The peptide motilin received a very appropriate name. Since its isolation by J.C. Brown in 1973, no other peptide has been described with such a pronounced effect on gastrointestinal motility, until the discovery in 1999 of ghrelin. The latter was identified as an endogenous ligand of the growth hormone secretagogue receptor, and was named for its effect on growth hormone release, but it seems more involved in the regulation of gastrointestinal function than in the regulation of growth hormone secretion.

The discovery, first in dog and then in man, of the relation between motilin and the pattern of fasted motor activity known as the migrating motor complex (MMC) was met with great excitement. Because endogenous motilin plasma levels rise before the start of phase 3 of the MMC in the stomach and because exogenous administration of motilin induces phase 3, it was thought that the regulation of fasted motor activity was the physiological role of motilin. Besides being an oversimplification, the lack of an important role of the MMC in pathophysiology pushed motilin almost into oblivion. This changed when it was shown that the long known antibiotic erythromycin was a motilin agonist. The availability of a cheap alternative to motilin, which moreover could be administered per os, allowed for an exploration of motilin’s effect on gastric emptying. When it was found that erythromycin accelerates gastric emptying in patients with diabetic gastroparesis, the motilin receptor became an interesting pharmacological target (for a review, see Itoh). However the development of more potent erythromycin derivatives, so-called motilides, basically natural non-peptide agonists, of motilin peptide analogues, or of new small synthetic non-peptide motilin agonists, has proven to be much more difficult than expected.

Ghrelin is functionally related to motilin. Thus ghrelin also induces the MMC and accelerates gastric emptying. Because the effects of ghrelin can be studied in rodents, which do not respond to motilin because they are natural motilin receptor KO’s, the mechanism of ghrelin’s prokinetic effects is already well understood. There is the involvement of ghrelin receptors on vagal afferents, in the nodose ganglion, in central nuclei involved in signaling information from the gastrointestinal tract, and on myenteric neurons. Their relative importance remains to be determined. Because ghrelin and motilin, and their receptors are structurally related, interaction with the motilin receptor could be considered, but is contrary to experimental evidence. Also, available data suggest that under physiological conditions ghrelin has a minor role, if any, in the regulation of gastrointestinal motility. The daily profile of ghrelin plasma levels, a continuous rise during fasting and a fall after a meal, is not compatible with the periodic induction of the MMC and an increase of postprandial motor activity. Interestingly, when the lowest dose of ghrelin still able to cause growth hormone release is used, the motility effects are lost. In addition, in ghrelin and in ghrelin receptor KO mice (unpublished) gastric emptying is not affected. Nevertheless, in certain conditions, ghrelin may become more important. For example, the data obtained following vagotomy may indicate that this leads to an increase in the expression of ghrelin receptors in the myenteric plexus allowing for a more prominent role of circulating ghrelin. This may partially explain the promising effects obtained in patients with diabetic gastroparesis in particular those with neuropathy. Applications in postoperative ileus are also being considered.

Both motilin and ghrelin agonists may therefore find application as prokinetics, but the problems encountered with the motilides suggest that perhaps two new concepts are worthwhile to explore.
Firstly, desensitization of the motilin receptor has been invoked as a possible reason for the failure of motilin agonists during prolonged treatment and there are already data suggesting that the ghrelin receptor is also subject to desensitization. As both peptides act via a different receptor, alternating both agonists in therapy could offer a solution to the loss of efficacy of prokinetic treatment.

Secondly, as yet a potential for the induction of the migrating motor complex has never been explored. However, inducing phase 3 activity may help to reduce exposure of the stomach wall and of the esophagus to acid secretions, and could be of benefit in reflux disease and in peptic ulcer. In addition it should be remembered that absence of the MMC was originally linked to bacterial overgrowth\textsuperscript{10}, a condition which is now considered to play a role in the development of IBS\textsuperscript{11}. Therefore there may be a new area of applications for peptides like ghrelin and motilin, more related to their physiological role.

**References**


