 20th century^{169,170}. In 1975, exogenous motilin administration was reported to induce 'hunger contractions'², but the link between motilin and hunger was largely forgotten after these early observations. Notably, these contractions have not been established to be directly responsible for the sensation of hunger.

To date, ghrelin is the only gastrointestinal hormone classified as an orexigenic hormone. Exogenous administration of ghrelin increases food intake in both rats and humans^{171,172}. Moreover, plasma levels of ghrelin increase before food intake^{173–175}. Interestingly, plasma levels of ghrelin are substantially lower in patients with obesity than in healthy individuals^{176,177}.

In 2016, our group reported that hunger scores in humans fluctuate with the different phases of the MMC and peak when phase III has a gastric origin (FIG. 3). Moreover, a positive correlation was found between endogenous plasma levels of motilin and hunger scores in the interdigestive state¹¹ (FIG. 4). Hunger peaks could also be generated by the administration of exogenous motilin or erythromycin A^{11,106}. The stimulation of hunger by motilin agonism is driven via a cholinergic pathway, as administration of atropine abolished the

orexigenic effect of erythromycin A¹⁰⁶. Contractions induced by either neostigmine (an acetylcholinesterase inhibitor) or ghrelin did not markedly increase hunger sensations during the fasted state, indicating that only motilin-induced gastric contractions or motilin itself increases hunger scores¹¹. Erythromycin A has also been shown to modulate brain regions related to homeostatic and hedonic control of appetite and feeding¹⁰⁷. Further support for a role of motilin in the control of food intake was provided by a study showing that a low dose of erythromycin A stimulated voluntary meal requests in healthy volunteers¹⁰⁶. However, total caloric intake from an ad libitum buffet meal after erythromycin A administration did not differ from placebo, nor were motilin levels of plasma increased before spontaneous meal requests¹⁷⁵. Taken together, these findings illustrate that motilin has a complex role in the regulation of food intake, with a main role in determining the return of hunger and initiation of meals.

Intragastric administration of the bitter compounds denatonium benzoate or quinine-hydrochloride substantially decreased plasma levels of motilin^{55–57}. In healthy controls, intragastric administration of denatonium benzoate also inhibited gastric accommodation, which was associated with increased satiation and decreased nutrient volume tolerance¹⁷⁸. However, plasma levels of motilin were not measured in this study.

Role of motilin in pathophysiology

Plasma levels of motilin have been described to be altered in several conditions with disturbed gastrointestinal motility. In patients with functional dyspepsia with delayed gastric emptying, plasma levels of motilin did not fluctuate as normal during the interdigestive state, and gastric phase III contractions were absent¹⁷⁹. In patients with diabetic gastroparesis, plasma levels of motilin were elevated but still fluctuating during the interdigestive state, although antral phase III activity was absent^{51,101}. In patients with morbid obesity, increased plasma levels of motilin were found during the MMC, with a loss of motilin plasma peaks before phase III and a suppression of gastric phase III contractions¹⁸⁰. Hunger scores were reduced in patients with obesity but could be restored after administration of erythromycin A¹⁸⁰. A year after Roux-en-Y gastric bypass surgery, plasma concentrations of motilin normalized to levels of healthy volunteers¹⁸⁰.

To date, there are no reports on plasma levels of motilin in patients with anorexia nervosa. In patients with unexplained loss of appetite, gastric phase III contractions are suppressed, but plasma levels of motilin were not measured in this study¹¹. A similar observation to that seen in patients with obesity has been reported for elderly individuals (that is, increased plasma levels of motilin during the MMC, with a loss of motilin plasma peaks before phase III and a suppression of gastric phase III contractions)^{181,182}. Patients with irritable bowel syndrome have been described to have increased plasma levels of motilin, although the cyclic variation with the MMC was still present in this population¹⁸³. One study reported that plasma levels of motilin were increased only in patients with diarrhoea-predominant irritable

Fig. 3 | Relationship between interdigestive motility and hunger ratings. Mean hunger ratings (100 mm visual analogue scales) and antral motility index in nine healthy volunteers are shown, with a spontaneous phase III with gastric origin. Gastric phase III motor activity and hunger ratings are closely correlated.

Fig. 4 | Relationship between interdigestive hunger ratings and plasma levels of hormones. The relationship between hunger score (100 mm visual analogue scales) during the spontaneous migrating motor complex cycle and plasma levels of motilin (left panel) and ghrelin (right panel) in nine healthy volunteers is shown. Plasma levels of motilin, but not ghrelin, are significantly correlated with hunger ratings.

bowel syndrome¹⁸⁴. A decrease in plasma levels of motilin has been reported in patients with long-standing idiopathic constipation and in patients with GERD^{185–187}. TABLE 2 summarizes changes in motilin levels in different diseases. The implication of altered plasma levels of motilin in these conditions is still unclear.

Motilin receptor agonists and antagonists

The effects of motilin on gastrointestinal motility, hunger and glucose metabolism identify the hormone and its receptor as interesting targets for the treatment of several clinical conditions. Motilin receptor agonists could be used to accelerate gastric emptying in patients with gastroparesis, to stimulate insulin secretion in patients with type 2 diabetes mellitus and to enhance LES pressure in patients with GERD. Moreover, motilin receptor agonists could also be used as appetite stimulants. Motilin antagonists, on the other hand, could improve impaired gastric accommodation and nutrient tolerance, for example, in patients with functional dyspepsia.

Erythromycin A

Erythromycin A, a macrolide antibiotic, induces gastric phase III contractions of the MMC⁷. Furthermore, intravenous administration of erythromycin A induces gastric phase III contractions in humans without increasing endogenous levels of motilin³⁴. Phase III contractions induced by erythromycin A do not differ substantially from spontaneous phase III contractions, except for having a longer duration of antral phase III contraction³⁴.

Direct stimulation of the motilin receptor by erythromycin A was proven by receptor-binding studies and in vitro contractility studies in the presence of a motilin receptor antagonist^{8,188,189}. Studies in HEK-293 cells expressing the cloned motilin receptor confirmed that erythromycin A is a motilin agonist⁸². Notably, only low dosages of intravenously administered erythromycin A (40 mg) induce gastric phase III contractions, whereas high dosages (200 mg and 350 mg) induce strong antral contractions that do not migrate caudally¹⁰⁰. Low doses of erythromycin A activate an intrinsic or vagal cholinergic pathway, whereas high dosages directly activate a

muscular receptor¹⁰⁴. Erythromycin A has proved to be a useful prokinetic for the treatment of gastroparesis in short-term studies^{99,144–146}. It might also be beneficial for the treatment of GERD, as it increases LES pressure and decreases the number of reflux episodes when administered intravenously^{133,190–192}. Azithromycin, another macrolide antibiotic, has also been shown to activate the motilin receptor and has a similar effect on gastric emptying as erythromycin A^{193,194}. Acid reflux episodes and oesophageal acid exposure were reduced in patients with GERD after treatment with azithromycin¹⁹⁵. However, the antibiotic properties and ability of erythromycin A and related macrolides to induce QT prolongation make these agents unsuitable candidates for the long-term treatment of gastroparesis¹⁹⁶.

Motilides

The findings with erythromycin A prompted the development of the so-called motilides, that is, derivatives of erythromycin A without antibacterial activity but with good motilin receptor activity¹⁹⁷. ABT-229 was shown to increase gastric emptying in healthy volunteers and dogs and to bind directly to the motilin receptor^{198–200}. However, treatment with ABT-229 did not relieve the gastrointestinal symptoms of patients with functional dyspepsia or type 1 diabetes mellitus with or without delayed gastric emptying compared with placebo^{201,202}. There was also no improvement of reflux symptoms in patients with GERD²⁰³. These results might indicate that other populations or subpopulations of patients should be selected or that the dose of ABT-229 was too high to provide symptom relief. Indeed, ABT-229 might have induced adverse effects on gastric accommodation and worsening of the symptoms by stimulating not only neural but also smooth muscle motilin receptors at the fairly high doses used¹⁰. Despite having a half-life of 20 hours, ABT-229 was dosed twice daily, which might have promoted desensitization of the motilin receptor^{93,96,204}.

KC 11458 stimulated gastric emptying in dogs and healthy volunteers but did not improve emptying in patients with diabetes mellitus²⁰⁵. Only GM-611 (miteminal) has been reported to accelerate gastric emptying

Table 2 | Conditions with altered plasma motilin levels

Condition	Fasting plasma level of motilin	Normal fluctuation of motilin levels with MMC	Gastric phase III	Refs
Idiopathic gastroparesis	Normal	Absent	Absent	179
Diabetic gastroparesis	↑	Normal	Absent	51,101
Obesity	↑	Absent	↓	180,231,232
Old age	↑	Absent	↓	181,182
Irritable bowel syndrome	↑	Normal	NS	183,184
Duodenal ulcer	↑	Normal	↓	44
Idiopathic constipation	↓	NS	NS	185,186
Gastro-oesophageal reflux	↓	NS	NS	187

MMC, migrating motor complex; NS, not studied

in a phase II study in patients with gastroparesis, but the drug was not advanced to phase III²⁰⁶.

Small-molecule motilin receptor agonists

Another class of motilin receptor agonists is derived from a benzylpiperazine molecular structure^{207,208}. Camicalin is one of these motilin receptor agonists²⁰⁹. This compound binds directly to the motilin receptor, increases gastrointestinal contractility and enhances gastric emptying in healthy volunteers and feed-intolerant critically ill patients^{210–215}. A phase II trial in patients with Parkinson disease showed that camicalin induced rapid absorption of L-DOPA and improved Parkinson disease symptoms, probably through decreased variability in speed of delivery of the drug to the duodenum for absorption²¹⁶. Camicalin has a short half-life and unlike motilin induces long-lasting facilitation of cholinergic activity in the human antrum without inducing desensitization, making it an interesting candidate for the treatment of gastroparesis^{110,209}. Similar long-lasting activity has previously been observed in the rabbit antrum with camicalin and erythromycin A^{109,210}. A phase II trial evaluating camicalin in patients with diabetic gastroparesis showed symptomatic benefit with the lower dose ranges of the drugs, while the higher doses were most effective in enhancing gastric emptying²¹⁷. The drug has not yet advanced to phase III studies.

The oligopeptide atilomotin increased gastric emptying without affecting colonic filling or transit²¹⁸. It also increased LES pressure but disrupted oesophageal peristalsis¹³⁰. RQ-00201894, another small molecule agonist, binds to the motilin receptor and has been shown to increase antral contractions in human smooth muscle strips through a cholinergic pathway²¹⁹. The oligopeptide SK-896 binds with similar affinity to the motilin receptor as motilin and contracted smooth muscle in in vitro preparations of the rabbit gastrointestinal tract with the same pharmacological profile as motilin²²⁰. In dogs, SK-896 induced interdigestive migrating contractions²²¹. Moreover, SK-896 improved gastrointestinal motility in postoperative ileus in dogs^{222,223}. The effects on gastrointestinal motility in healthy human volunteers were less pronounced²²⁴. DS-3801b is the latest nonmacrolide, selective motilin receptor agonist to be developed. In a phase I study in healthy individuals, DS-3801b

accelerated gastric emptying²²⁵. Of these agents, only camicalin has been studied in large clinical trials.

Motilin receptor antagonists

MA-2029, GM-109, TZP-201 and RWJ-68023 are all motilin receptor antagonists^{226–229}. In dogs, MA-2029 inhibited gastrointestinal motility induced by motilin without affecting gastric emptying²³⁰. TZP-201 reduced motilin-induced contractions of the colon in *S. murinus*²²⁸. In humans, RWJ-68023 antagonized the tonic effect of motilin on the proximal stomach²²⁹. None of these antagonists have been advanced to large clinical trials, at least in part because of a lack of established end points (patient-reported outcomes) and issues with patient selection and magnitude of therapeutic effect.

Studies with bitter tastants have shown that it is possible to inhibit motilin release by activating chemosensory receptors on the motilin cell^{155–157}. This approach should be explored further, including studies with other tastants and the effects of repeated administration.

Conclusions

The notion that motilin is a gastrointestinal hormone involved in only stimulation of gastrointestinal motility needs to be revised. Its potential role in the regulation of food intake and glucose metabolism deserves further attention. The fluctuation in plasma levels of motilin during the fasting state and the variable outcome on motilin levels after meal ingestion demand standardized protocols to evaluate the physiological role of endogenous motilin. In vitro studies should further characterize the neuropeptide and chemosensory receptors that regulate motilin release, as these findings might explain altered plasma levels of motilin in disease states.

In the past, the development of successful motilin receptor agonists has been hampered by the rapid desensitization of its receptor. Future candidate motilin receptor agonists should be tested for their ability to stimulate the motilin receptor, desensitize the motilin receptor and facilitate cholinergic neural contractile responses instead of smooth muscle contractions (which might not only enhance gastric emptying but also reduce symptoms of nausea in patients with gastroparesis by facilitating hunger signalling).

Luminal stimuli have the potential to alter motilin release, as shown by the inhibitory effect of bitter tastants on motilin release and hunger signalling. Exploring this pathway holds potential for designing totally different approaches to altering motilin signalling for treatment of gastrointestinal diseases or disorders of appetite and food intake. Motilin and ghrelin share many of the same characteristics, but their involvement in gastrointestinal motility, food intake and glucose metabolism is still very different. Future research should evaluate the relationship between these two peptides.

In conclusion, this Review summarizes the main findings of motilin research from the previous and current century and shows that further research is warranted to fully characterize the physiological role of the gastrointestinal hormone motilin.

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Competing interests

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