



# The gastrointestinal tract in hunger and satiety signalling

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#### Abstract

**Background:** Different peripheral pathways are implicated in the regulation of the food ingestion-digestion cycle.

**Methods:** Narrative review on gastrointestinal mechanisms involved in satiety and hunger signalling.

**Results:** Combined mechano- and chemoreceptors, peripherally released peptide hormones and neural pathways provide feedback to the brain to determine sensations of hunger (increase energy intake) or satiation (cessation of energy intake) and regulate the human metabolism. The gastric accommodation reflex, which consists of a transient relaxation of the proximal stomach during food intake, has been identified as a major determinant of meal volume, through activation of tension-sensitive gastric mechanoreceptors. Motilin, whose release is the trigger of gastric Phase 3, has been identified as the major determinant of return of hunger after a meal. In addition, the release of several peptide hormones such as glucagon-like peptide 1 (GLP-1), cholecystokinin as well as motilin and ghrelin contributes to gut-brain signalling with relevance to control of hunger and satiety. A number of nutrients, such as bitter tastants, as well as pharmacological agents, such as endocannabinoid receptor antagonists and GLP-1 analogues act on these pathways to influence hunger, satiation and food intake.

**Conclusion:** Gastrointestinal mechanisms such as gastric accommodation and motilin release are key determinants of satiety and hunger.

#### KEYWORDS

CCK, gastric accommodation, GLP-1, hunger, migrating motor complex, motilin, satiety

Jan Tack takes responsibility for the integrity of the work as a whole, from inception to published article. All authors approved the final version of the manuscript.

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## INTRODUCTION: GASTROINTESTINAL PERSPECTIVE ON HUNGER AND SATIATION

The ingestion and digestion of food is a vital function, which is controlled by the interplay between the gastrointestinal tract (GIT) and the brain. Hormonal and neural signals from the GIT are key players in this bidirectional signalling pathway. When food is absent from the GIT, hunger signals are generated and food intake is stimulated. Conversely, when food is present in the GIT, satiety signals will overrule hunger signals and food intake will be inhibited. Disruption of the delicate balance between hunger and satiety signals induces an imbalance between energy intake and energy expenditure which may lead to either weight gain or weight loss. Understanding which GIT-derived signals contribute to this mechanism is crucial to improve our understanding of the pathogenesis of food intake disorders and may create new opportunities to treat these disorders.<sup>1</sup>

Hunger is expected to be maximal before the start of the meal. During the meal, hunger decreases and satiation rises, both contributing to the decision to stop further intake of food. Immediately after the meal, hunger is expected to be absent and satiation is maximal. The cycle restarts with the return of hunger and fading of satiety as preparation for the next meal (Figure 1).<sup>1</sup>

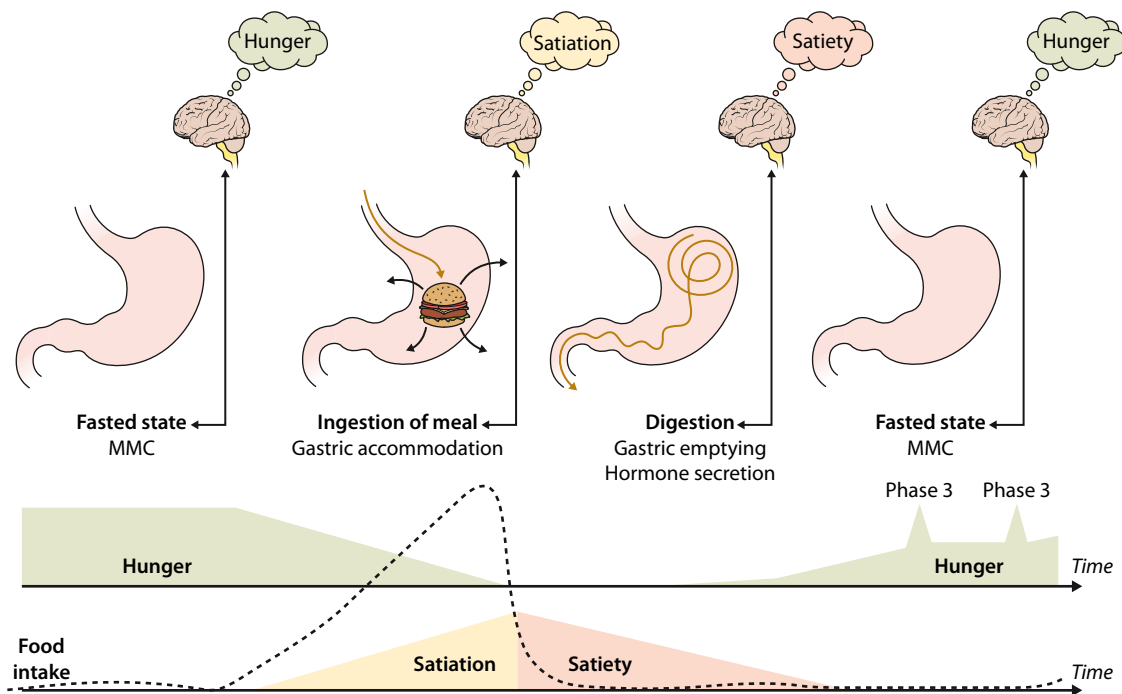
Different processes controlled by the GIT may contribute to two crucial aspects of the control of food intake: (1) determination of the amount of food ingested during a meal and (2) determination of the return of hunger and the ingestion of the next meal. The last decade

has seen several publications on how the GIT sense absence, presence and amount of nutrients and how this impacts on food intake. Based on this progress, it seems timely to take stock by appraising the current understanding and identifying issues of uncertainty that indicate directions for future research. The following sections will summarize our understanding of the role of the GIT in these aspects of control of hunger and satiety in man. We based the review on our own research in this area, as well as a Pubmed and Medline search for English language papers, reviews, meta-analyses, case series and randomized controlled trials using the following keywords and their associations: gastric motility, gastric emptying, gastric accommodation, nutrient tolerance, hunger ratings, satiety ratings, food intake, nutrient load test, gastric accommodation, anorexigenic peptides and orexigenic peptides.

## GASTROINTESTINAL SIGNALS INVOLVED IN DETERMINING MEAL SIZE

### Gastric accommodation as a determinant of meal-induced satiation

Older studies using the barostat showed that impaired gastric accommodation is associated with early satiation and weight loss in patients with functional dyspepsia.<sup>2,3</sup> Based on these observations, the hypothesis was put forward that gastric accommodation



**FIGURE 1** Overview of the cycles of hunger and satiation/satiety, with timing relative to the events of food intake and gastrointestinal physiological markers. Hunger is high in the fasting state and decreases as food is ingested, which is paralleled by the rise in satiation. At maximum satiation, meal intake stops, hunger is absent and satiety is at its highest. As satiety drops over time, hunger rises gradually. Gastric emptying is a permissive parameter for return of hunger, but not a main determinant. Peaks of hunger coincide with gastric Phase III of the migrating motor complex

determines meal nutrient volume-induced satiation. The site of gastric accommodation and hence the site of most likely satiation signalling is the proximal stomach.<sup>2-4</sup> First in animal studies, a minimally invasive method to quantify gastric accommodation was developed and validated using intra-gastric pressure (IGP) monitoring.<sup>5,6</sup> In man, contrary to what is written in physiology textbooks ('gastric accommodation serves to prevent a rise in IGP during food intake'), it was observed that nutrient ingestion induces an initial drop in IGP, followed by gradual recovery<sup>7</sup> (Figure 2). Fasting IGP in man fluctuates with the phases of the interdigestive migrating motor complex (MMC),<sup>8</sup> with maximum value during gastric Phase 3 and minimum value during Phase 1. Artefacts caused by movement, coughing, sneezing or swallowing are eliminated by calculating a moving median per channel. From the moving median, a preprandial baseline value is calculated per channel as the average pressure over the last 10 min before meal intake.<sup>7-9</sup> Upon ingestion of a meal, a pressure drop of 5–6 mm Hg on average, followed by a gradual recovery (Figure 2).

This method was further validated as a measure of gastric accommodation, by showing its dependence on nitric oxide synthase and its link with meal-induced satiation during liquid nutrient drink challenge, identifying the rise in IGP from nadir as a determinant of satiation.<sup>7-9</sup> A combined IGP-nutrient-infusion scintigraphy study confirmed that impaired intra-gastric distribution of nutrient (less accumulation in the fundus, more in the antrum), a marker for impaired accommodation, is associated with suppressed drop in IGP upon nutrient infusion and earlier satiation.<sup>10</sup>

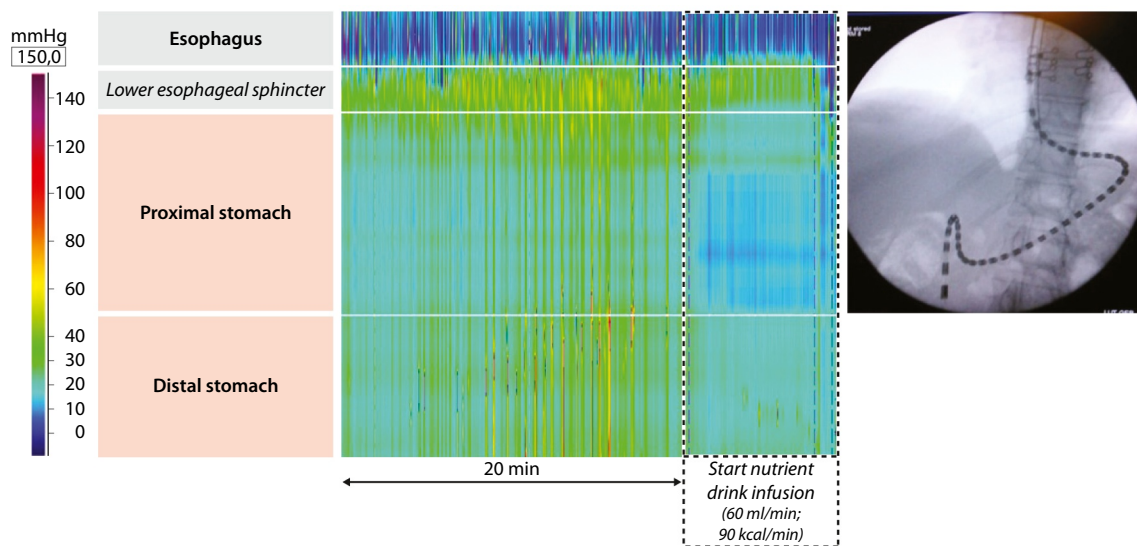
The drop in IGP is accompanied by alterations in mechanosensitivity signalling from the stomach which allow nutrient volume tolerance. In theory, gastric mechanoreceptor types comprise both

tension- and elongation-sensitive mechanoreceptors. Based on analysis of sensitivity to isobaric and isovolumetric balloon distensions, it has been shown that tension-sensitive mechanoreceptors mediate gastric filling-related satiation signals<sup>11</sup> (Figure 3). Hence, relaxation of the stomach will decrease activation of tension-sensitive mechanoreceptors, which will be restored as IGP rises during filling. The mechanosensitive signalling is conveyed to the brain stem through vagal afferents. In the nucleus of the tractus solitarius (NTS), leptin signalling is probably involved, as injections of leptin into the NTS reduce both meal size and increase the efficacy of vagus-mediated satiation signals.<sup>12</sup>

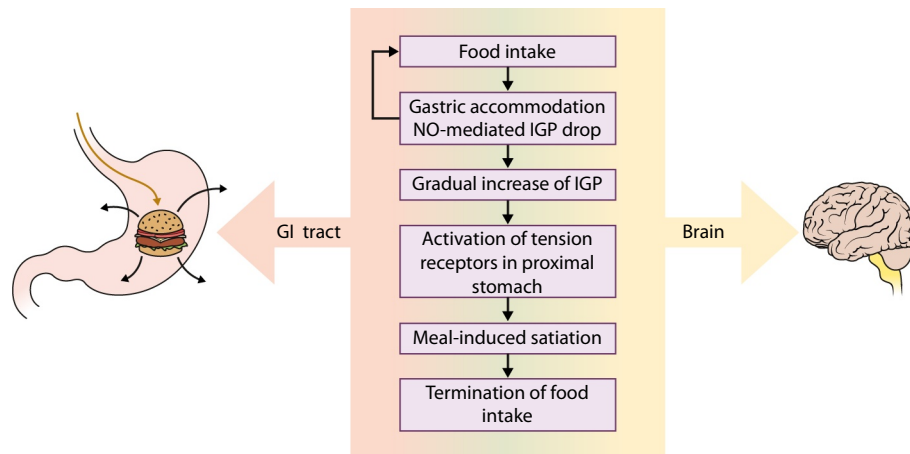
## Duodenal gut peptide response

Peristaltic contractions in the stomach advance the fragmented meal components into the duodenum where mucosal entero-endocrine cells sense nutrient composition. This activates a negative feedback system which enhances gastric accommodation and slows gastric emptying rate.<sup>13-15</sup> Duodenal entero-endocrine cells respond to nutrient exposure by the basolateral release of satiation peptides such as glucagon-like peptide 1 (GLP-1) or cholecystikinin (CCK), which subsequently activate vagal afferents or go into circulation.

GLP-1 is mainly known as an incretin, but exerts an important role in the suppression of motility in the antrum and small bowel.<sup>16</sup> Subcutaneous administration of the GLP-1 analogue liraglutide impairs gastric accommodation, while earlier it was shown that intravenous GLP-1 infusion enhances gastric relaxation.<sup>17,18</sup> Differences in agents and methodologies are likely to explain the discrepancy between both studies. GLP-1 further delays gastric emptying through



**FIGURE 2** Representative tracing of high-resolution manometry in the stomach and adjacent anatomical regions, as shown in the picture on the left. The infusion of a nutrient drink induces a drop in intra-gastric pressure, seen as a shift towards dark blue colour. The vertical appearing lines in the plot before administration of the nutrient drink represent aborally propagated contractions, predominantly in the antrum, of a spontaneous Phase III of the migrating motor complex. The image on the right illustrates the position of the high-resolution manometry on a plain X-ray



**FIGURE 3** Overview of the role of gastric pressure drop and recovery in the control of meal volume

activation of a nitrergic neuronal circuit.<sup>18,19</sup> When the truncal vagal nerves are damaged, GLP-1 infusion becomes ineffective and patients even experience an accelerated gastric emptying.<sup>20</sup> Lastly, GLP-1 infusion at physiological levels results in increased satiety, making it an important anorexigenic hormone.<sup>21</sup>

CCK is the gut peptide responsible for the processing of ingested fat and proteins. It induces gallbladder contraction which releases bile in the duodenum.<sup>19,22</sup> CCK exerts negative feedback on gastric motility.<sup>23</sup> Furthermore, enzyme mixtures are secreted into the duodenum by CCK activation. To avoid an overflow of fat and proteins in the small bowel, CCK has the property to slow down motility. First, in a rat model was shown that CCK induced relaxation of the proximal stomach by the vagal and splanchnic circuit.<sup>24</sup> In a dog study, CCK also contracted the pyloric sphincter.<sup>25</sup> In man, the CCK-1 receptor agonist dexloxiglumide has proven to relieve functional dyspepsia patients from symptoms after a lipid infusion.<sup>26</sup> Gastric emptying time is prolonged by an oral dose of GI18177X, another CCK-1 receptor agonist. Moreover, Goyal and colleagues suggested several CCK-dependent pathways to influence stomach motility and stimulate satiety or satiation, but more of these studies should be performed in humans.<sup>27</sup> However, clinical development of ligands for these receptors has been hampered by rapid development of desensitization.

### Alterations in disease states and role as a target for therapy

In functional dyspepsia, both in adults and in children, gastric accommodation is impaired in a subset of patients and this is associated with early satiety and weight loss.<sup>2,3,25</sup> In contrast, a subset of obese children have an increased nutrient volume tolerance, suggestive of enhanced accommodation or decreased sensitivity of tension-sensitive mechanoreceptors.<sup>28</sup>

Gastric accommodation, either measured with the barostat balloon or as IGP drop during nutrient infusion, has been the topic of intense research. In animals, peptide YY and pancreatic polypeptide

inhibit the pressure drop during nutrient infusion.<sup>5,6</sup> In healthy human controls, GLP-1 infused at physiological and supra-physiological levels dose-dependently diminished fundic tone and inhibited fundic volume waves, increased gastric volumes and suppressed gastric emptying rate, possibly through inhibition of vagal function.<sup>29,30</sup> Somewhat paradoxically, the GLP-1 analogue liraglutide inhibits gastric accommodation and this is associated with early satiety.<sup>17</sup> These effects were partially reproduced by administration of vildagliptin, an inhibitor of dipeptidyl peptidase IV, the enzyme which inactivates GLP-1.<sup>31</sup> In addition, the endocannabinoid type 1 receptor antagonist rimonabant and peripherally or non-selective opioid receptor antagonists all inhibit gastric accommodation.<sup>32,33</sup>

The drop in IGP is also sensitive to luminal factors. We observed that intra-gastric administration of a bitter agonists, denatonium benzoate (DB) induces a significant inhibition of gastric accommodation and decreases in nutrient volume tolerance in man.<sup>34</sup> The mechanism is likely to involve activation of bitter taste receptors, but their exact location and the associated pathway is unknown. In rats, intra-gastric administration of DB activates neurons in the NTS, suggesting involvement of a vagal pathway.<sup>35</sup> The effects of DB on food intake and IGP were mimicked by the bitter tastant quinine hydrochloride, confirming that this is likely to involve bitter taste receptor activation.<sup>36</sup> In a follow-up placebo-controlled, single-blind, randomized crossover study in healthy volunteers, intra-gastric administration of quinine was superior to DB for inhibiting hunger and food intake and intra-duodenal administration of these bitter tastants had no significant effects.<sup>37</sup>

In addition, fermentable oligo-, di-, monosaccharides and polyols (FODMAPs) also influence the drop in IGP during food intake and its subsequent rise, indicating that the size of gastric accommodation may respond to meal nutrient composition and be involved in triggering of meal-induced symptoms.<sup>38</sup> Traditionally, FODMAPs are thought to induce bowel symptoms through osmotic and fermentation effects in the colon, but immediate changes in IGP upon intra-gastric administration suggest involvement of a local mechanism. Taken together, the observation that intra-gastric FODMAPs and intra-gastric, but not intra-duodenal, administration of bitter tastants

inhibit the drop in IGP indicate, contrary to existing dogma, involvement of a gastric nutrient sensing capacity.<sup>39</sup> The nature and precise location of the nutrient sensing activity in the stomach remains to be elucidated. Several candidate nutrient sensing are expressed in the mouse stomach,<sup>40</sup> but this has not yet been addressed in detail in human studies.

## GASTROINTESTINAL SIGNALS INVOLVED IN DETERMINING THE RETURN OF HUNGER

### Interdigestive motility and motilin

Upper GIT motility in the fasting state is characterized by a complex contractility pattern, better known as the MMC, originating from the proximal GIT and migrating distally.<sup>41</sup> This complex is subdivided into three phases of activity: Phase I is characterized by a lack of contractility. During phase II, contractility increases steadily in frequency and amplitude to finally reach its maximum state of activity during Phase III, which is the most distinctive part of the MMC. This latter phase can either start in the stomach or the small intestine. Phase I will start immediately after Phase III has stopped and this cycle will continue at intervals of approximately 130 min until the next meal is consumed.<sup>41</sup>

The MMC is controlled by both hormonal and neural factors. The main hormone involved in the regulation of the MMC is motilin, a peptide hormone produced in the small intestine. Plasma motilin levels fluctuate in accordance with the phases of the MMC and reach a peak before the occurrence of a Phase III with gastric, but not with small intestinal onset.<sup>42-44</sup> The release and role of motilin are poorly studied as this peptide is not expressed in small rodents such as mice and rats, nor in cell lines, in which most of the recent experimental work on gut peptide release and control of food intake is conducted.<sup>41,45</sup> Ghrelin, a well-established orexigenic gut peptide which shows some homology with motilin, has been intensely investigated. In terms of the MMC, motilin is the main regulator in humans, as ghrelin plasma levels do not fluctuate concurrently with the phases of the MMC in man but rather rise towards meal times, and infusion of motilin or a motilin agonist rather than ghrelin provides the closest mimic to spontaneous phase III<sup>43,46-48</sup> (Figure 4).

### Motilin-induced gastric phase III as a determinant of the return of hunger after a meal

We have reported fluctuations of hunger ratings during the phases of the MMC with the occurrence of a 'hunger peak' during gastric phase III (Figure 2).<sup>47</sup> Gastric phase III is characterized by at least 3 min of high amplitude (>50 mm Hg) antral contractions at the maximum rate of three per minute, which is followed by Phase 1 motor quiescence and propagates to a duodenal Phase 3 (11 contractions per minute for at least 3 min).<sup>42-44,47</sup> These hunger peaks could be mimicked by administration of a low dose of erythromycin, a motilin

receptor agonist, and were controlled via a cholinergic pathway.<sup>48</sup> Moreover, we found close correlations of fluctuations of hunger ratings with fluctuations in motilin plasma levels, but not with ghrelin plasma levels.<sup>47</sup> Intravenous administration of erythromycin activated brain regions involved in homeostatic and hedonic control of appetite and food intake, and these activations were correlated to hunger ratings.<sup>49</sup>

### Motilin-induced gastric phase III: Alterations in disease states and role as a target for therapy

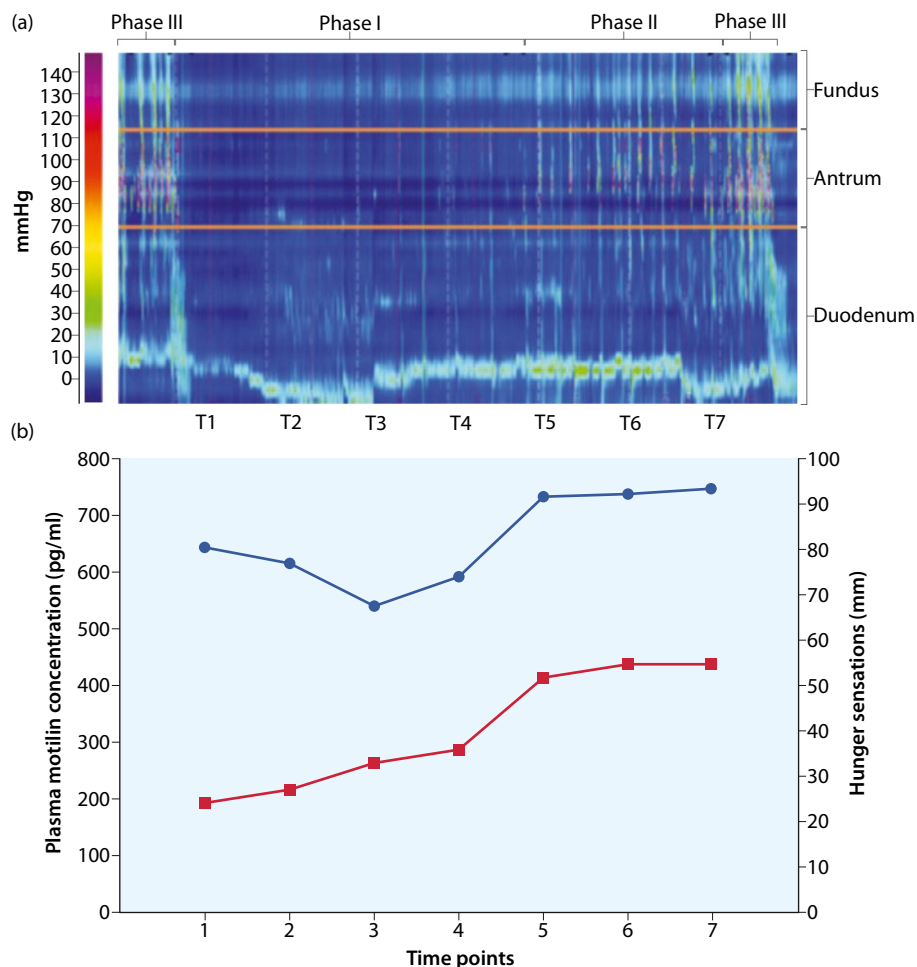
In patients with unexplained loss of appetite, gastric Phase III activity was absent.<sup>37</sup> Surprisingly, morbidly obese patients also lacked the motilin plasma peak prior to Phase III, necessary to trigger hunger.<sup>50</sup> Hunger scores during Phase III were significantly lower in obese patients, but could still be restored through administration of the motilin receptor agonist erythromycin. After Roux-en-Y gastric bypass surgery, motilin, but not ghrelin plasma levels decreased in parallel with lower hedonic hunger scores.<sup>50</sup> In a preliminary report, endocannabinoid type 1 receptor antagonist rimonabant was also found to inhibit gastric phase III and the associated hunger peaks.<sup>51</sup>

The mechanisms controlling the release of motilin from duodenal entero-endocrine cells in health and disease are poorly understood and need to be studied in further detail. Fasting antral contractility episodes (MMCs) are reduced to zero over a period of 4 h after GLP-1 infusion in healthy volunteers.<sup>16</sup> It is not known whether the GLP-1 analogue liraglutide reduces active MMC episodes, or whether this is motilin-dependent. Intra-gastric, but not intra-duodenal, administration of bitter tastants, both DB and quinine hydrochloride, was shown to suppress interdigestive hunger ratings, also through inhibition of motilin release.<sup>37,52</sup> Interestingly, at the doses used, these bitter tastants only showed a significant suppressive effect on interdigestive hunger ratings in female volunteers, confirming that the gender difference in bitter sensitivity is not only present on the tongue, but also in the GIT.<sup>52-55</sup> In female healthy volunteers, intra-gastric administration of quinine suppressed prospective and actual food intake, which is associated with changes in activation of homeostatic and hedonic brain circuits and correlated to changes in ghrelin and motilin plasma levels.<sup>56</sup> Taken together, these observations identify motilin as a potential target for controlling hunger in food intake disorders, and bitter tastants as potential mediators of an appetite-inhibitory action.

## FUTURE DIRECTIONS

The concepts above identified a number of novel players and potential targets for the control of hunger and food intake by signals from the GIT.

The studies demonstrated that food intake by man is associated with a drop in IGP and a gradual recovery. These events, through



**FIGURE 4** Top picture: Representative tracing of high-resolution manometry of the stomach and the duodenum in the interdigestive period in a single healthy volunteer. The phases of the migrating motor complex are indicated above. The interval between time points is 10 min. In the lower picture, fluctuations in plasma motilin levels (circles) and hunger ratings (squares) are shown in the same time frame

changes in gastric mechanosensory signaling, underlie meal-induced satiation and determine nutrient volume tolerance. Further characterization of the tension-sensitive mechanoreceptors that mediate satiation during meal intake is needed. If their molecular nature can be identified, specific modulators can be considered. Until then, studies can focus on altering the magnitude and kinetics of IGP changes after the meal, through pharmacological and nutrient manipulation.

The return of hunger seems driven by the release of motilin, which triggers gastric Phase III occurrence, simultaneous with a hunger peak. These observations identify motilin as a potential target for suppressing hunger and food intake, either through motilin receptor antagonism or through modulation of its release. The mechanisms controlling motilin release are poorly understood and require additional studies, which will have to focus on man as motilin and its receptor are not expressed in rodents. Nutrient sensing receptors, probably expressed on the motilin cells, are a potentially attractive target for changing the dynamics of motilin release.

The relevance of these concepts is illustrated by the observation that both mechanisms, gastric accommodation and motilin release, are influenced by a number of interventions with already established effects on hunger and food intake. These include the endocannabinoid type 1 receptor antagonist rimonabant, the opioid receptor antagonists naloxone, the GLP-1 analogue liraglutide and the dipeptidyl peptidase-4 inhibitor vildagliptin.

In addition, bitter tastants were identified as an attractive novel approach to inhibit both meal-induced gastric accommodation and motilin release, thereby enhancing meal-induced satiation as well as inhibiting the return of hunger after a meal. Bitter taste receptors are expressed on entero-endocrine cells, allowing them to serve as a target to modulate release of orexigenic and anorexigenic peptides from the proximal GIT. Our recent research identified the stomach as the site of action, for bitter tastants to target the two crucial aspects of the control of food intake: (1) determination of the amount of food ingested during a meal (GA) and (2) determination of the return of hunger and the ingestion of the next meal (motilin release). Using capsules which open up in the stomach will allow their application for



control of food intake without lingual taste effects. Lingual detection of bitter tastants is often associated with a repellent reaction, a likely evolutionary necessity to recognize noxious or spoiled food items before digestion.<sup>57</sup> Nowadays, the bitter flavour has gained more appreciation, is part of our daily diet, being present in cabbages, coffee, tea and as food additives, and also has hedonic qualities.<sup>57,58</sup> Taking into account the existence of 25 different bitter taste receptors in man, this offers multiple opportunities but also a high level of complexity. Additional studies will be required to select suitable ligands. Studies with repeated administration, in health and obesity will be required to assess the potential as longer-term intervention in obesity.

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## CONFLICT OF INTEREST

None of the authors state any conflict of interest regarding to this study.

## ETHICAL APPROVAL

Not ethical approval needed for a review paper.

## AUTHOR CONTRIBUTIONS

Jan Tack wrote the draft of the manuscript. All other authors edited and changed as needed. All authors approved the final version.

## DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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