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Review article: Role of gastric motility in the control of food intake.

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Review **article**: Role of gastric motility in the control of food intake.

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Short Title Regulation of food intake by gastric motility

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

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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

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3 stomach, consisting of the fundus and the proximal part of the corpus, and the distal
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5 stomach consisting of the distal part of the corpus and the antrum. With regard to
6
7 motility the proximal stomach is characterized by tonic contractions but no slow wave
8
9 activity, while the distal stomach is characterized by slow wave activity and peristaltic
10
11 contractions. Two very different motor patterns can be distinguished in the stomach:
12
13 an interdigestive and a postprandial motor pattern. During the interdigestive phase,
14
15 the proximal stomach muscle tone is high while the distal stomach is engaged in a
16
17 recurrent contraction pattern known as the migrating myoelectrical (or motor)
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19 complex (MMC). It has been suggested that the MMC serves to clear the stomach of
20
21 secretions, debris, and microbes during fasting {Szurszewski, 1981 1001 /id}. Upon
22
23 food intake the motor pattern of the stomach changes drastically: the proximal
24
25 stomach relaxes and serves initially as a reservoir. After food intake, a tonic
26
27 contraction of the proximal stomach pushes the food distally, while the distal stomach
28
29 mixes and grinds the food by a powerful and regular peristaltic contraction pattern ¹².
30
31 This postprandial motor pattern serves three major mechanical stomach functions:
32
33 (1) the proximal stomach can act as a reservoir that enables ingestion of a large
34
35 amount of food without a major intragastric pressure increase, (2) the mechanical
36
37 aspect of food digestion is started by antral contractions that mix and grind food to
38
39 smaller particles for further processing by the intestine and (3) tonic and peristaltic
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41 contractions generate a steadily controlled flow of food to the duodenum.
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51 The role of gastric motility and its influence on appetite regulation will be discussed in
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53 three parts, corresponding to the sequence of events during and after food intake.
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55 During food intake, when gastric emptying, especially of solids, is limited, gastric
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57 distension and gastric accommodation play an important function in the regulation of
58
59 satiation as discussed in the first part. After food intake, when the stomach gradually
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3 empties, the role of gastric distension in the determination of appetite decreases and
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5 the focus will shift to gastric emptying and intestinal exposure to nutrients. Finally, we
6
7 will discuss the role of the empty stomach and the MMC in the regulation of hunger
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9 signals.
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11

12 13 14 15 **SATIATION DURING FOOD INTAKE** 16 17

18
19 Gastric emptying of a solid meal follows a typical biphasic pattern: during the lag
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21 phase, which can take up to 30-60 minutes, solids are redistributed in the stomach
22
23 and broken down to small particles, less than 1 mm in diameter, which in turn can
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25 pass through the pylorus during the emptying phase ^{13,14}. Although it is likely that
26
27 some initial gastric emptying will occur (especially part of the liquid phase of the
28
29 meal), most of the solid meal will remain in the stomach during food intake ¹⁵, and
30
31 sensations from the stomach will play a prominent role in the regulation of satiation.
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40 **Satiation signals from the stomach** 41 42

43
44 Gastric mechanosensation is an important factor in the regulation of satiation during
45
46 food intake. Several authors have demonstrated that distension of the stomach
47
48 induces a satiating effect: **in a magnetic resonance imaging study fullness was found**
49
50 **to be related to total gastric volumes for nutrient and non-nutrient meals** ¹⁶. **In healthy**
51
52 **volunteers** inflation of an intra-gastric balloon induces a range of sensations from
53
54 fullness and satiation to pain ¹⁷. Furthermore, the presence of an inflated intragastric
55
56 balloon has been used in the treatment for obesity and was shown to induce
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58 premature satiation during a normal meal ^{18,19}. These studies mainly used balloons
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3 which were placed in the proximal stomach, indicating an important role for the
4 proximal stomach in generating sensations from the stomach. On the other hand,
5
6 proximal stomach in generating sensations from the stomach. On the other hand,
7
8 ultrasound and scintigraphy measurements show a direct correlation between antral
9
10 volume and the amount of ingested food or administered liquids ^{20,21}, indicating that
11
12 distal stomach filling is also a determinant of satiation. Most likely, distal and proximal
13
14 stomach have comparable mechanosensitivity and are both contributing to
15
16 sensations of satiation and satiety ¹⁷. The presence of a balloon, besides directly
17
18 distending the proximal stomach, may promote antral distention during food intake
19
20 and this may contribute to the satiation-enhancing effect.
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26 Gastric distension has been shown to trigger stretch as well as tension
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28 mechanosensitive receptors that in turn relay their information via vagal and
29
30 splanchnic nerves ²²⁻²⁶ to the hindbrain and several other brain areas ²⁷⁻²⁹ (Figure
31
32 1A). Distension of the proximal stomach in physiological ranges is known to activate
33
34 a neuronal network in the central nervous system consistent with the 'visceral pain
35
36 neuromatrix' ³⁰. In a recent study from our group, we used positron emission
37
38 tomography imaging to compare regional brain activity during balloon distension or
39
40 during intragastric infusion of a nutrient drink. Stepwise gastric balloon distension
41
42 progressively activated the "visceral pain neuromatrix" (primary & secondary
43
44 somatosensory cortex, lateral orbitofrontal cortex, insula, anterior cingulate cortex
45
46 and cerebellum), which was associated with the generation of discomfort and/or pain
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51 ³¹. In contrast, continuous or stepwise nutrient infusions to equal or higher intragastric
52
53 volumes induced progressive deactivation of the visceral pain neuromatrix ³². We
54
55 hypothesize that the latter phenomenon is a prerequisite for tolerance of meal
56
57 volumes in healthy subjects. The difference between gastric balloon distension and
58
59 nutrient distension might be related to neurohormonal signaling induced by detection
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3 of the presence of nutrients further down the gastrointestinal tract, and/or to changes
4
5 in gastric muscle tone associated with nutrient ingestion.
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12 There is evidence that gastric distension-induced satiation can also be regulated by
13
14 gut hormones. Indeed, the satiating effect of gastric distention has been shown to be
15
16 enhanced by cholecystokinin (CCK) ³³. Another example is glucagon-like peptide 1
17
18 (GLP-1), known to reduce food intake in humans ³⁴: GLP-1-containing neurons in the
19
20 nucleus of the solitary tract are activated by gastric distension within the physiological
21
22 range, suggesting a role for GLP-1 in gastric distension-induced appetite signaling ³⁵.
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26 GLP-1 receptor antagonism in the nucleus tractus solitarius attenuated feeding
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28 suppression after gastric distension but not after intraduodenal infusion of a nutrient
29
30 drink, indicating that central release of GLP-1 and activation of hindbrain GLP-1
31
32 receptors mediate specifically gastric satiation signals, while peripheral release of
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34 GLP-1, mediated by the L cells in the distal small intestine, is not related to gastric
35
36 distension ³⁶.
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41 In contrast to mechanosensation, nutrient sensation in the stomach is less likely to be
42
43 an important factor in the regulation of satiation during food intake: in rats equipped
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45 with inflatable cuffs around the pylorus that prevent content from leaving the
46
47 stomach, infusion of non-nutritive solutions such as saline, results in volumetrically
48
49 proportionate decreases in food intake and this is as efficacious as infusion with a
50
51 nutrient solution ^{37,38}. In humans, postprandial hunger and satiety were correlated to
52
53 postprandial gastric volumes, without a significant influence of the nutrient
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55 composition (lipids, carbohydrates or proteins) of the meal ³⁹. Only a few studies
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60 have found evidence for a role of nutrient sensation in the stomach: it has been

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3 suggested that the pylorus can sense the energy content of food and might play a
4
5 role in the regulation of the energy load towards the duodenum ⁴⁰. However, most
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7 authors agree that distension is the main determinant for gastric sensations of
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9 satiation and satiety, and that the stomach does not meaningfully detect the nutrient
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11 or caloric composition of a meal ⁴.
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20 **Role of gastric accommodation**

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23 In between meals the proximal stomach maintains a high basal muscle tone. This
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25 tone is partially due to the myoelectrical properties of the fundus: the resting
26
27 membrane potential in the fundic muscles is near or above the mechanical threshold
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29 ⁴¹. In addition, muscle tone in the proximal stomach is sustained by constant
30
31 cholinergic input mediated by the vagal nerve ⁴². Proximal gastric tone decreases
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33 during food intake, and this process of active relaxation is mediated by several
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35 different (para)sympathetic reflex pathways that have been shown to decrease the
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37 contractile cholinergic input and activate the release of nitric oxide ⁴³. This reflex, also
38
39 referred to as gastric accommodation will enhance the storage capacity of the
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41 stomach by increasing the compliance of the stomach muscles and thus keeps the
42
43 intragastric pressure low during food intake ⁴⁴.
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52 When gastric accommodation is impaired, intragastric pressure will be relatively high
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54 during food intake. This has been shown during air insufflation or intra-gastric balloon
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56 distension: while in healthy subjects during stomach distension the intragastric
57
58 pressure increase is minor or stable and does not increase despite further distension,
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60 intragastric pressure increase is much more pronounced in patients with impaired

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3 gastric accommodation e.g. after vagotomy, patients with Chagas' disease (a tropical
4 parasitic disease characterized by extensive lesions of the myenteric plexus) and
5 patients with functional dyspepsia ⁴⁵⁻⁴⁸. Increased intragastric pressure is associated
6 with increased postcibal perception ⁴⁹. We recently showed that, during intragastric
7 infusion of a nutrient drink, intragastric pressure is directly correlated to satiation,
8 indicating that intragastric pressure is a determinant of satiation ⁵⁰.

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17 Whether perception is driven by intragastric pressure, or by another
18 mechanosensitivity modality that is influenced by intragastric pressure, is a matter of
19 controversy ^{51,52}. According to the simplified law of Laplace, increased intragastric
20 pressure will be associated with increased wall tension for the same intragastric
21 volume. Studies using isovolumetric and isobaric gastric distensions indicate that
22 gastric wall tension receptors may be most relevant for mediating distension-induced
23 sensation ^{53,54}. In fact, by using a tensostat that keeps an intragastric bag at a
24 constant tension (calculated according to the simplified Laplace's law) it was shown
25 that sensations from the proximal stomach depend on gastric wall tension, whereas
26 intragastric volume and expansion seem less relevant ⁵⁵.

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43 Although increased tension by itself can increase sensation, it can also cause
44 redistribution of the food from the proximal stomach to the antrum as shown in
45 imaging studies ^{56,57}. Since the antrum is less compliant than the proximal stomach it
46 is more sensitive to distension, and increased feelings of fullness and satiation in
47 patients with impaired gastric accommodation can originate from the antrum ²¹.
48 Furthermore, increased tonic pressure exerted by the stomach could increase gastric
49 emptying of liquid but also of solid food ^{14,58,59} which in turn could influence satiety
50 and food intake ⁶⁰.

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3 A number of studies have investigated the importance of gastric accommodation in
4 relation to food intake. Using the barostat it was demonstrated that a subgroup of
5 functional dyspeptic patients has early satiation and weight loss that can be attributed
6 to impaired gastric accommodation ⁶¹. This was confirmed in a later study in which
7 we demonstrated a clear relationship between meal-induced gastric accommodation
8 and caloric intake in healthy volunteers as well as functional dyspeptic patients ⁶². In
9 healthy volunteers we showed that artificially increasing gastric muscle tone (by
10 means of motilin administration or nitric oxide synthase inhibition) also increased
11 meal-induced satiation ^{43,63}. In a recent study we demonstrated that in the presence
12 of a balloon blocking gastric outflow, slow ingestion of a liquid meal was able to
13 induce satiation albeit less than in a comparable control situation without pyloric
14 obstruction, indicating, as we have discussed before, that nutrient accumulation in
15 the stomach alone is able to induce a feeling of satiation and that duodenal nutrient
16 exposure adds to feelings of satiation but is not a prerequisite for the occurrence of
17 meal-induced satiation ⁶⁴. On the other hand, in the same study we showed that
18 gastric accommodation during pyloric outflow obstruction was decreased as
19 compared with the control condition, furthermore supporting the hypothesis that
20 impaired accommodation decreases tolerance of a nutrient load. In addition, the
21 intragastric pressure during nutrient drink ingestion at a constant rate show is
22 significantly correlated to the corresponding satiation scores and the nutrient volume
23 required to induce maximal satiation ⁶⁵.

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53 Other groups have reported a possible correlation between gastric accommodation
54 and food intake or satiety in binge eating disorder, bulimia nervosa and cancer
55 patients ⁶⁶⁻⁶⁸. Another observation in favor of such a relationship comes from gastric
56 banding, a frequently-used gastric restrictive bariatric approach for the treatment of
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3 morbid obesity: by reducing the size of the proximal stomach early satiation and
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5 fullness lead to substantial weight loss. Although the exact mechanism of early
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7 satiation and weight loss in gastric banding is incompletely elucidated, it was
8
9 suggested that changes in gastric accommodation are responsible ⁶⁹.

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12 These findings all indicate that gastric accommodation is an important determinant of
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14 food intake, and that impaired gastric accommodation is associated with decreased
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16 food intake. The question remains whether this could affect long-term body weight. In
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18 patients there are indications that impaired gastric accommodation and weight loss
19
20 are related e.g. in functional dyspepsia, in some anorexia patients and in cancer
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22 patients with loss of appetite ^{61,68}. On the other hand there is hardly any evidence
23
24 that gastric accommodation is enhanced in obese people. Unfortunately, there is no
25
26 medication that can selectively impair or enhance gastric accommodation and can be
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28 administered over a longer period, and studies that examine the relationship between
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30 gastric accommodation and satiation on one hand and body weight on the other hand
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32 are lacking.
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43 **SATIETY SIGNALING AFTER FOOD INTAKE**

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

Although the intestines, like the stomach, are sensitive to distension⁷⁰, 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^{4,6} (Figure 1B).

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)⁷¹, whereas PYY reaches its peak plasma level after about 1 hour⁷². 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-opiomelanocortin/cocaine- and amphetamine-regulated transcript) neurons that modulate amongst others the mediobasal hypothalamic and the paraventricular

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3 nuclei which eventually send signals to other brain areas ^{3,73}. For CCK, GLP-1 and
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5 PYY the resulting effect is a well-described increase in satiety ^{33,34,72}.
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9 When released locally, peptides and small molecules can influence the activation of
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11 enteric and (para)sympathetic nerves. 5-HT, for example, is released from
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13 enterochromaffin cells and mediates vagal nerve activation via 5-HT₃ receptors ⁷⁴.
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15 Vagal nerves signal to the nucleus tractus solitarius in the hindbrain from which
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17 region efferent fibers project to the hypothalamus using the parabrachial nucleus as
18
19 the main relay. Indeed, administration of the 5-HT₃ receptor agonist m-
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21 chlorophenylbiguanide can reduce food intake in rats ⁷⁵ while the 5-HT₃ receptor
22
23 antagonist ondansetron has been shown to attenuate CCK-induced suppression of
24
25 food intake in rats ⁷⁶. The role of 5-HT₃ receptors in the control of satiation, however,
26
27 is less clear: while some groups claim ondansetron by itself does not influence food
28
29 intake in rats, other groups showed that ondansetron is able to reduce food intake in
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31 rats ⁷⁷ and binge-eating behavior in bulimia patients ⁷⁸.
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41 **Role of gastric emptying**

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43 From a mechanical point of view, gastric emptying of a meal relies on a complex
44
45 interplay between the major motor patterns of the stomach. Upon food intake, and
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47 after an initial relaxation, the proximal stomach propels gastric contents forward by
48
49 means of a tonic contraction and hereby provides a driving force for gastric emptying.
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51 Simultaneously, peristaltic contractions emerging from the mid-corpus progress in the
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53 direction of the antrum, hereby grinding and sieving solid food. This repetitive motor
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55 pattern breaks down the food particles, mixes them with juice and forms a second
56
57 drive that pushes the food content distally. A third mechanical factor in the regulation
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3 of gastric emptying is opening and closure of the pyloric sphincter. This narrow high-
4
5 pressure zone closes the stomach during the terminal phase of a peristaltic
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7 contraction wave, so that any content from the antrum is prevented from entering into
8
9 the duodenum during mixing and grinding ⁷⁹. The relative importance of each of
10
11 these three mechanical functions depends on the consistency of the food: for liquids
12
13 the pressure elicited by the proximal stomach and opening of the pylorus will be
14
15 dominant in the control of gastric emptying, while the peristaltic pump of the antrum is
16
17 more dominant for solid food ⁸⁰. Non-caloric liquids, for instance, empty without lag
18
19 phase, directly proportional to the gastric volume and in an exponential process.
20
21 Solids on the other hand typically empty in a biphasic manner: after a lag-phase
22
23 where hardly any emptying occurs, gastric emptying rate of the grinded and mixed
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25 contents is more or less stable until the stomach is emptied ¹⁴. The emptying speed
26
27 of a meal is inversely correlated to its caloric content. Interestingly it has been shown
28
29 that gastric emptying is independent on the nature of the calories so that a constant
30
31 delivery of energy to the bowel is maintained ⁸¹. Besides caloric content, a
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33 relationship has been described between gastric emptying rate and the acidity,
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35 osmolarity and viscosity of the meal ^{82,83}. Many of these relationships can be
36
37 explained by a duodenal-gastric feedback mechanism: exposure of the small
38
39 intestine to nutrients activates vago-vagal reflex mechanisms and hormonal signals
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41 (e.g. GLP-1, PYY and CCK) that modulate gastric emptying ^{14,84,85}.
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51 The relation between gastric emptying and appetite is complex and only few studies
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53 directly investigated this relationship. Physiological or artificially-induced delay of
54
55 gastric emptying appears to be linked with increased feelings of satiety and fullness
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57 and termination of food intake ⁸⁶⁻⁸⁸. Also, at least a subgroup of patients with anorexia
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59 nervosa have markedly delayed gastric emptying, while in some studies obese
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3 people were shown to have enhanced gastric emptying⁸⁹⁻⁹¹. There is no obvious
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5 candidate hormone to explain these findings: leptin, the plasma levels of which
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7 directly positively correlate with adiposity, has no major effects on gastric emptying
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10⁹², and circulating ghrelin has been reported to be lower in obese subjects than in
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12 healthy controls. Furthermore, in healthy controls a correlation was found between
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14 the gastric emptying rate of solids and body surface area and weight⁹³.

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16
17 It has been suggested that larger intragastric volume and hence increased
18
19 (dis)tension as a result of delayed gastric emptying is responsible for increased
20
21 feelings of satiety and delayed return of hunger^{86,94}. This interpretation seems to be
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23 acknowledged by a study in which a significant correlation was found between ratings
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25 of postprandial increase in hunger and the time needed for 90% of the meal to
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27 empty. The authors of this latter study also suggested that the reduction of gastric
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29 distension may be the determinant factor in the development of hunger after a meal
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34⁹⁵. The interaction between gastric distension, gastric emptying and feelings of
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36 appetite was studied in more detail by a series of experiments that combined
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38 ultrasound and scintigraphy: satiety and satiation were found to be inversely
39
40 correlated to gastric emptying, more precisely, a close relationship was found
41
42 between antral area (and presumably antral distension), satiation and satiety^{21,96,97}.

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45 Other studies suggest that not (only) gastric distension is important in the regulation
46
47 of satiety: in a study in which a concentrated and a diluted meal of 2500 kJ were
48
49 served to healthy volunteers satiety scores and gastric emptying of solids and liquids
50
51 did not differ between the meals. A significant correlation however was observed
52
53 between satiety scores and emptying of the solid fraction in both meals. It was
54
55 concluded that it is not the volume of the meal that influences satiety but rather the
56
57 gastric emptying rate of the solid meal fraction of that meal, indicating that gastric
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3 emptying of energy and not volume of the ingested meal is the major determinant of
4
5 satiety⁹⁸. Other studies confirm that feelings of hunger or satiation are dependent on
6
7 gastric emptying of fat and indeed intestinal exposure to the nutrients^{99,100}.
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11 From the findings in the studies above we can conclude that a complex relationship
12
13 exists between gastric emptying and appetite. We postulate that both gastric
14
15 (dis)tension and intestinal exposure play a role in the regulation of appetite, but the
16
17 relative emphasis shifts towards intestinal exposure when the stomach empties.
18
19 Interestingly, several anorexigenic hormones such as CCK, PYY, GLP-1 etc. inhibit
20
21 gastric emptying (and at the same time increase gastric compliance)^{14,101,102}, and
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23 these effects on gastric motility can contribute to their effects on satiation.
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33 **Return of hunger: role of gastric Phase III contractions**

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36 Feelings of hunger have long been associated with contractions of the empty
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38 stomach. A little less than 100 years ago Cannon & Washburn described powerful
39
40 contractions of the empty stomach and showed that they were invariably correlated
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42 with hunger pangs that were also perceived as rumbling in the epigastrium¹⁰³. They
43
44 suggested that the hunger sensation resulted from these contractions. Interestingly,
45
46 these 'hunger contractions' persisted after vagotomy, indicating that their initiation is
47
48 independent of the central nervous system¹⁰⁴. The 'hunger contractions' could later
49
50 be identified as being part of the MMC. Indeed, when stomach and small intestines
51
52 are emptied after a meal a very typical myoelectrical and contraction pattern emerges
53
54 that is characterized by 3-4 phases: phase I is a quiescent period with virtually no
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56 contractions, phase II consists of random irregular contractions with low amplitude,
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3 while phase III is a short burst of regular high-amplitude contractions; phase IV
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5 represents a short transition period back to the quiescence of phase I {Szurszewski,
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7 1981 1001 /id;Szurszewski, 1969 1325 /id;Itoh, 1981 1327 /id}. Phase III contractions
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9 are made up of a group of contractile waves that migrate from the oral to the anal
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11 side successively over a constant period, characterized by an interval of 100-150
12
13 minutes during fasting. In man, about half of all phase III onsets are located in the
14
15 stomach and the other half is located in the duodenum. The immediate physiological
16
17 role of the phase III contractions is believed to provide a pulsatile flow to clear the
18
19 stomach and small intestines of secretions, debris, and microbes during fasting and
20
21 let the stomach be ready to receive a next meal. The regulation of phase III
22
23 contractions and the MMC in general is still not completely resolved. Although there
24
25 is some evidence that the MMC can be influenced by the CNS, it has been shown to
26
27 run largely independent of the CNS ¹⁰⁷. It is well-established that the MMC is
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29 propagated through the enteric nervous system. Furthermore, there is good evidence
30
31 that the initiation of the phase III contractions in the stomach might be regulated by
32
33 gut hormones such as somatostatin and motilin. Indeed, a close relationship between
34
35 plasma motilin levels and phase III contractions is well-established: plasma motilin
36
37 concentrations fluctuate during the interdigestive state and peak directly before the
38
39 occurrence of phase III contractions in the stomach or upper duodenum ¹⁰⁸.
40
41 Immunoneutralization of circulating motilin suppresses these activity fronts ^{109,110} and
42
43 exogenous administration of motilin initiates premature phase III contractions in the
44
45 stomach in dogs ^{111,112} and humans ¹¹³. Plasma somatostatin levels are associated
46
47 with phase III activity fronts in the duodenum and somatostatin infusion can induce
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49 intestinal activity fronts ^{114,115}.
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3 Although the association between phase III contractions and hunger pangs was
4 recently confirmed (Figure 3) the underlying mechanism remains unexplained ¹¹⁶. By
5 means of ultrasound, the typical sensation of rumbling in the epigastrium or
6 'borborygmia' has been linked to movement of air within the gastric lumen during
7 phase III contractions, possibly from the proximal stomach to the antrum, and in the
8 intestines ¹¹⁷. This movement of air could explain the rumbling sensation during
9 phase III, however strong contractions in the stomach that can displace air are not
10 exclusively linked to phase III contractions. We recently described that administration
11 of motilin in individuals with an empty stomach induced phase III contractions and
12 associated hunger pangs. Interestingly, antral contractions of a similar amplitude
13 induced by a cholinesterase inhibitor are not associated with hunger, indicating that
14 hunger sensations require a typical phase III pattern or motilin receptor stimulation
15 ¹¹⁸. Although administration of both motilin and ghrelin are known to induce phase III
16 contractions, only motilin plasma levels fluctuate with the MMC, indicating that motilin
17 is closely related to hunger pangs ¹¹⁹. Furthermore, while significant correlations were
18 found between motilin, phase III contractions and hunger scores, the best correlation
19 was found between hunger ratings and plasma motilin levels ^{120,120}. These findings
20 indicate that sensation of hunger is closely associated with plasma motilin levels as
21 well as phase III contractions ¹²⁰. Whether it is the rise in motilin plasma levels or
22 gastric phase III contractions themselves that trigger the sensation of hunger pangs
23 still remains to be properly investigated. A third option is that the motor and hormonal
24 changes are merely epiphenomena to the hunger pangs but this has not been
25 studied experimentally.
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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^{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 distention¹²³.

Sibutramine is a centrally-acting serotonin and norepinephrine reuptake inhibitor and is used for the treatment of obesity¹²⁴. 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 emptying¹²⁴. In a barostat study in dogs, sibutramine increased gastric tone and impaired gastric accommodation to an orally ingested meal¹²⁵. 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

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2
3 (increased lipolysis and thermogenesis) ¹²⁶. In a barostat study we showed that
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5 rimonabant decreased gastric accommodation to a meal, however in the same study,
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7 nutrient tolerance during a drinking test was not affected ¹²⁶. The effect of rimonabant
8
9 on gastric emptying in humans is at present unknown, however in rats rimonabant
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11 has been shown to reverse the endocannabinoids-induced delay in gastric emptying
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13 ¹²⁷. Although impaired gastric accommodation and increased gastric emptying could
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15 increase satiation, it is unclear whether these effects of rimonabant contribute to its
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17 effects on food intake and body weight.
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23 The role of opioids in the regulation of food intake is complex: in general opioid
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25 agonists enhance feeding and opioid antagonists such as naloxone and naltrexone
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27 but also the peripherally-restricted antagonist methylnaltrexone decrease feeding ¹²⁸⁻
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29 ¹³¹ but these effects are dependent for example on the treatment duration and
30
31 whether normal weight, low weight (anorexia patients) or obese volunteers/patients
32
33 are selected ¹³². We recently showed that the peripherally-restricted opioid receptor
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35 antagonist methylnaltrexone increased satiation and that this effect on food intake
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37 was more pronounced compared to the centrally-acting antagonist naloxone ⁵⁰.
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39 Interestingly, methylnaltrexone impaired gastric accommodation to a meal and this
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41 effect was more pronounced than that of naloxone, suggesting that endogenous
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43 opioids mediate gastric accommodation and satiation via peripheral mu-opioid
44
45 receptors. The existence of a peripheral opioid-related mechanism in control of food
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47 intake was confirmed in a study in rats, although in the latter study the effect was
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49 mediated via potentiation of the effect of leptin ¹³³.
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57 The effect of sibutramine, rimonabant, naloxone and methylnaltrexone on gastric
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59 motility may contribute to their effects on food intake and body weight. However, so
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far, a contribution of changes in gastric motility to their effects on body weight has not

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3 been established for any of the drugs described above and it remains unclear
4
5 whether the effects on gastric motility are crucial or just an epiphenomenon. More
6
7 research is needed to investigate directly the link between the effect on gastric
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9 motility and decreased food intake and weight loss.
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13 GLP-1 is a well-known regulator of food intake ³⁴ and is at the same time known to
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15 delay gastric emptying, inhibit antral contractility, decrease fasting tone of the
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17 proximal stomach and enhance gastric accommodation ^{102,134,135}. However, GLP-1 is
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19 rapidly inactivated by dipeptidyl peptidase 4 (DPP4), which limits its usefulness as a
20
21 treatment option. Also long-acting GLP-1 analogues exenatide and liraglutide reduce
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23 body weight and have been shown to reduce appetite and promote satiety ^{136,137}.
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27 **Although these peptides are known to induce nausea (most likely mediated through**
28
29 **central mechanisms)** exenatide and liraglutide are also known to slow down gastric
30
31 emptying. **The latter** might explain, at least in part, the effect on food intake ¹³⁸. So far
32
33 their effect on gastric accommodation is unknown. The effect of DPP4 inhibitors on
34
35 body weight is less clear: no or small changes of the body weight have been
36
37 observed in patients on vildagliptin ^{139,140}. In concordance, no effects have been
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39 observed on gastric emptying, while effects on gastric accommodation have not yet
40
41 been investigated ¹⁴¹.
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48 Other drugs used in the treatment of diabetes also affect body weight and gastric
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50 function. Pramlintide, an analog of the pancreatic hormone amylin which is used in
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52 the management of diabetes mellitus, reduces hunger and food intake in healthy
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54 volunteers. Similar effects have been shown in a 6-week study in obese subjects ¹⁴².
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56 The effect of pramlintide on food intake can partly be explained by the fact that it
57
58 markedly delays gastric emptying ¹⁴³⁻¹⁴⁵.
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Intraluminal devices

As discussed previously, inflation of an intragastric balloon induces fullness and satiation¹⁷. Based on this principle implantation of an intragastric balloon has been used in the treatment of obesity^{18,19}. 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 loss¹⁸.

Adjustable totally implantable intragastric prosthesis (ATIIP) - Endogast® (Districlass Médical S.A., Chaponnay, France) is a new technique for the treatment of morbid obesity¹⁴⁶. 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 patients¹⁴⁶.

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^{147,148}. 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 intake¹⁴⁹, 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

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3 distension from delayed gastric emptying interacts with a direct stimulation of central
4
5 satiety centers by hormonal and neural signals, to reduce hunger and energy intake.
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10 11 12 **Bariatric surgery** 13 14

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16 For morbid obese patients bariatric surgery is an effective treatment that induces
17 sufficient and sustained weight loss ¹⁵⁰. Three major types of bariatric surgery are
18 used to treat obese patients: restrictive procedures (e.g. gastric banding, and sleeve
19 gastrectomy), malabsorptive procedures (e.g. jejuno-ileal bypass) and combination
20 restrictive-malabsorptive procedures (e.g. Roux-en-Y gastric and duodenal switch
21 bypass).
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31 With all types of bariatric surgery patients experience not only early satiation while
32 eating but feel satiated longer after the meal. Hence, they eat considerably less as
33 compared to before the operation. The mechanisms responsible for the effects on
34 satiation and satiety are not well understood however there are indications that
35 sensory signals from the upper gastrointestinal tract play a major role.
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43 During the jejuno-ileal bypass procedure a substantial part of the small intestine is
44 bypassed from the alimentary tract and it is believed that malabsorption of nutrients is
45 responsible for the observed weight loss, although an association with delayed
46 gastric emptying and altered gut hormone patterns has been described ¹⁵¹. Due to
47 the many complications associated with this procedure this type of bariatric surgery is
48 not longer recommended.
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56 Also for sleeve gastrectomy and Roux-en-Y gastric bypass it has been shown that
57 the levels of different (gut) hormones as ghrelin, GLP-1, insulin and PYY are altered
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3 after surgery ¹⁵²⁻¹⁵⁴. These changes in (gut) hormone levels are held responsible for
4 the increased satiation and satiety and are likely caused because food is delivered
5 faster to the duodenum and into the ileum (activating the ileal break as discussed
6 above) after surgery and does not reside in the stomach as it did before surgery ¹⁴⁹.
7
8 Increased gastric emptying has indeed been observed after sleeve gastrectomy ³⁵⁻³⁷
9 and might be caused by the reduced gastric volume which impairs gastric
10 accommodation and leads to increased tension for the same meal volume. This
11 directly increases satiation but also leads to more rapid delivery of the contents to the
12 intestines, and release gut hormones as described above.
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29 CONCLUSION

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

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FIGURES

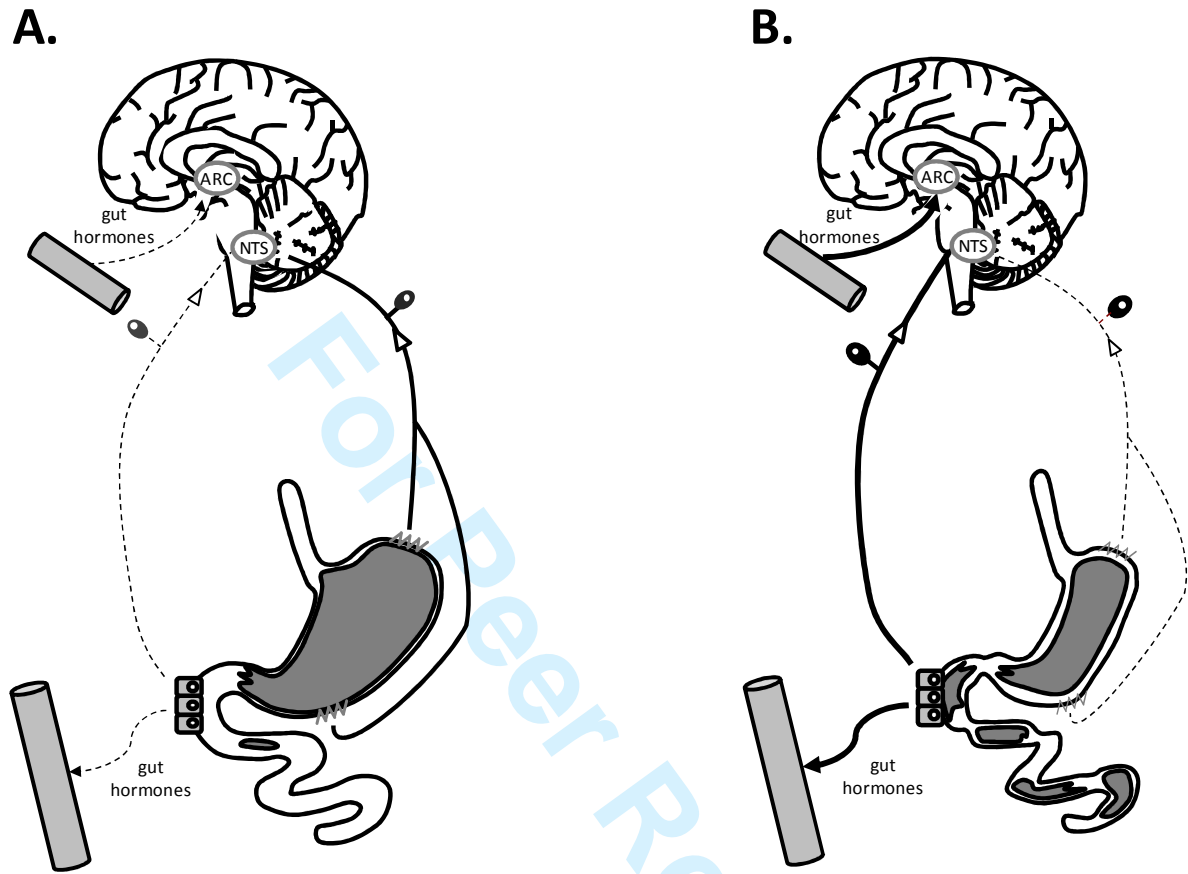


Figure 1. Satiety and satiety signaling during and after food intake. **A)** During food intake and shortly thereafter, emptying of especially solid meals is limited, and gastric distension and accommodation are major determinants in the regulation of satiety. Sensations of satiety are mainly mediated 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

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3 and small molecules, that can act locally (and activate vagal nerves that signal to the
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5 NTS) or enter the blood stream and work as hormones (and signal to the arcuate
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7 nucleus (ARC) in the hypothalamus).
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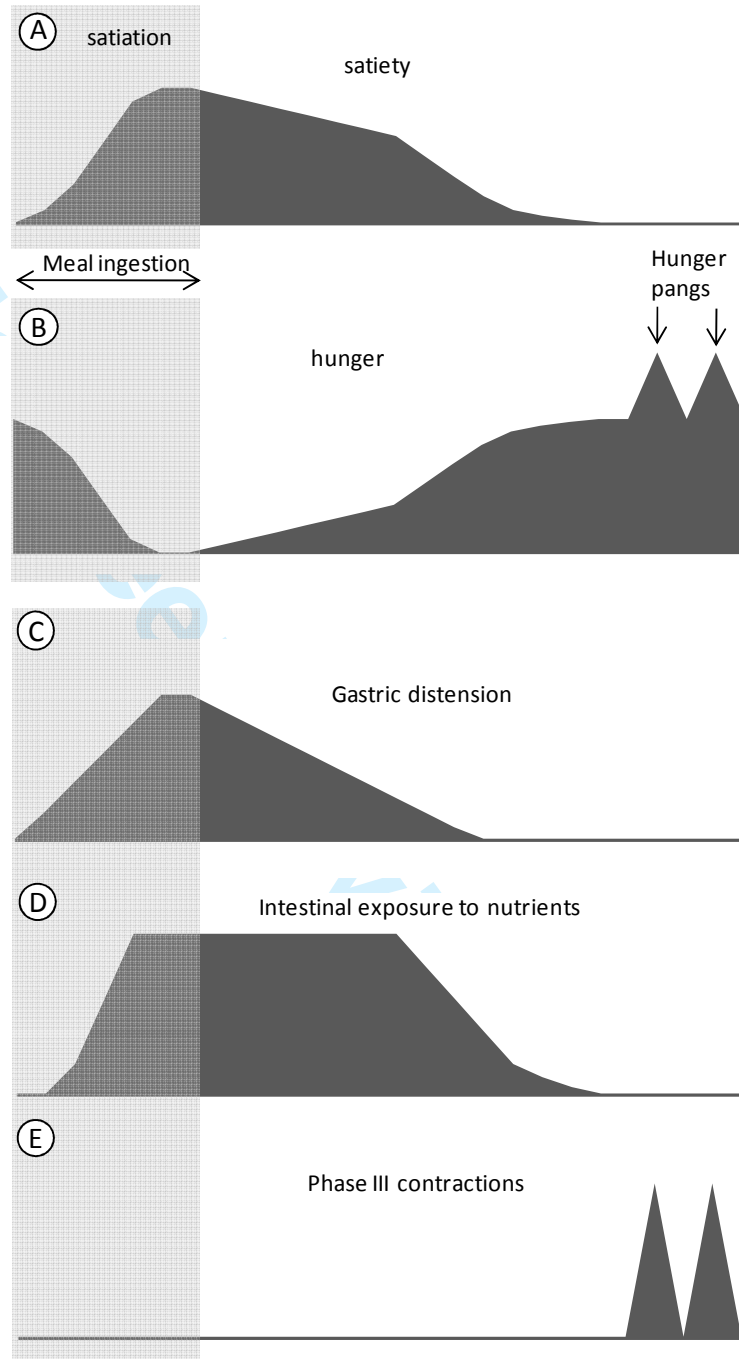
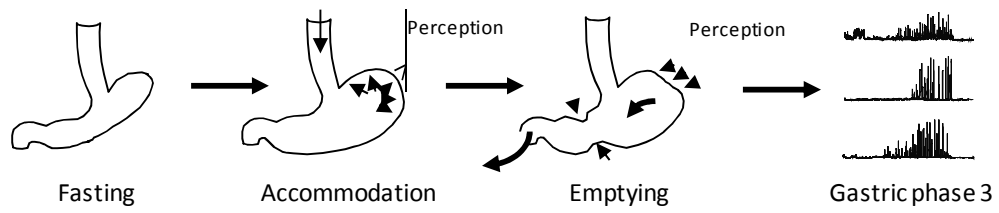


Figure 2. A hypothetical model of the regulation of satiation, satiety and hunger by gastric motility-controlled processes. All graphs represent a period during (grey area)

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3 and after food intake. **A)** satiation and satiety during and after food intake
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5 respectively, **B)** hunger, **C)** gastric (dis)tension, **D)** intestinal exposure of nutrients,
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7 and **E)** phase III contractions. In this model gastric (dis)tension, intestinal exposure
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9 and phase III contractions have an equal maximal contribution. Summation of graph
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11 C and D result in graph A, while graph E deduced with graph C and D result in graph
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13 B.
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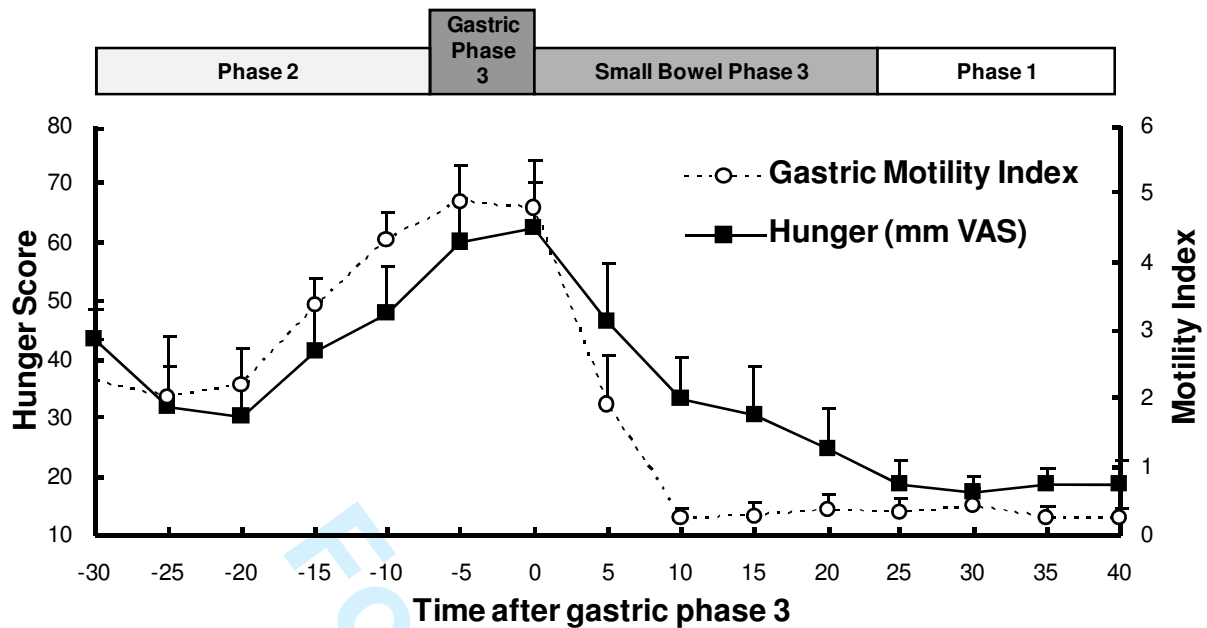


Figure 3. Gastric phase III contractions are closely associated with increased hunger scores. Healthy volunteers underwent interdigestive gastroduodenal manometry. Hunger was scored on a 100 mm visual analogue scale. Motility index (MI) was automatically analyzed with a computer. Results are represented as mean \pm 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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