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HAL Id: hal-00616288
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Submitted on 22 Aug 2011

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<th>Journal:</th>
<th><em>Alimentary Pharmacology &amp; Therapeutics</em></th>
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<td>Manuscript ID:</td>
<td>APT-0032-2011.R1</td>
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<tr>
<td>Wiley - Manuscript type:</td>
<td>Review Article</td>
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<tr>
<td>Date Submitted by the Author:</td>
<td>02-Feb-2011</td>
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</tbody>
</table>
| Complete List of Authors: | Janssen, Pieter; KULeuven, Translational Research Center for Gastrointestinal Disorders  
                          Vanden Berghe, Pieter; KULeuven, Translational Research Center for Gastrointestinal Disorders  
                          Verschueren, Sofie; KULeuven, Translational Research Center for Gastrointestinal Disorders  
                          Lehmann, Anders; AstraZeneca R&D, Area CV/GI, Disease Area Diabetes/Obesity  
                          Depoortere, Inge; KULeuven, Translational Research Center for Gastrointestinal Disorders  
                          Tack, Jan; KULeuven, Translational Research Center for Gastrointestinal Disorders |
| Keywords:       | Stomach and duodenum < Organ-based, Gastric emptying <  
                          Topics, Motility < Topics, Obesity < Topics |
Review article: Role of gastric motility in the control of food intake.

Authors ¹Pieter Janssen, ¹Pieter Vanden Berghe, ¹Sofie Verschueren, ²Anders Lehmann, ¹Inge Depoortere & ¹Jan Tack

Affiliations ¹Department of Internal Medicine, Division of Gastroenterology, University Hospital Gasthuisberg, University of Leuven, Leuven, Belgium. ²Research Area CV/GI, Disease Area Diabetes/Obesity, AstraZeneca R&D Möln达尔, Möln达尔, Sweden

Short Title Regulation of food intake by gastric motility

Keywords gastric accommodation, gastric emptying, migrating motor complex, hunger, appetite

Correspondence Pieter Janssen, KULeuven Campus Gasthuisberg O&N I, Dept. Gastroenterology, Herestraat 49 - Box 701, 3000 Leuven, Belgium, E-mail: Pieter.Janssen@Med.Kuleuven.be, Tel +32 (0)16 33 01 47, Fax +32 (0)16 34 59 39
ABSTRACT

Background From a classical point of view gastric motility acts to clear the stomach in between meals, while postprandial motility acts to provide a reservoir for food, mix and grind the food and assures a controlled flow of food to the intestines.

Aim In this review we want to summarize findings that support the role of gastric motility as a central mediator of hunger, satiation and satiety.

Methods A literature review using the search terms ‘satiety’, ‘satiation’ and ‘food intake’ was combined with specific terms corresponding to the sequence of events during and after food intake.

Results During food intake, when gastric emptying of especially solids is limited, gastric distension and gastric accommodation play an important function in the regulation of satiation. After food intake, when the stomach gradually empties, the role of gastric distension in the determination of appetite decreases and the focus will shift to gastric emptying and intestinal exposure of the nutrients. Finally, we have discussed the role of the empty stomach and the migrating motor complex in the regulation of hunger signals.

Conclusions Our findings indicate that gastric motility is a key mediator of hunger, satiation and satiety. More specifically gastric accommodation and gastric emptying play important roles in the regulation of gastric (dis)tension and intestinal exposure of nutrients and hence control satiation and satiety. Correlations between gastric accommodation, gastric emptying and body weight indicate that gastric motility can also play a role in the long-term regulation of body weight.
INTRODUCTION

The regulation of food intake relies on a balance between hunger, satiation (the disappearance of hunger during a meal), and satiety (the sensation of satisfaction after a meal that gradually disappears to make way for hunger). These sensations of appetite are the result of complex interactions between central nervous system circuitries and peripheral sensations, which mainly originate from the gastrointestinal tract, the liver \(^1\), and adipose tissue \(^2\). Since the gut is the first and main organ in which food is processed it is set to sense meal volume and composition and thus plays a vital role in the regulation of appetite \(^3\)\(^-\)\(^6\). For the stomach this central role is illustrated by the efficacy of bariatric surgery: resection or bypass of the stomach results in important and sustained weight loss \(^7\)\(^,\)\(^8\).

Appetite regulation by the gastrointestinal tract is mediated through sensation of meal volume and nutrient composition and can be influenced by different factors such as secretion \(^9\) and visceral sensitivity \(^10\) but also by gastrointestinal motility. In this review we focus on the role of motility, and more specific gastric motility in the regulation of (solid) food intake through a literature review using the keywords: satiety, satiation and food intake in combination with specific search terms corresponding to the different subdivisions.

GASTRIC INTERDIGESTIVE AND POSTPRANDIAL MOTILITY

Anatomically, the stomach is divided into a fundus, corpus and antrum region, but when it comes to motor function two parts can be distinguished: the proximal
stomach, consisting of the fundus and the proximal part of the corpus, and the distal stomach consisting of the distal part of the corpus and the antrum. With regard to motility the proximal stomach is characterized by tonic contractions but no slow wave activity, while the distal stomach is characterized by slow wave activity and peristaltic contractions. Two very different motor patterns can be distinguished in the stomach: an interdigestive and a postprandial motor pattern. During the interdigestive phase, the proximal stomach muscle tone is high while the distal stomach is engaged in a recurrent contraction pattern known as the migrating myoelectrical (or motor) complex (MMC). It has been suggested that the MMC serves to clear the stomach of secretions, debris, and microbes during fasting (Szurszewski, 1981). Upon food intake the motor pattern of the stomach changes drastically: the proximal stomach relaxes and serves initially as a reservoir. After food intake, a tonic contraction of the proximal stomach pushes the food distally, while the distal stomach mixes and grinds the food by a powerful and regular peristaltic contraction pattern. This postprandial motor pattern serves three major mechanical stomach functions: (1) the proximal stomach can act as a reservoir that enables ingestion of a large amount of food without a major intragastric pressure increase, (2) the mechanical aspect of food digestion is started by antral contractions that mix and grind food to smaller particles for further processing by the intestine and (3) tonic and peristaltic contractions generate a steadily controlled flow of food to the duodenum.

The role of gastric motility and its influence on appetite regulation will be discussed in three parts, corresponding to the sequence of events during and after food intake. During food intake, when gastric emptying, especially of solids, is limited, gastric distension and gastric accommodation play an important function in the regulation of satiation as discussed in the first part. After food intake, when the stomach gradually
empties, the role of gastric distension in the determination of appetite decreases and
the focus will shift to gastric emptying and intestinal exposure to nutrients. Finally, we
will discuss the role of the empty stomach and the MMC in the regulation of hunger
signals.

SATIATION DURING FOOD INTAKE

Gastric emptying of a solid meal follows a typical biphasic pattern: during the lag
phase, which can take up to 30-60 minutes, solids are redistributed in the stomach
and broken down to small particles, less than 1 mm in diameter, which in turn can
pass through the pylorus during the emptying phase \(^{13,14}\). Although it is likely that
some initial gastric emptying will occur (especially part of the liquid phase of the
meal), most of the solid meal will remain in the stomach during food intake \(^{15}\), and
sensations from the stomach will play a prominent role in the regulation of satiation.

Satiation signals from the stomach

Gastric mechanosensation is an important factor in the regulation of satiation during
food intake. Several authors have demonstrated that distension of the stomach
induces a satiating effect: in a magnetic resonance imaging study fullness was found
to be related to total gastric volumes for nutrient and non-nutrient meals \(^{16}\). In healthy
volunteers inflation of an intra-gastric balloon induces a range of sensations from
fullness and satiation to pain \(^{17}\). Furthermore, the presence of an inflated intragastric
balloon has been used in the treatment for obesity and was shown to induce
premature satiation during a normal meal \(^{18,19}\). These studies mainly used balloons
which were placed in the proximal stomach, indicating an important role for the proximal stomach in generating sensations from the stomach. On the other hand, ultrasound and scintigraphy measurements show a direct correlation between antral volume and the amount of ingested food or administered liquids \(^{20,21}\), indicating that distal stomach filling is also a determinant of satiation. Most likely, distal and proximal stomach have comparable mechanosensitivity and are both contributing to sensations of satiation and satiety \(^{17}\). The presence of a balloon, besides directly distending the proximal stomach, may promote antral distention during food intake and this may contribute to the satiation-enhancing effect.

Gastric distension has been shown to trigger stretch as well as tension mechanosensitive receptors that in turn relay their information via vagal and splanchnic nerves \(^{22-26}\) to the hindbrain and several other brain areas \(^{27-29}\) (Figure 1A). Distension of the proximal stomach in physiological ranges is known to activate a neuronal network in the central nervous system consistent with the ‘visceral pain neuromatrix’ \(^{30}\). In a recent study from our group, we used positron emission tomography imaging to compare regional brain activity during balloon distension or during intragastric infusion of a nutrient drink. Stepwise gastric balloon distension progressively activated the “visceral pain neuromatrix” (primary & secondary somatosensory cortex, lateral orbitofrontal cortex, insula, anterior cingulate cortex and cerebellum), which was associated with the generation of discomfort and/or pain \(^{31}\). In contrast, continuous or stepwise nutrient infusions to equal or higher intragastric volumes induced progressive deactivation of the visceral pain neuromatrix \(^{32}\). We hypothesize that the latter phenomenon is a prerequisite for tolerance of meal volumes in healthy subjects. The difference between gastric balloon distension and nutrient distension might be related to neurohormonal signaling induced by detection
of the presence of nutrients further down the gastrointestinal tract, and/or to changes
in gastric muscle tone associated with nutrient ingestion.

There is evidence that gastric distension-induced satiation can also be regulated by
gut hormones. Indeed, the satiating effect of gastric distention has been shown to be
enhanced by cholecystokinin (CCK) \textsuperscript{33}. Another example is glucagon-like peptide 1
(GLP-1), known to reduce food intake in humans \textsuperscript{34}: GLP-1-containing neurons in the
nucleus of the solitary tract are activated by gastric distension within the physiological
range, suggesting a role for GLP-1 in gastric distension-induced appetite signaling \textsuperscript{35}.
GLP-1 receptor antagonism in the nucleus tractus solitarius attenuated feeding
suppression after gastric distension but not after intraduodenal infusion of a nutrient
drink, indicating that central release of GLP-1 and activation of hindbrain GLP-1
receptors mediate specifically gastric satiation signals, while peripheral release of
GLP-1, mediated by the L cells in the distal small intestine, is not related to gastric
distension \textsuperscript{36}.

In contrast to mechanosensation, nutrient sensation in the stomach is less likely to be
an important factor in the regulation of satiation during food intake: in rats equipped
with inflatable cuffs around the pylorus that prevent content from leaving the
stomach, infusion of non-nutritive solutions such as saline, results in volumetrically
proportionate decreases in food intake and this is as efficacious as infusion with a
nutrient solution \textsuperscript{37,38}. In humans, postprandial hunger and satiety were correlated to
postprandial gastric volumes, without a significant influence of the nutrient
composition (lipids, carbohydrates or proteins) of the meal \textsuperscript{39}. Only a few studies
have found evidence for a role of nutrient sensation in the stomach: it has been
suggested that the pylorus can sense the energy content of food and might play a role in the regulation of the energy load towards the duodenum. However, most authors agree that distension is the main determinant for gastric sensations of satiation and satiety, and that the stomach does not meaningfully detect the nutrient or caloric composition of a meal.

Role of gastric accommodation

In between meals the proximal stomach maintains a high basal muscle tone. This tone is partially due to the myoelectrical properties of the fundus: the resting membrane potential in the fundic muscles is near or above the mechanical threshold. In addition, muscle tone in the proximal stomach is sustained by constant cholinergic input mediated by the vagal nerve. Proximal gastric tone decreases during food intake, and this process of active relaxation is mediated by several different (para)sympathetic reflex pathways that have been shown to decrease the contractile cholinergic input and activate the release of nitric oxide. This reflex, also referred to as gastric accommodation will enhance the storage capacity of the stomach by increasing the compliance of the stomach muscles and thus keeps the intragastric pressure low during food intake.

When gastric accommodation is impaired, intragastric pressure will be relatively high during food intake. This has been shown during air insufflation or intra-gastric balloon distension: while in healthy subjects during stomach distension the intragastric pressure increase is minor or stable and does not increase despite further distension, intragastric pressure increase is much more pronounced in patients with impaired
gastric accommodation e.g. after vagotomy, patients with Chagas’ disease (a tropical parasitic disease characterized by extensive lesions of the myenteric plexus) and patients with functional dyspepsia. Increased intragastric pressure is associated with increased postcibal perception. We recently showed that, during intragastric infusion of a nutrient drink, intragastric pressure is directly correlated to satiation, indicating that intragastric pressure is a determinant of satiation.

Whether perception is driven by intragastric pressure, or by another mechanosensitivity modality that is influenced by intragastric pressure, is a matter of controversy. According to the simplified law of Laplace, increased intragastric pressure will be associated with increased wall tension for the same intragastric volume. Studies using isovolumetric and isobaric gastric distensions indicate that gastric wall tension receptors may be most relevant for mediating distension-induced sensation. In fact, by using a tensostat that keeps an intragastric bag at a constant tension (calculated according to the simplified Laplace’s law) it was shown that sensations from the proximal stomach depend on gastric wall tension, whereas intragastric volume and expansion seem less relevant.

Although increased tension by itself can increase sensation, it can also cause redistribution of the food from the proximal stomach to the antrum as shown in imaging studies. Since the antrum is less compliant than the proximal stomach it is more sensitive to distension, and increased feelings of fullness and satiation in patients with impaired gastric accommodation can originate from the antrum. Furthermore, increased tonic pressure exerted by the stomach could increase gastric emptying of liquid but also of solid food, which in turn could influence satiety and food intake.
A number of studies have investigated the importance of gastric accommodation in relation to food intake. Using the barostat it was demonstrated that a subgroup of functional dyspeptic patients has early satiation and weight loss that can be attributed to impaired gastric accommodation. This was confirmed in a later study in which we demonstrated a clear relationship between meal-induced gastric accommodation and caloric intake in healthy volunteers as well as functional dyspeptic patients. In healthy volunteers we showed that artificially increasing gastric muscle tone (by means of motilin administration or nitric oxide synthase inhibition) also increased meal-induced satiation. In a recent study we demonstrated that in the presence of a balloon blocking gastric outflow, slow ingestion of a liquid meal was able to induce satiation albeit less than in a comparable control situation without pyloric obstruction, indicating, as we have discussed before, that nutrient accumulation in the stomach alone is able to induce a feeling of satiation and that duodenal nutrient exposure adds to feelings of satiation but is not a prerequisite for the occurrence of meal-induced satiation. On the other hand, in the same study we showed that gastric accommodation during pyloric outflow obstruction was decreased as compared with the control condition, furthermore supporting the hypothesis that impaired accommodation decreases tolerance of a nutrient load. In addition, the intragastric pressure during nutrient drink ingestion at a constant rate show is significantly correlated to the corresponding satiation scores and the nutrient volume required to induce maximal satiation.

Other groups have reported a possible correlation between gastric accommodation and food intake or satiety in binge eating disorder, bulimia nervosa and cancer patients. Another observation in favor of such a relationship comes from gastric banding, a frequently-used gastric restrictive bariatric approach for the treatment of
morbid obesity: by reducing the size of the proximal stomach early satiation and fullness lead to substantial weight loss. Although the exact mechanism of early satiation and weight loss in gastric banding is incompletely elucidated, it was suggested that changes in gastric accommodation are responsible. These findings all indicate that gastric accommodation is an important determinant of food intake, and that impaired gastric accommodation is associated with decreased food intake. The question remains whether this could affect long-term body weight. In patients there are indications that impaired gastric accommodation and weight loss are related e.g. in functional dyspepsia, in some anorexia patients and in cancer patients with loss of appetite. On the other hand there is hardly any evidence that gastric accommodation is enhanced in obese people. Unfortunately, there is no medication that can selectively impair or enhance gastric accommodation and can be administered over a longer period, and studies that examine the relationship between gastric accommodation and satiation on one hand and body weight on the other hand are lacking.

SATIETY SIGNALING AFTER FOOD INTAKE

During and after food intake (dis)tension of the stomach plays an important role in the determination of appetite. However, after the lag phase of gastric emptying, when the stomach gradually empties into the small intestine, the (dis)tension of the stomach decreases and is therefore likely to play a gradually decreasing role in satiety signaling. The emphasis shifts towards satiety mechanisms that are controlled by the rate of gastric emptying: intestinal exposure of nutrients (Figure 2).
Satiety signals from the intestine

Although the intestines, like the stomach, are sensitive to distension, most authors agree that sensation of intestinal contents is mainly based on mucosal recognition of luminal content such as osmolarity, lipid content, products of carbohydrate digestion and mucosal mechanical stimulation. Enteroendocrine cells in the mucosa of the small intestine react to different properties of luminal content by releasing a variety of peptides (e.g. CCK, GLP-1, oxyntomodulin and peptide YY (PYY)) and small molecules (e.g. serotonin (5-HT)), that can act locally or enter the blood stream and work as hormones. Gut hormones, released in response to gut content, have their peak plasma level at various time points after meal intake: e.g. CCK release peaks early after food intake (within 15 minutes), whereas PYY reaches its peak plasma level after about 1 hour. The time and magnitude of the release is generally dependent on the caloric content and macro-nutrient composition of the meal. Gut hormones exert their action either directly via the bloodstream by leaking through permeable capillaries in the median eminence, and the incomplete blood-brain barrier at the level of the hypothalamic arcuate nucleus, or indirectly via the vagus nerve thereby signaling to the area postrema and the nucleus tractus solitarius in the hindbrain where afferent fibers project to the hypothalamus. In the arcuate nucleus these hormonal signals can in turn activate different populations of orexigenic (neuropeptide Y / agouti-related peptide neurons, activated by ghrelin) and anorexigenic (pro-opiomelanocartin/cocaine- and amphetamine-regulated transcript) neurons that modulate amongst others the mediobasal hypothalamic and the paraventricular...
nuclei which eventually send signals to other brain areas\textsuperscript{3,73}. For CCK, GLP-1 and PYY the resulting effect is a well-described increase in satiety\textsuperscript{33,34,72}.

When released locally, peptides and small molecules can influence the activation of enteric and (para)sympathetic nerves. 5-HT, for example, is released from enterochromaffin cells and mediates vagal nerve activation via 5-HT\textsubscript{3} receptors\textsuperscript{74}. Vagal nerves signal to the nucleus tractus solitarius in the hindbrain from which region efferent fibers project to the hypothalamus using the parabrachial nucleus as the main relay. Indeed, administration of the 5-HT\textsubscript{3} receptor agonist m-chlorophenylbiguanide can reduce food intake in rats\textsuperscript{75} while the 5-HT\textsubscript{3} receptor antagonist ondansetron has been shown to attenuate CCK-induced suppression of food intake in rats\textsuperscript{76}. The role of 5-HT\textsubscript{3} receptors in the control of satiation, however, is less clear: while some groups claim ondansetron by itself does not influence food intake in rats, other groups showed that ondansetron is able to reduce food intake in rats\textsuperscript{77} and binge-eating behavior in bulimia patients\textsuperscript{78}.

Role of gastric emptying

From a mechanical point of view, gastric emptying of a meal relies on a complex interplay between the major motor patterns of the stomach. Upon food intake, and after an initial relaxation, the proximal stomach propels gastric contents forward by means of a tonic contraction and hereby provides a driving force for gastric emptying. Simultaneously, peristaltic contractions emerging from the mid-corpus progress in the direction of the antrum, hereby grinding and sieving solid food. This repetitive motor pattern breaks down the food particles, mixes them with juice and forms a second drive that pushes the food content distally. A third mechanical factor in the regulation
of gastric emptying is opening and closure of the pyloric sphincter. This narrow high-pressure zone closes the stomach during the terminal phase of a peristaltic contraction wave, so that any content from the antrum is prevented from entering into the duodenum during mixing and grinding. The relative importance of each of these three mechanical functions depends on the consistency of the food: for liquids the pressure elicited by the proximal stomach and opening of the pylorus will be dominant in the control of gastric emptying, while the peristaltic pump of the antrum is more dominant for solid food. Non-caloric liquids, for instance, empty without lag phase, directly proportional to the gastric volume and in an exponential process. Solids on the other hand typically empty in a biphasic manner: after a lag-phase where hardly any emptying occurs, gastric emptying rate of the grinded and mixed contents is more or less stable until the stomach is emptied. The emptying speed of a meal is inversely correlated to its caloric content. Interestingly it has been shown that gastric emptying is independent on the nature of the calories so that a constant delivery of energy to the bowel is maintained. Besides caloric content, a relationship has been described between gastric emptying rate and the acidity, osmolarity and viscosity of the meal. Many of these relationships can be explained by a duodenal-gastric feedback mechanism: exposure of the small intestine to nutrients activates vago-vagal reflex mechanisms and hormonal signals (e.g. GLP-1, PYY and CCK) that modulate gastric emptying.

The relation between gastric emptying and appetite is complex and only few studies directly investigated this relationship. Physiological or artificially-induced delay of gastric emptying appears to be linked with increased feelings of satiety and fullness and termination of food intake. Also, at least a subgroup of patients with anorexia nervosa have markedly delayed gastric emptying, while in some studies obese
people were shown to have enhanced gastric emptying. There is no obvious candidate hormone to explain these findings: leptin, the plasma levels of which directly positively correlate with adiposity, has no major effects on gastric emptying, and circulating ghrelin has been reported to be lower in obese subjects than in healthy controls. Furthermore, in healthy controls a correlation was found between the gastric emptying rate of solids and body surface area and weight.

It has been suggested that larger intragastric volume and hence increased (dis)tension as a result of delayed gastric emptying is responsible for increased feelings of satiety and delayed return of hunger. This interpretation seems to be acknowledged by a study in which a significant correlation was found between ratings of postprandial increase in hunger and the time needed for 90% of the meal to empty. The authors of this latter study also suggested that the reduction of gastric distension may be the determinant factor in the development of hunger after a meal. The interaction between gastric distension, gastric emptying and feelings of appetite was studied in more detail by a series of experiments that combined ultrasound and scintigraphy: satiety and satiation were found to be inversely correlated to gastric emptying, more precisely, a close relationship was found between antral area (and presumably antral distension), satiation and satiety.

Other studies suggest that not (only) gastric distension is important in the regulation of satiety: in a study in which a concentrated and a diluted meal of 2500 kJ were served to healthy volunteers satiety scores and gastric emptying of solids and liquids did not differ between the meals. A significant correlation however was observed between satiety scores and emptying of the solid fraction in both meals. It was concluded that it is not the volume of the meal that influences satiety but rather the gastric emptying rate of the solid meal fraction of that meal, indicating that gastric
emptying of energy and not volume of the ingested meal is the major determinant of satiety \(^98\). Other studies confirm that feelings of hunger or satiation are dependent on gastric emptying of fat and indeed intestinal exposure to the nutrients \(^99,100\).

From the findings in the studies above we can conclude that a complex relationship exists between gastric emptying and appetite. We postulate that both gastric (dis)tension and intestinal exposure play a role in the regulation of appetite, but the relative emphasis shifts towards intestinal exposure when the stomach empties. Interestingly, several anorexigenic hormones such as CCK, PYY, GLP-1 etc. inhibit gastric emptying (and at the same time increase gastric compliance) \(^14,101,102\), and these effects on gastric motility can contribute to their effects on satiation.

**Return of hunger: role of gastric Phase III contractions**

Feelings of hunger have long been associated with contractions of the empty stomach. A little less than 100 years ago Cannon & Washburn described powerful contractions of the empty stomach and showed that they were invariably correlated with hunger pangs that were also perceived as rumbling in the epigastrum \(^103\). They suggested that the hunger sensation resulted from these contractions. Interestingly, these ‘hunger contractions’ persisted after vagotomy, indicating that their initiation is independent of the central nervous system \(^104\). The ‘hunger contractions’ could later be identified as being part of the MMC. Indeed, when stomach and small intestines are emptied after a meal a very typical myoelectrical and contraction pattern emerges that is characterized by 3-4 phases: phase I is a quiescent period with virtually no contractions, phase II consists of random irregular contractions with low amplitude,
while phase III is a short burst of regular high-amplitude contractions; phase IV represents a short transition period back to the quiescence of phase I (Szurszewski, 1981 1001; Szurszewski, 1969 1325; Itoh, 1981 1327). Phase III contractions are made up of a group of contractile waves that migrate from the oral to the anal side successively over a constant period, characterized by an interval of 100-150 minutes during fasting. In man, about half of all phase III onsets are located in the stomach and the other half is located in the duodenum. The immediate physiological role of the phase III contractions is believed to provide a pulsatile flow to clear the stomach and small intestines of secretions, debris, and microbes during fasting and let the stomach be ready to receive a next meal. The regulation of phase III contractions and the MMC in general is still not completely resolved. Although there is some evidence that the MMC can be influenced by the CNS, it has been shown to run largely independent of the CNS 107. It is well-established that the MMC is propagated through the enteric nervous system. Furthermore, there is good evidence that the initiation of the phase III contractions in the stomach might be regulated by gut hormones such as somatostatin and motilin. Indeed, a close relationship between plasma motilin levels and phase III contractions is well-established: plasma motilin concentrations fluctuate during the interdigestive state and peak directly before the occurrence of phase III contractions in the stomach or upper duodenum 108. Immunoneutralization of circulating motilin suppresses these activity fronts 109,110 and exogenous administration of motilin initiates premature phase III contractions in the stomach in dogs 111,112 and humans 113. Plasma somatostatin levels are associated with phase III activity fronts in the duodenum and somatostatin infusion can induce intestinal activity fronts 114,115.
Although the association between phase III contractions and hunger pangs was recently confirmed (Figure 3) the underlying mechanism remains unexplained \(^{116}\). By means of ultrasound, the typical sensation of rumbling in the epigastrium or ‘borborygmia’ has been linked to movement of air within the gastric lumen during phase III contractions, possibly from the proximal stomach to the antrum, and in the intestines \(^{117}\). This movement of air could explain the rumbling sensation during phase III, however strong contractions in the stomach that can displace air are not exclusively linked to phase III contractions. We recently described that administration of motilin in individuals with an empty stomach induced phase III contractions and associated hunger pangs. Interestingly, antral contractions of a similar amplitude induced by a cholinesterase inhibitor are not associated with hunger, indicating that hunger sensations require a typical phase III pattern or motilin receptor stimulation \(^{118}\). Although administration of both motilin and ghrelin are known to induce phase III contractions, only motilin plasma levels fluctuate with the MMC, indicating that motilin is closely related to hunger pangs \(^{119}\). Furthermore, while significant correlations were found between motilin, phase III contractions and hunger scores, the best correlation was found between hunger ratings and plasma motilin levels \(^{120},^{120}\). These findings indicate that sensation of hunger is closely associated with plasma motilin levels as well as phase III contractions \(^{120}\). Whether it is the rise in motilin plasma levels or gastric phase III contractions themselves that trigger the sensation of hunger pangs still remains to be properly investigated. A third option is that the motor and hormonal changes are merely epiphenomena to the hunger pangs but this has not been studied experimentally.
POTENTIAL FOR THERAPEUTIC INTERVENTION

Pharmacological agents

To date there are no drugs on the market that have been developed to modify gastric motility in order to treat over or underweight. However, different drugs that are used to treat obesity have also known effects on gastric motility.

The weight loss effect of the lipase inhibitor orlistat is attributed to the decreased absorption of dietary fat. Interestingly, orlistat does not affect gastric accommodation and meal-induced satiety and, if anything, increases appetite and food consumption\textsuperscript{121,122}. The latter effect can be attributed to the decreased postprandial release of GIP, GLP-1, CCK and PYY, furthermore orlistat is known to accelerate gastric emptying, which decreases gastric distention\textsuperscript{123}.

Sibutramine is a centrally-acting serotonin and norepinephrine reuptake inhibitor and is used for the treatment of obesity\textsuperscript{124}. The anorexigenic effect of sibutramine is thought to be mediated through serotonergic and adrenergic mechanisms in the hypothalamic nuclei that regulate appetite. In overweight patients however sibutramine is known to delay gastric emptying\textsuperscript{124}. In a barostat study in dogs, sibutramine increased gastric tone and impaired gastric accommodation to an orally ingested meal\textsuperscript{125}. The inhibitory effect of sibutramine on gastric emptying and accommodation may partially explain the reduced food intake with sibutramine in patients with obesity.

The selective cannabinoid receptor antagonist rimonabant was marketed for obesity and its anorectic properties are mediated through decreased food intake (actions on the hypothalamus and the limbic system) and by increasing energy expenditure.
(increased lipolysis and thermogenesis)\textsuperscript{126}. In a barostat study we showed that rimonabant decreased gastric accommodation to a meal, however in the same study, nutrient tolerance during a drinking test was not affected\textsuperscript{126}. The effect of rimonabant on gastric emptying in humans is at present unknown, however in rats rimonabant has been shown to reverse the endocannabinoids-induced delay in gastric emptying\textsuperscript{127}. Although impaired gastric accommodation and increased gastric emptying could increase satiation, it is unclear whether these effects of rimonabant contribute to its effects on food intake and body weight.

The role of opioids in the regulation of food intake is complex: in general opioid agonists enhance feeding and opioid antagonists such as naloxone and naltrexone but also the peripherally-restricted antagonist methylnaltrexone decrease feeding\textsuperscript{128-131} but these effects are dependent for example on the treatment duration and whether normal weight, low weight (anorexia patients) or obese volunteers/patients are selected\textsuperscript{132}. We recently showed that the peripherally-restricted opioid receptor antagonist methylnaltrexone increased satiation and that this effect on food intake was more pronounced compared to the centrally-acting antagonist naloxone\textsuperscript{50}. Interestingly, methylnaltrexone impaired gastric accommodation to a meal and this effect was more pronounced than that of naloxone, suggesting that endogenous opioids mediate gastric accommodation and satiation via peripheral mu-opioid receptors. The existence of a peripheral opioid-related mechanism in control of food intake was confirmed in a study in rats, although in the latter study the effect was mediated via potentiation of the effect of leptin\textsuperscript{133}.

The effect of sibutramine, rimonabant, naloxone and methylnaltrexone on gastric motility may contribute to their effects on food intake and body weight. However, so far, a contribution of changes in gastric motility to their effects on body weight has not
been established for any of the drugs described above and it remains unclear whether the effects on gastric motility are crucial or just an epiphenomenon. More research is needed to investigate directly the link between the effect on gastric motility and decreased food intake and weight loss.

GLP-1 is a well-known regulator of food intake and is at the same time known to delay gastric emptying, inhibit antral contractility, decrease fasting tone of the proximal stomach and enhance gastric accommodation. However, GLP-1 is rapidly inactivated by dipeptidyl peptidase 4 (DPP4), which limits its usefulness as a treatment option. Also long-acting GLP-1 analogues exenatide and liraglutide reduce body weight and have been shown to reduce appetite and promote satiety. Although these peptides are known to induce nausea (most likely mediated through central mechanisms) exenatide and liraglutide are also known to slow down gastric emptying. The latter might explain, at least in part, the effect on food intake. So far their effect on gastric accommodation is unknown. The effect of DPP4 inhibitors on body weight is less clear: no or small changes of the body weight have been observed in patients on vildagliptin. In concordance, no effects have been observed on gastric emptying, while effects on gastric accommodation have not yet been investigated.

Other drugs used in the treatment of diabetes also affect body weight and gastric function. Pramlintide, an analog of the pancreatic hormone amylin which is used in the management of diabetes mellitus, reduces hunger and food intake in healthy volunteers. Similar effects have been shown in a 6-week study in obese subjects. The effect of pramlintide on food intake can partly be explained by the fact that it markedly delays gastric emptying.
Intraluminal devices

As discussed previously, inflation of an intragastric balloon induces fullness and satiation. Based on this principle implantation of an intragastric balloon has been used in the treatment of obesity. Although this procedure initially restricts food intake and is able to decrease feelings of hunger, the effect is transient and not associated with lower energy intake or weight loss.

Adjustable totally implantable intragastric prosthesis (ATIIP) - Endogast® (Districlass Médical S.A., Chaponnay, France) is a new technique for the treatment of morbid obesity. During a minimally invasive procedure an air-filled prosthesis is fixated to the wall of the proximal stomach. The ATIIP induces early satiation and this effect was attributed to impaired gastric accommodation. In a preliminary study 20-40% excess weight loss was achieved in 40 obese patients.

Based on the principles of bariatric surgery but less invasive is the duodenojejunal bypass liner (EndoBarrier® Gastrointestinal Liner, GI Dynamics, Inc, Lexington, MA, USA), an endoscopically placed and removable intestinal liner that creates a duodenojejunal bypass. In obese patients 12-23% excess weight loss was achieved after 3 months. This device indicates the importance of the distal gut and the ileal brake in the regulation of body weight. The ileal brake is mediated through release of PYY, GLP-1 and vagal nerve stimulation. Activation of the ileal brake leads to a reduction in hunger and in food intake, but it is uncertain whether this effect results from direct stimulation of central satiety centers in the brain, or if the ileal brake effect on hunger and satiety is achieved indirectly via the delay in gastric emptying. It is most likely that, after activation of the ileal brake, the enhanced gastric
distension from delayed gastric emptying interacts with a direct stimulation of central satiety centers by hormonal and neural signals, to reduce hunger and energy intake.

**Bariatric surgery**

For morbid obese patients bariatric surgery is an effective treatment that induces sufficient and sustained weight loss \(^ {150}\). Three major types of bariatric surgery are used to treat obese patients: restrictive procedures (e.g. gastric banding, and sleeve gastrectomy), malabsorptive procedures (e.g. jejun-ileal bypass) and combination restrictive-malabsorptive procedures (e.g. Roux-en-Y gastric and duodenal switch bypass).

With all types of bariatric surgery patients experience not only early satiation while eating but feel satiated longer after the meal. Hence, they eat considerably less as compared to before the operation. The mechanisms responsible for the effects on satiation and satiety are not well understood however there are indications that sensory signals from the upper gastrointestinal tract play a major role.

During the jejun-ileal bypass procedure a substantial part of the small intestine is bypassed from the alimentary tract and it is believed that malabsorption of nutrients is responsible for the observed weight loss, although an association with delayed gastric emptying and altered gut hormone patterns has been described \(^ {151}\). Due to the many complications associated with this procedure this type of bariatric surgery is not longer recommended.

Also for sleeve gastrectomy and Roux-en-Y gastric bypass it has been shown that the levels of different (gut) hormones as ghrelin, GLP-1, insulin and PYY are altered
after surgery\textsuperscript{152-154}. These changes in (gut) hormone levels are held responsible for the increased satiation and satiety and are likely caused because food is delivered faster to the duodenum and into the ileum (activating the ileal break as discussed above) after surgery and does not reside in the stomach as it did before surgery\textsuperscript{149}. Increased gastric emptying has indeed been observed after sleeve gastrectomy\textsuperscript{35-37} and might be caused by the reduced gastric volume which impairs gastric accommodation and leads to increased tension for the same meal volume. This directly increases satiation but also leads to more rapid delivery of the contents to the intestines, and release gut hormones as described above.

CONCLUSION

From a classical point of view gastric motility acts to clear the stomach in between meals, while postprandial motility acts to provide a reservoir for food, mix and grind the food and assures a controlled flow of food to the intestines. In this review we summarized findings that support the role of gastric motility as a key mediator of hunger, satiation and satiety. We showed that gastric accommodation and gastric emptying play an important role in the regulation of gastric (dis)tension and intestinal exposure of nutrients and hence control satiation and satiety. Moreover, phase III contractions are closely correlated with hunger pangs, intense feelings of acute hunger on top of a more tonic sensation of returning hunger. Apart from acute effects on food intake, we described correlations between gastric accommodation, gastric emptying and body weight that indicate that gastric motility can also play a role in the long-term regulation of body weight. Although pharmacological and surgical interventions aimed at reducing weight have sometimes profound effects on gastric
motility, it is unclear how relevant these changes in gastric motor function are to their effects on appetite and body weight.
ACKNOWLEDGMENTS

Pieter Janssen is a research fellow of the ‘Fonds voor Wetenschappelijk onderzoek – Vlaanderen, Belgium’. This work was supported by an FWO grant and a Methusalem grant to Jan Tack, M.D., Ph.D. All of the authors have nothing to disclose.
Figure 1. Satiation and satiety signaling during and after food intake. **A)** During food intake and shortly thereafter, emptying of especially solid meals is limited, and gastric distension and accommodation are major determinants in the regulation of satiation. Sensations of satiation are mainly mediated by gastric mechanosensitive receptors that relay their information via vagal nerves to the nucleus of the solitary tract (NTS) in the hindbrain. **B)** After food intake, when the stomach gradually empties, the role of gastric distension in the determination of appetite decreases and the regulation of satiety is shifted to gastric emptying and intestinal exposure of the nutrients. Sensations of satiety are mainly mediated by enteroendocrine cells in the mucosa of the small intestine that sense intestinal contents and release a variety of peptides
and small molecules, that can act locally (and activate vagal nerves that signal to the NTS) or enter the blood stream and work as hormones (and signal to the arcuate nucleus (ARC) in the hypothalamus).
Figure 2. A hypothetical model of the regulation of satiation, satiety and hunger by gastric motility-controlled processes. All graphs represent a period during (grey area)
and after food intake. **A)** satiation and satiety during and after food intake respectively, **B)** hunger, **C)** gastric (dis)tension, **D)** intestinal exposure of nutrients, and **E)** phase III contractions. In this model gastric (dis)tension, intestinal exposure and phase III contractions have an equal maximal contribution. Summation of graph C and D result in graph A, while graph E deduced with graph C and D result in graph B.
Figure 3. Gastric phase III contractions are closely associated with increased hunger scores. Healthy volunteers underwent interdigestive gastroduodenal manometry. Hunger was scored on a 100 mm visual analogue scale. Motility index (MI) was automatically analyzed with a computer. Results are represented as mean±S.E.M. (n=12). Compared to gastric phase I, phase II or small bowel phase III contractions, hunger scores were significantly higher during spontaneous gastric phase III.
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