

The effects of weight loss strategies on gastric emptying and appetite control

Horner, K. M.; Byrne, N. M.; Cleghorn, G. J.; Näslund, E.; King, N. A.

Published in:
Obesity Reviews

DOI:
[10.1111/j.1467-789X.2011.00901.x](https://doi.org/10.1111/j.1467-789X.2011.00901.x)

Licence:
Other

[Link to output in Bond University research repository.](#)

Recommended citation(APA):

Horner, K. M., Byrne, N. M., Cleghorn, G. J., Näslund, E., & King, N. A. (2011). The effects of weight loss strategies on gastric emptying and appetite control. *Obesity Reviews*, 12(11), 935-951.
<https://doi.org/10.1111/j.1467-789X.2011.00901.x>

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

For more information, or if you believe that this document breaches copyright, please contact the Bond University research repository coordinator.

Horner, K. M., Byrne, N. M., Cleghorn, G. J., Näslund, E. and King, N. A. (2011), The effects of weight loss strategies on gastric emptying and appetite control. *Obesity Reviews*. doi: 10.1111/j.1467-789X.2011.00901.x

The effects of weight loss strategies on gastric emptying and appetite control

Horner KM^{1*}, Byrne NM¹, Cleghorn GJ², Näslund E³, King NA¹

¹Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane, Australia; ²School of Medicine, The University of Queensland, Brisbane, Australia; ³Department of Clinical Sciences, Danderyd Hospital, Karolinska Institutet, Stockholm, Sweden.

Keywords: Gastric emptying, gut peptides, appetite, weight loss, compensatory responses.

Running Head: Weight loss, gastric emptying and appetite

*Correspondence:

K Horner, Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane, Qld 4059, Australia.

E-mail: k1.horner@qut.edu.au

Conflicts of Interest Statement

There are no conflicts of interest.

Abstract

The gastrointestinal tract plays an important role in the improved appetite control and weight loss in response to bariatric surgery. Other strategies which similarly alter gastrointestinal responses to food intake could contribute to successful weight management. The aim of this review is to discuss the effects of surgical, pharmacological and behavioural weight loss interventions on gastrointestinal targets of appetite control, including gastric emptying. Gastrointestinal peptides are also discussed because of their integrative relationship in appetite control. This review shows that different strategies exert diverse effects and there is no consensus on the optimal strategy for manipulating gastric emptying to improve appetite control. Emerging evidence from surgical procedures (e.g., sleeve gastrectomy and Roux en-Y gastric bypass) suggests a faster emptying rate and earlier delivery of nutrients to the distal small intestine may improve appetite control. Energy restriction slows gastric emptying, while the effect of exercise-induced weight loss on gastric emptying remains to be established. The limited evidence suggests that chronic exercise is associated with faster gastric emptying which we hypothesise will impact on appetite control and energy balance. Understanding how behavioural weight loss interventions (e.g., diet and exercise) alter gastrointestinal targets of appetite control may be important to improve their success in weight management.

Introduction

The World Health Organization estimates that by 2015 approximately 2.3 billion adults will be overweight and more than 700 million will be obese (1). Strategies which lead to a decreased energy intake and/or increased physical activity are commonly advised in an attempt to combat the epidemic; yet often only modest weight loss is achieved (2-3). This may be due in part to compensatory responses in energy intake (for a review of the complete range of responses to an energy deficit see (4)). Bariatric surgery is associated with sustained weight loss and a persistent reduction of energy intake (5) but in light of the large number of patients that qualify for a surgical procedure, the associated costs and lack of surgical resources, surgery remains impractical on a population level. However, in addition to gastric restriction, some procedures appear to reduce weight by changing the profile of circulating gut peptides implicated in appetite control (6-8) suggesting there is potential for substantial and sustainable weight loss with other strategies if these effects can be replicated. Recent evidence suggests this increased gut peptide response may be due in part to alterations in the emptying rate of the gastric remnant (9-15). An increased understanding of the effects of diet, exercise, pharmacological and surgical weight loss interventions on gastrointestinal targets of appetite control may help to explain the variability in compensatory responses and could facilitate the more effective use of non-surgical strategies in weight management in future.

Energy homeostasis: tonic and episodic processes

To understand why changes in energy intake might vary with different strategies, the processes controlling food intake should first be considered. It is widely recognised that energy homeostasis is governed by a complex neuroendocrine feedback system between the periphery and the central nervous system which involves the interaction of tonic (i.e., long term) and episodic (i.e., short term) signals with a network of hypothalamic, mesolimbic, and hindbrain circuits (16). While knowledge of the neurocircuitries governing metabolic homeostasis may also be instrumental for developing more effective antiobesity strategies (for a review see (17)), the focus of this review concerns the responses of peripheral signals to weight loss. Although tonic signals can influence episodic signals (18-19), both processes appear to have different roles in the control of appetite (20), and are discussed separately in this section.

Tonic signals, of which leptin and insulin are well established, reflect the metabolic state of adipose tissue (20) and appear to respond similarly to weight loss, regardless of the type of weight loss intervention. In response to an energy deficit induced by bariatric surgery (21-23), diet (22, 24-26) and/or exercise (27-31), leptin and insulin levels decrease, which would be expected to stimulate appetite. This increase in appetite can be reduced by exogenous administration of leptin (32). These findings, together with evidence of tonic signals responding to changes in energy availability (33-34)

suggest that tonic signals respond primarily to changes in energy balance and body weight, and that their primary role may be to resist energy deficits.

Episodic signals including gastric distension, and orexigenic (ghrelin) and anorexigenic peptides, arise largely from the GI tract and oscillate periodically with the act of eating (20). Ghrelin, unlike other gut peptides detailed in this review stimulates appetite and rises before meals suggesting a role in meal initiation (35). Some evidence suggests that it is the state of energy balance (i.e., in energy balance or in negative energy balance) that influences fasting ghrelin levels (21, 33-34). Fasting levels of ghrelin increase in response to diet- and exercise-induced energy deficits (30, 36-38). Following bariatric surgery, changes in ghrelin levels are equivocal (39). However, in one study increased fasting ghrelin levels were observed in individuals who were in negative energy balance and not in those in energy balance (21), suggesting the energy balance state could explain some of the ambiguity in findings. Other evidence suggests that fasting appetite sensations respond to changes in energy availability and body weight. Data collated from several weight loss intervention studies shows that fasting appetite sensations are strongly associated with body weight changes (40). However, meal-induced appetite responses are not strongly associated with energy availability or body weight (33-34, 40-41). In essence these are two different measures. The fasting state reflects the homeostatic energy state after a period of reduced body energy (exercise-induced energy expenditure or food deprivation) and the postprandial state reflects the interactions between the physiologic system and the physiologic action of food on satiety signalling (20, 41). Changes in postprandial appetite sensations may therefore occur in response to the direct effects of the weight loss intervention *per se* and could help to explain why changes in energy intake vary with different weight loss strategies. The changes in episodic signals implicated to have a role in meal induced appetite responses are discussed further.

Episodic signals are typified by mechanical factors such as gastric distension and gut peptides such as cholecystokinin (CCK) (42) both of which may be influenced by the rate of gastric emptying. Numerous reviews have considered the effects of weight loss strategies on appetite related gut peptides (see (23, 43-45)). This review will concentrate on the overlooked issue of gastric emptying; gut peptides will also be discussed because of their integrative relationship in appetite control. The role of gastric emptying in appetite control is discussed and relationships between changes in gastric emptying, gut peptides and appetite in response to different weight loss strategies highlighted. A particular emphasis is placed on lifestyle interventions and future directions for weight management.

Gastric emptying and appetite control

Persuasive evidence suggests that gastric emptying influences appetite and energy intake (46-49). As food enters the stomach and subsequently empties into the small intestine, a variety of factors

including gastric distension, nutrient stimulation of intestinal mechanoreceptors and chemoreceptors (see (50-51)) and several gut peptides released from the GI tract contribute to satiation (control of meal size) and satiety (post-meal inhibition of eating). Although it is intuitive that a faster gastric emptying leads to increased appetite, the role of gastric emptying in appetite control is complex. Gastric distension influences appetite by triggering stretch and tension mechanoreceptors which relay information to the brain (see (52-53)). There is a close relationship between the sensation of fullness and antral distension (54-55). Furthermore, food intake at a buffet meal has been shown to be inversely related to the volume of gastric contents remaining from a previous meal (56). These findings suggest that an accelerated rate of gastric emptying and hence reduced gastric distension might predispose to overeating. However, in addition to gastric distension, the presence of nutrients in the small intestine is critical to satiation and satiety (57). A number of gut peptides are released in response to intestinal nutrients and act by entering the bloodstream and indirectly via the vagus nerve to inhibit appetite (58-59). After food intake, CCK is released into the circulation from endocrine I-cells of the duodenum and the jejunum (60) whereas glucagon-like peptide-1 (GLP-1) and polypeptide YY (PYY) are released from L cells located mainly in the distal small intestine. Both GLP-1 and PYY show a biphasic response to meal ingestion (59). It is most likely duodenal nutrients initiate a neural and/or humoral signal to the distal gut contributing to their early release (61-64), which is then followed by direct nutrient stimulation of L cells in the ileum (59, 65). In the early postprandial period, a more rapid gastric emptying is directly correlated with increases in plasma levels of CCK (66-67), glucagon-like peptide-1 (GLP-1) (11, 62) and peptide YY (PYY) (67-68). Further evidence suggests a threshold rate of gastric emptying exists which must be exceeded to stimulate GLP-1 release (62). Upon release GLP-1, PYY and CCK in turn act to inhibit gastric emptying (69) but the inhibition of gastric emptying is not necessary for the control of food intake by intestinal stimulation (51, 70) and a direct effect on satiety centres is also very likely (51, 70-71). In contrast, ghrelin acts to accelerate gastric emptying (72). However, a more rapid gastric emptying rate is correlated with lower postprandial ghrelin concentrations (73-74), which in turn are associated with reduced appetite (73). Taken together these findings suggest that a slowing of the emptying rate might increase and prolong gastric distension but also result in a delayed or reduced release of CCK, PYY and GLP-1 and reduced ghrelin suppression. Therefore, satiety due to gastric distension would be increased but intestinal satiety signalling to the brain diminished (75).

Collectively, the release and maintenance of episodic signals arising from the GI tract likely have an additive effect in satiation, satiety and the ability to compensate accurately for prior energy intake (51, 76-78). Factors such as the time interval between meals (see Figure 1) will influence the relative contributions of gastric and intestinal signals to appetite control. Gastric distension by food may play a major role in the sensation of fullness whereas the reduction of hunger feelings after a meal result from an interaction of nutrients with receptors in the small intestine (51). Differences in the initial versus subsequent rate of gastric emptying (79) may explain why accuracy in compensation for prior energy intake diminishes as the time interval to the next meal increases (80) - thus highlighting the importance of considering the kinetic and temporal pattern of gastric emptying in relation to

appetite control. The characteristics of the meal (52, 81) (see Figure 1) will also have a role. In the absence of nutrients for example gastric distension appears to be a major factor in the return of hunger (81). Overall, there appears to be an important integrative relationship between gastric emptying and gut peptides in appetite control.

- Figure 1 here -

The efficacy of bariatric surgery in weight loss: what is the role of the emptying rate?

Elucidating the mechanisms behind changes in appetite with surgery is firstly important because such knowledge may facilitate the development and modification of anti-obesity treatments to achieve at least some of the weight loss of surgery (87). Early studies indicated that after gastric bypass solids emptied at a slower rate from the small gastric pouch (88-90). However, there was no correlation with weight loss (88-89) suggesting other mechanisms caused weight loss (88). These studies were cross sectional and comparisons were made either with controls or other surgeries. Although now an abandoned procedure, with jejunoileal bypass (JIB), gastric emptying was slowed 9 months after surgery (91) and unchanged in patients 20 years after JIB compared to controls (92). Today, the most commonly performed bariatric procedures are Roux-en-Y gastric bypass (RYGB), adjustable gastric banding and sleeve gastrectomy (SG) (see (93) for a detailed description of surgical procedures). RYGB, a procedure that both minimizes gastric capacity and accelerates delivery of nutrients to the distal small intestine, produces greater weight loss and earlier resolution of diabetes than gastric banding, which is a purely restrictive procedure (94). Various mechanisms have been proposed to contribute to weight loss and post-surgical reductions in appetite after RYGB (see (87) for a more complete review). There is no doubt that gastric restriction plays a role in weight loss (95). A gastric pouch with a volume of 30ml restricts the amount of food that can be consumed and accommodated following RYGB. However, gastric restriction does not account for the increase in weight loss with RYGB when compared with gastric banding. Evidence suggests that the restrictive and malabsorptive components alone are insufficient to account for the resulting weight loss with RYGB (23). Reduced ghrelin levels after RYGB have also been implicated (24). However, increased, decreased and unchanged fasting ghrelin levels after surgery have been reported (39). Instead, the majority of studies suggest that the efficacy of RYGB in reducing appetite and promoting weight loss may relate predominantly to distal small intestinal effects (95). After gastric bypass the pyloric 'meter' or brake is absent and the diversionary component allows rapid transit of nutrients to the jejunum (51). One hypothesis is that the expedited delivery of nutrients to the hindgut may stimulate a faster and enhanced postprandial release of anorexigenic gut peptides (87). The higher levels and early appearance of PYY and GLP-1 are consistent observations following RYGB (69) but not after gastric banding (96) and could explain the difference in weight loss (97). A faster emptying rate from the small pouch has been suggested to contribute to the greater anorexigenic neurohormonal response following RYGB (9, 11-12). Following RYGB, GLP-1 levels about 5 fold higher than observed after

meal ingestion in healthy lean individuals have been reported (12). In this study similar patterns of decreased hunger, increased fullness and a faster delivery of nutrients to the intestine were observed at 3 days, 2 months and 1 year post RYGB (12). At 6 weeks after RYGB compared to pre-surgery, Morinigo et al (11) observed an accelerated emptying of the small pouch, an increased postprandial GLP-1 and PYY release, reduced hunger and increased satiety. In contrast, with gastric banding, the emptying rate is unchanged (98-100).

An accelerated emptying rate has also been observed after SG, a procedure which does not bypass the duodenum, and may contribute to the increased GLP-1 (101) and PYY (13) secretion after SG. Following RYGB and SG inducing similar weight losses, postprandial PYY levels increased which corresponded to an increase in satiety (13). Two possible explanations were proposed: 1) SG changes neuronal or humoral signalling that regulate postprandial PYY secretion, and 2) SG produces a decrease in gastric acid secretion and a faster gastric emptying; both changes which would lead to a faster delivery of undigested nutrients to the intestine and increase the PYY response (13). Studies demonstrating an accelerated gastric emptying following SG in both the initial (10, 101-102) and overall emptying rate (10, 14, 101) support the latter explanation. The duodenal switch procedure has also been associated with accelerated gastric emptying and an increased PYY response (15). Although, it should be noted that the non-operated controls were given a larger meal with a higher energy content in this study. Findings from studies investigating the effects of different surgical procedures on gastric emptying (or emptying of the small pouch in the case of gastric bypass) are summarised in Table 1. Collectively, the evidence indicates that in addition to gastric restriction, bariatric surgery and in particular RYGB and SG reduce weight by changing the profile of circulating gut peptides implicated in appetite control (6-8, 43) which may partially be due to a faster emptying rate and increased delivery of nutrients to the distal small intestine.

- Table 1 here -

Additional surgical and pharmacological weight loss strategies: contrasting effects on gastric emptying

Other surgical methods such as gastric pacing and gastric electrical stimulation which do not alter normal GI anatomy are also being explored as obesity treatments, but to date have produced inconsistent results with amount of weight loss (see (103) for a review). Their exact mechanism of action has not yet been identified; however, changes in gastric emptying have been implicated. Delayed gastric emptying in the initial 45 minutes after eating and reduced food intake was demonstrated with a system of stimulation through temporary fundic mucosal electrodes (104). In contrast, accelerated gastric emptying was observed with the TANTALUS system of stimulation (105); a system found to achieve long term weight loss comparable to gastric banding (106). One

explanation may be that unlike other gastric electrical stimulation devices, the TANTALUS system is activated only following food ingestion.

Both delayed and accelerated gastric emptying has also been implicated in improved appetite control and weight loss in pharmacological studies. The majority of strategies have been directed towards slowing gastric emptying. Initial studies indicated that slower gastric emptying was associated with weight loss after 12 weeks of Sibutramine treatment (107). Recent drug developments have focused on targeting gut peptides such as GLP-1 (exenatide and liraglutide), amylin (pramlintide) and PYY [intranasal PYY (3–36) and AC-162325], which have been demonstrated to slow gastric emptying and reduce appetite and food intake (108-116). In contrast, findings of slowed gastric emptying with the cannabinoid dronabinol led to speculation that faster gastric emptying and enhanced satiation may be one mechanism behind the appetite and weight reducing effects of Rimonabant; a cannabinoid antagonist (117). Torra et al (118) provided the first evidence supporting the hypothesis that pharmacologically accelerating gastric emptying could enhance satiation and reduce meal size. Erythromycin administration in obese individuals exerted a faster gastric emptying in the first 15 minutes after initiation of eating which translated into a small reduction in energy intake (135 kcal) compared to individuals who received placebo. However, the most commonly studied prokinetic drugs including erythromycin, metoclopramide, domperidone and cisapride have side effects such as nausea (119, 120), making it difficult to separate their effects on appetite. Furthermore, the neurotransmitter systems affected by drugs do not exclusively affect appetite. Another explanation for contradictory findings of both delayed and accelerated gastric emptying being implicated in reduced appetite and energy intake may be that some pharmacological approaches can interfere with or override the endogenous release of gut peptides implicated in appetite control such as CCK (121-122), GLP-1 (122-123) and PYY (115, 122). For example delayed gastric emptying caused by exendin-4 may cause duodenal nutrient delivery to decrease to such an extent that little endogenous GLP-1 is released (123). Furthermore, a drug-induced delay in gastric emptying results in reduced ghrelin suppression (74). These effects are much different to the normal physiological regulation of food intake whereby the endogenous release of various peptides and suppression of ghrelin play a key role in appetite control. As a result it is difficult to apply findings from pharmacological studies manipulating gastric emptying to strategies such as lifestyle interventions.

Summary of effects of surgical and pharmacological weight loss strategies on gastric emptying

The majority of recent gastric bypass and SG studies have been found to accelerate the emptying rate, while gastric banding appears not to alter gastric emptying. Other surgical interventions and pharmacological strategies targeting appetite control have been demonstrated to both accelerate and delay gastric emptying. The ability of these varied strategies to reduce appetite and promote weight loss while having opposite effects of gastric emptying could suggest that modulation of gastric emptying may only have a minor role in weight loss. However, these contrasting findings could also

be attributed to differences between interventions and methodologies. Overall, when accounting for methodological differences and the emerging evidence from gastric bypass and SG studies in particular, the literature reviewed suggests that other strategies which accelerate gastric emptying and the delivery of nutrients to the distal small intestine may stimulate an earlier and enhanced endogenous release of anorexigenic gut peptides and improve appetite control.

Lifestyle Interventions, gastric emptying and gut peptides

Understanding the effects of energy restriction and exercise-induced energy deficits on GI targets of appetite control may be important for tailoring lifestyle interventions to minimise the impact of weight loss on appetite in future. Studies that have measured the effects of lifestyle interventions on gastric emptying and on both fasting and postprandial gut peptide responses are summarised in Tables 2 and 3 respectively.

- Tables 2 and 3 here -

Energy restriction

There is some evidence that energy restriction is associated with a slower gastric emptying. Patients with anorexia nervosa experience delayed gastric emptying (141-144), which returns to typical rates when re-fed (142-143). After a 4-day fast, gastric emptying of a glucose drink was slower in lean and obese subjects (126). Postprandial PYY also decreased after 4 days of a 25% energy restriction (134). The few studies which have examined the effects of energy restriction-induced weight loss on gastric emptying have also indicated a slower emptying (124-125, 131), although some report no change (127, 132). Four months of energy restriction and marked weight loss resulted in slower gastric emptying in 20 morbidly obese individuals (125). Following 16 weeks of dietary intervention achieving a mean weight loss of 18.8kg and a further 8 weeks of weight stabilisation, gastric emptying was slowed during the initial 30 minutes but the overall emptying rate was unaffected in 19 obese subjects (124). The authors suggested that this slowing of the initial emptying rate might postpone meal-termination and thereby pre-dispose to overconsumption and regain of a weight loss. This contention is supported by evidence that energy restriction-induced weight loss is associated with a blunted postprandial release of PYY and GLP-1 after a solid meal (135, 137). Following a 10kg weight loss induced by energy restriction or RYGB, postprandial PYY (22) and GLP-1 (25) levels during an oral glucose tolerance test were increased after surgery compared to no change after energy restriction. This could partially explain the relative efficacy of RYGB compared with energy restriction

in weight loss. The authors speculated this may be due to a more rapid delivery of nutrients to the intestine after gastric bypass. One explanation for findings of unchanged postprandial PYY and GLP-1 levels after energy restriction in these studies (22, 25) is the use of a low-energy liquid meal. With regard to CCK, no significant differences in fasting or postprandial CCK concentrations following diet induced weight loss have been observed (26, 145), although peak values occurred 30 minutes later following 8 weeks of energy restriction, suggesting that pancreatic or gastric and intestinal functions might have changed to cause this shift (26).

While further studies are needed, these findings collectively suggest that an energy deficit induced by energy restriction may delay and/or reduce the release of postprandial gut peptides involved in the episodic control of appetite, possibly mediated by a slower delivery of nutrients to the intestine. These changes could contribute to reduced appetite control and hence be a contributing factor to the relative lack of efficacy of energy restriction in long term weight loss and maintenance.

Exercise

The effects of an exercise-induced energy deficit on gastrointestinal mechanisms of appetite control and gastric emptying in particular have received little investigation. Instead, as gastric emptying plays a major role in the availability of ingested drinks during exercise (146), research has focused on determining the optimal properties of sports drinks to enhance performance. In general, the evidence clearly supports a delay in gastric emptying during strenuous exercise (147-153), and although there is some disparity (154-155), there is an acceleration in gastric emptying during mild to moderate exercise (150, 156-157). Few studies have examined the effects of short term exercise on gastric emptying. Therefore, although the role of gastric emptying in appetite regulation is well understood, the influence of exercise is not. Any adaptations in gastric emptying that occur due to exercise could influence the compensatory responses in energy intake. One study reported no significant change in gastric emptying after a moderate intensity 7 week intervention in adolescent girls compared to a control group (130), but no significant weight loss was observed with exercise. The effect of exercise-induced weight loss on gastric emptying is unknown. Nevertheless, changes in postprandial gut peptide levels (see Table 3) and appetite (41) have been observed following exercise interventions with and without weight loss suggesting exercise may also influence gastric emptying independent of weight loss or energy balance.

In terms of chronic adaptation to regular exercise (and hence potentially an influence on appetite in weight maintenance), two cross sectional studies provide limited evidence that gastric emptying is faster in habitually active individuals. Faster gastric emptying was reported in marathon runners compared to sedentary individuals (129) and in a small sample of elderly active compared to inactive individuals (128). In a cross sectional study of 20 men representing a wide range of daily

physical activity levels, energy and nutrient intakes increasing energy intake was significantly correlated with faster orocecal transit time (OCTT) (158). Although it was suggested that the high energy intake associated with chronic exercise may be associated with significant gastrointestinal adaptations (i.e. accelerated OCTT), it could also be speculated that increased physical activity levels may have led to faster OCTT, and thus higher caloric intakes as a result of a shorter satiety period. The causal nature of this relationship may be critical to understanding the long term effects of exercise on energy intake. A high-fat diet-induced increase in gastric emptying is associated with diminished sensitivity to the appetite suppressing effects of gut peptides (for a review, see (159)) as central nervous system sensitivity to peripheral signals is reduced (18). Therefore, it is possible that faster gastric emptying in chronic exercisers may reflect an adaptation to a higher energy intake and be similarly associated with diminished sensitivity to the appetite suppressing effects of episodic gut peptides. However, given consistent evidence of improved appetite control in chronic exercisers (160-161), the following hypothetical model outlines one possible mechanism contributing to the efficacy of exercise in weight maintenance (Figure 2). Further, it identifies one mechanism to explain why activity-induced energy expenditure could mediate the inverse relationship between meal frequency and adiposity, despite a higher energy intake (162).

- Figure 2 here -

Collectively, while the limited evidence suggests chronic exercisers have a faster gastric emptying, further studies are needed to determine the temporal patterns of changes in gastric emptying with exercise programmes and with exercise induced weight loss.

Combining energy restriction and exercise

A common method of improving weight loss is to combine energy restriction with exercise training. Findings from studies which have investigated the effects of combined exercise and dietary intervention on gut physiology are not conclusive, mainly due to differences in how the diet was manipulated and the volume of exercise employed. Varying degrees of weight loss have been observed, along with differing effects on appetite and gut peptides (see Table 3). Gastric emptying was unchanged after both 4 and 8 weeks of energy restriction combined with exercise advice but the overall emptying rate was delayed after 1 year of the same intervention (131). Following a combination of a reduced-fat energy-restricted diet and 12 weeks of exercise intervention, the PYY response was increased (31). In contrast, when energy restriction was combined with 180min/week of exercise, the PYY response decreased (13). The effects of different combinations of diet and exercise manipulations on gastrointestinal mechanisms of appetite control warrant further investigation.

Methodological Issues: comparing the effects of different strategies

The literature reviewed highlights a number of important methodological issues. It is worth noting that the effects of different strategies on GI targets could vary depending on the magnitude of weight loss. Further, the effects may vary temporally – that is, acute changes may differ from chronic changes. It is critical to determine whether alterations in GI function occur in response to weight loss or the treatment strategy *per se* and to distinguish between changes in fasting and postprandial and exogenous and endogenous levels of peptides. While bariatric surgery may be used as a model to understand physiological weight loss (39), the mechanisms influencing the emptying rate after surgery may be different to those that influence gastric emptying after other interventions. This review has considered the effects of different strategies on gut peptides as currently measured in the systemic circulation. However, peripheral plasma levels may not necessarily reflect the local effects of gut peptides as they may also exert their action by paracrine or neurocrine routes (163-164). As a result the measurement of subjective appetite sensations should not be undervalued as increases or decreases of endogenous plasma levels, particularly of a peptide measured in isolation, may not translate to changes in hunger or fullness. However, subjective appetite sensations are not reported in many studies (9, 13, 15, 22, 24-26, 31, 101-102, 127, 137-138), and when they are reported the measures vary. The behavioural expression of appetite being measured (e.g. meal size, meal frequency) should also be considered. Similarly, the gastric emptying parameters and methods used need to be taken into account as there may be no relationship between the initial (i.e., lag phase) and overall emptying (165). Although beyond the scope of the current review, in addition to gastric emptying, the efficiency of intestinal absorption (determined by factors such as the viscosity and structure of the meal (see (166)) will influence the release of gut peptides. A liquid meal for example, despite a faster gastric emptying, may be absorbed entirely in the duodenum and not reach the lower part of the ileum to directly stimulate L cells (25, 167). Collectively, these methodological issues are important to acknowledge as they may have different implications for appetite control.

Future Directions: GI targets of appetite control for weight loss

A large percentage of weight loss with Roux-en-Y gastric bypass could be attributed to the associated neuroendocrine changes (23). Dietary, pharmacological and surgical strategies attempting to mimic the effects of bariatric surgery on GI responses are likely to be an ongoing area of intense research. The focus of pharmacological strategies may centre on gut peptides and their receptors (168), developing long acting peptides (43) and combination strategies of long acting adiposity signals with short term episodic signals as has recently been shown to be effective with a combination of pramlintide and metreleptin (16). Others are working to identify a drug that accelerates gastric emptying when administered orally to limit meal size (169). The major issue related to dietary

manipulations using functional foods is how to minimise the increase in hunger while maintaining an energy deficit (170). The development of novel foods targeting G protein-coupled receptors (171) and foods designed to reach the distal small intestine earlier and so stimulate an earlier and enhanced postprandial release of PYY and GLP-1 may counteract the blunted response of these gut peptides to energy restriction. Doucet and Cameron (2007) (45) proposed that offering low calorie snacks specifically designed to elicit maximal post snack PYY and GLP-1 levels to coincide with main courses could lead to better dietary control and compliance. However, the same group recently reported the timing of a high protein preload had no effect on PYY, GLP-1 or energy intake (172).

Currently, there is limited evidence concerning the effects of exercise on GI mechanisms of appetite control and weight loss. Exercise is universally available and has the added attraction of many additional health benefits (173) including weight maintenance (174). One hypothesis by which exercise facilitates weight maintenance, based on the early work of Mayer (175) is that exercise alters sensitivity to episodic hunger and fullness signals (160-161, 176) through an increase in postprandial satiety signalling driven by changes in gut peptides (30, 41, 177). Faster gastric emptying may have a role in improved appetite control with chronic exercise as hypothesised in this review. However, this is based on limited cross sectional evidence; therefore integrative studies of gastrointestinal responses are vital. Changes in gastric emptying that result from exercise interventions designed to assess the efficacy of exercise for weight loss should also be examined as they may not be identical to chronic adaptations that occur in habitual exercisers over longer periods of time. Short term evidence suggests exercise-induced energy expenditure (EE) and energy intake (EI) are only weakly coupled (178-179).

A further issue is whether it would be possible to structure a combination of dietary and exercise regimes to favourably alter gastric emptying and endogenous levels of peptides in such a way that the effects of weight loss on appetite and other compensatory mechanisms could be minimised. The independent and combined effects of dietary manipulations and exercise are important. For example, a high-fat diet may undermine any potential beneficial effects of exercise on GI mechanisms of appetite control. It is possible that in some people exercise increases the selection of high-fat energy dense foods (4), which could therefore contribute to the large inter-individual variability observed in weight loss response to exercise (180). In contrast, individuals successful at losing weight with a 12 week intensive exercise intervention increased their fruit and vegetable intake (181). Chaput et al (2007) (182) demonstrated that using a combination of exercise with a diet designed to maximise satiation, significant weight loss could be achieved, indicating that the combination of a healthy satiating diet and exercise allows the achievement of metabolic benefits while potentially avoiding body weight relapse. GI mechanisms were not measured in these studies. Future studies investigating the individual effects of different manipulations of diet and exercise on gastric emptying and gut peptides along with different temporal combinations will advance the understanding of manipulating these lifestyle factors for better use in both weight loss and maintenance.

GI targets of appetite control: part of an integrated process

Changes in the expression of appetite influenced by gastric emptying may be expressed behaviourally as changes in meal size, meal frequency and snacking behaviour between meals. Increasing post-ingestive negative feedback (e.g., anorexigenic gut peptides) has been emphasised as one optimal therapeutic goal in the treatment of obesity (183). Strategies which accelerate gastric emptying represent a reasonable target for preventing overconsumption by increasing the release of anorexigenic gut peptides. However, an overall faster gastric emptying time, despite potentially enhancing the magnitude of satiety sensations from intestinal factors between meals is likely to lead to decreased feelings of fullness arising from the stomach and shorten the interval to the onset of the next meal. Thus meal frequency may be increased and hence net energy intake may not be reduced (118). For weight loss, the most effective strategy to reduce energy intake will be one that targets satiation, satiety and snacking behaviour by manipulating the emptying rate to maximise both the sensation of fullness from the stomach, and the early onset and prolonged release of gut peptides from the intestine.

The concept that appetite may be consciously overridden in the short-term but this is superseded in the longer term by a biologically determined set-point has been proposed as one mechanism by which lifestyle interventions fail to sustain weight loss (43). As there is a strong volitional control over eating behaviour, psychological influences should not be undervalued (184). Reward pathways, stress, social values, diurnal rhythm, learned behaviours and eating behaviour related traits (e.g. dietary restraint) could have a strong influence on food intake. The resulting eating patterns may be influenced by and also contribute to alterations in gut physiology. Following RYGB, the 'supra-normal' nutrient stimulated gut peptide response (12, 96-97, 185) may override both homeostatic defences of body weight and non-homeostatic factors influencing food intake. Changes in gastric emptying and gut peptides induced by lifestyle interventions are unlikely to be of the same magnitude as those following surgery - other factors such as the hedonic response to foods could over-ride signals from the GI tract (186). While developing a strategy to target the GI tract to maximise satiation and satiety may have a critical role in facilitating weight loss with lifestyle strategies, the greatest weight loss will be achieved by adopting a multidisciplinary approach.

Conclusions

A key factor in the long term success of a weight loss intervention is to minimise the impact of weight loss on compensatory responses including energy intake. The complexity of appetite control should not be limited to gastric emptying and gut peptides but their measurement becomes essential to understand the mechanisms by which weight loss strategies may act to increase or decrease appetite and food intake and thus influence weight regain. This review demonstrates that different strategies exert diverse postprandial effects. The existing literature is still limited and the study designs vary in the methods used and parameters reported. Relative to lifestyle interventions, surgical interventions

produce greater short and long term weight loss which may be explained by changes in appetite. From the evidence so far it is likely that in addition to gastric restriction, gut peptides play a key role in the improved appetite control experienced by those who undergo surgical procedures such as sleeve gastrectomy and Roux-en-Y gastric bypass. Although findings remain associative, this response may be due in part to an accelerated delivery of nutrients to the distal small intestine. A better understanding of how lifestyle interventions such as diet and exercise affect gastrointestinal targets of appetite control and the associated implications for food intake is urgently needed to facilitate their more effective use in weight management and so combat the current obesity epidemic on a population level.

References

- 1 World Health Organisation. Factsheet number 311: Obesity and overweight. September 2006; <http://www.who.int/mediacentre/factsheets/fs311/en/index.html>.
- 2 Shai I, Schwarzfuchs D, Henkin Y, Shahar DR, Witkow S, Greenberg I, Golan R, Fraser D, Bolotin A, Vardi H, Tangi-Rozental O, Zuk-Ramot R, Sarusi B, Brickner D, Schwartz Z, Sheiner E, Marko R, Katorza E, Thiery J, Fiedler GM, Blüher M, Stumvoll M, Stampfer MJ. Weight loss with a low-carbohydrate, mediterranean, or low-fat diet. *N Engl J Med* 2008; **359**: 229-241.
- 3 Catenacci VA, Wyatt HR. The role of physical activity in producing and maintaining weight loss. *Nat Clin Pract End Met* 2007; **3**: 518-529.
- 4 King NA, Caudwell P, Hopkins M, Byrne NM, Colley R, Hills AP, Stubbs JR, Blundell JE. Metabolic and behavioral compensatory responses to exercise interventions: Barriers to weight loss. *Obesity* 2007; **15**: 1373-1383.
- 5 Colquitt J, Clegg A, Loveman E, Royle P, Sidhu MK. Surgery for morbid obesity. *Cochrane Database Syst Rev* 2005: CD003641.
- 6 Korner J, Bessler M, Cirilo LJ, Conwell IM, Daud A, Restuccia NL, Wardlaw SL. Effects of Roux-en-Y gastric bypass surgery on fasting and postprandial concentrations of plasma ghrelin, peptide yy, and insulin. *J Clin Endocrinol Metab* 2005; **90**: 359-365.
- 7 Korner J, Inabnet W, Conwell IM, Taveras C, Daud A, Olivero-Rivera L, Restuccia NL, Bessler M. Differential effects of gastric bypass and banding on circulating gut hormone and leptin levels. *Obesity (Silver Spring)* 2006; **14**: 1553-1561.
- 8 Vincent RP, le Roux CW. Changes in gut hormones after bariatric surgery. *Clin Endocrinol (Oxf)* 2008; **69**: 173-179.
- 9 Akkary E, Sidani S, Boonsiri J, Yu S, Dziura J, Duffy A, Bell R. The paradox of the pouch: Prompt emptying predicts improved weight loss after laparoscopic Roux-Y gastric bypass. *Surg Endosc* 2009; **23**: 790-794.
- 10 Melissas J, Daskalakis M, Koukouraki S, Askoxylakis I, Metaxari M, Dimitriadis E, Stathaki M, Papadakis J. Sleeve gastrectomy—a “food limiting” operation. *Obes Surg* 2008; **18**: 1251-1256.

- 11 Morinigo R, Moize V, Musri M, Lacy AM, Navarro S, Marin JL, Delgado S, Casamitjana R, Vidal J. Glucagon-like peptide-1, peptide YY, hunger, and satiety after gastric bypass surgery in morbidly obese subjects. *J Clin Endocrinol Metab* 2006; **91**: 1735-1740.
- 12 Falkén Y, Hällstrom PM, Holst JJ, Näslund E. Changes in glucose homeostasis after Roux-en-Y gastric bypass surgery for obesity at day three, two months, and one year after surgery: Role of gut peptides. *J Clin Endocrinol Metab* 2011; **96**: doi: 10.1210/jc.2010-2876.
- 13 Valderas JP, Iribarra V, Boza C, de la Cruz R, Liberona Y, Acosta AM, Yolito M, Maiz A. Medical and surgical treatments for obesity have opposite effects on peptide YY and appetite: A prospective study controlled for weight loss. *J Clin Endocrinol Metab* 2010; **95**: 1069-1075.
- 14 Shah S, Shah P, Todkar J, Gagner M, Sonar S, Solav S. Prospective controlled study of effect of laparoscopic sleeve gastrectomy on small bowel transit time and gastric emptying half-time in morbidly obese patients with type 2 diabetes mellitus. *Surg Obes Relat Dis* 2010; **6**: 152-157.
- 15 Hedberg J, Hedenström H, Karlsson F, Edén-Engström B, Sundbom M. Gastric emptying and postprandial PYY response after biliopancreatic diversion with duodenal switch. *Obes Surg* 2011; **21**: 609-615.
- 16 Ravussin E, Smith SR, Mitchell JA, Shringarpure R, Shan K, Maier H, Koda JE, Weyer C. Enhanced weight loss with pramlintide/metreleptin: An integrated neurohormonal approach to obesity pharmacotherapy. *Obesity (Silver Spring)* 2009; **17**: 1736-1743.
- 17 Vianna CR, Coppari R. A treasure trove of hypothalamic neurocircuitries governing body weight homeostasis. *Endocrinology* 2011; **152**: 11-18.
- 18 Anini Y, Brubaker PL. Role of leptin in the regulation of glucagon-like peptide-1 secretion. *Diabetes* 2003; **52**: 252-259.
- 19 Morton GJ, Blevins JE, Williams DL, Niswender KD, Gelling RW, Rhodes CJ, Baskin DG, Schwartz MW. Leptin action in the forebrain regulates the hindbrain response to satiety signals. *J Clin Invest* 2005; **115**: 703-710.
- 20 Blundell JE, Levin F, King NA, Barkeling B, Gustafson T, Hällstrom PM, Holst JJ, Näslund E. Overconsumption and obesity: Peptides and susceptibility to weight gain. *Regul Pept* 2008; **149**: 32-38.
- 21 Faraj M, Havel PJ, Phelis S, Blank D, Sniderman AD, Cianflone K. Plasma acylation-stimulating protein, adiponectin, leptin, and ghrelin before and after weight loss induced by gastric bypass surgery in morbidly obese subjects. *J Clin Endocrinol Metab* 2003; **88**: 1594-1602.
- 22 Olivan B, Teixeira J, Bose M, Bawa B, Chang T, Summe H, Lee H, Laferrere B. Effect of weight loss by diet or gastric bypass surgery on peptide YY3-36 levels. *Ann Surg* 2009; **249**: 948-953.
- 23 Ochner CN, Gibson C, Shanik M, Goel V, Geliebter A. Changes in neurohormonal gut peptides following bariatric surgery. *Int J Obes* 2011; **35**: 153-166.
- 24 Cummings DE, Weigle DS, Frayo RS, Breen PA, Ma MK, Dellinger EP, Purnell JQ. Plasma ghrelin levels after diet-induced weight loss or gastric bypass surgery. *New England Journal of Medicine* 2002; **346**: 1623-1630.
- 25 Laferrere B, Teixeira J, McGinty J, Tran H, Egger JR, Colarusso A, Kovack B, Bawa B, Koshy N, Lee H, Yapp K, Olivan B. Effect of weight loss by gastric bypass surgery versus hypocaloric diet on

glucose and incretin levels in patients with type 2 diabetes. *J Clin Endocrinol Metab* 2008; **93**: 2479-2485.

26 Chearskul S, Delbridge E, Shulkes A, Proietto J, Kriketos A. Effect of weight loss and ketosis on postprandial cholecystokinin and free fatty acid concentrations. *Am J Clin Nutr* 2008; **87**: 1238-1246.

27 Keim N, Stern J, Havel P. Relation between circulating leptin concentrations and appetite during a prolonged, moderate energy deficit in women. *Am J Clin Nutr* 1998; **68**: 794-801.

28 Hansen TK, Dall R, Hosoda H, Kojima M, Kangawa K, Christiansen JS, Jørgensen JOL. Weight loss increases circulating levels of ghrelin in human obesity. *Clin Endocrinol (Oxf)* 2002; **56**: 203-206.

29 Kim HJ, Lee S, Kim TW, Kim HH, Jeon TY, Yoon YS, Oh SW, Kwak H, Lee JG. Effects of exercise-induced weight loss on acylated and unacylated ghrelin in overweight children. *Clin Endocrinol (Oxf)* 2008; **68**: 416-422.

30 Martins C, Kulseng B, King NA, Holst JJ, Blundell JE. The effects of exercise-induced weight loss on appetite-related peptides and motivation to eat. *J Clin Endocrinol Metab* 2010; **95**: 1609-1616.

31 Kelly KR, Brooks LM, Solomon TPJ, Kashyap SR, O'Leary VB, Kirwan JP. The glucose-dependent insulinotropic polypeptide and glucose-stimulated insulin response to exercise training and diet in obesity. *Am J Physiol Endocrinol Metab* 2009; **296**: 1269-1274.

32 Westerterp-Plantenga MS, Saris WH, Hukshorn CJ, Campfield LA. Effects of weekly administration of pegylated recombinant human ob protein on appetite profile and energy metabolism in obese men. *Am J Clin Nutr* 2001; **74**: 426-434.

33 Hagobian T, Sharoff C, Braun B. Effects of short-term exercise and energy surplus on hormones related to regulation of energy balance. *Metabolism* 2008; **57**: 393-398.

34 Borer KT. Nonhomeostatic control of human appetite and physical activity in regulation of energy balance. *Exerc Sport Sci Rev* 2010; **38**: 114-121.

35 Cummings DE, Purnell JQ, Frayo RS, Schmidova K, Wisse BE, Weigle DS. A preprandial rise in plasma ghrelin levels suggests a role in meal initiation in humans. *Diabetes* 2001; **50**: 1714-1719.

36 Hilton LK, Loucks AB. Low energy availability, not exercise stress, suppresses the diurnal rhythm of leptin in healthy young women. *Am J Physiol Endocrinol Metab* 2000; **278**: E43-49.

37 Leidy HJ, Gardner JK, Frye BR, Snook ML, Schuchert MK, Richard EL, Williams NI. Circulating ghrelin is sensitive to changes in body weight during a diet and exercise program in normal-weight young women. *J Clin Endocrinol Metab* 2004; **89**: 2659-2664.

38 Leidy HJ, Dougherty KA, Frye BR, Duke KM, Williams NI. Twenty-four-hour ghrelin is elevated after calorie restriction and exercise training in non-obese women. *Obesity* 2007; **15**: 446-455.

39 Bueter M, le Roux CW. Sir David Cuthbertson medal lecture Bariatric surgery as a model to study appetite control. *Proc Nutr Soc* 2009; **68**: 227-233.

40 Drapeau V, King N, Hetherington M, Doucet E, Blundell J, Tremblay A. Appetite sensations and satiety quotient: Predictors of energy intake and weight loss. *Appetite* 2007; **48**: 159-166.

- 41 King NA, Caudwell PP, Hopkins M, Stubbs JR, Näslund E, Blundell JE. Dual-process action of exercise on appetite control: Increase in orexigenic drive but improvement in meal-induced satiety. *Am J Clin Nutr* 2009; **90**: 921-927.
- 42 Wren AM, Bloom SR. Gut hormones and appetite control. *Gastroenterology* 2007; **132**: 2116-2130.
- 43 Salem V, Bloom SR. Approaches to the pharmacological treatment of obesity. *Expert Review of Clinical Pharmacology* 2010; **3**: 73-88.
- 44 Hagobian T, Braun B. Physical activity and hormonal regulation of appetite: Sex differences and weight control. *Exerc Sport Sci Rev* 2010; **38**: 25-30.
- 45 Doucet E, Cameron J. Appetite control after weight loss: What is the role of bloodborne peptides? *Appl Physiol Nutr Metab* 2007; **32**: 523-532.
- 46 Sepple CP, Read NW. Gastrointestinal correlates of the development of hunger in man. *Appetite* 1989; **13**: 183-191.
- 47 Bergmann JF, Chassany O, Petit A, Triki R, Caulin C, Segrestaa JM. Correlation between echographic gastric emptying and appetite: Influence of psyllium. *Gut* 1992; **33**: 1042-1043.
- 48 Nair NS, Brennan IM, Little TJ, Gentilcore D, Hausken T, Jones KL, Wishart JM, Horowitz M, Feinle-Bisset C. Reproducibility of energy intake, gastric emptying, blood glucose, plasma insulin and cholecystokinin responses in healthy young males. *Br J Nutr* 2009; **101**: 1094-1102.
- 49 Delgado-Aros S, Camilleri M, Cremonini F, Ferber I, Stephens D, Burton DD. Contributions of gastric volumes and gastric emptying to meal size and postmeal symptoms in functional dyspepsia. *Gastroenterology* 2004; **127**: 1685-1694.
- 50 Powley TL, Spaulding RA, Haglof SA. Vagal afferent innervation of the proximal gastrointestinal tract mucosa: Chemoreceptor and mechanoreceptor architecture. *J Comp Neurol* 2011; **519**: 644-660.
- 51 Näslund E, Hellström PM, Kral JG. The gut and food intake: An update for surgeons. *Journal of Gastrointestinal Surgery* 2001; **5**: 556-567.
- 52 Powley TL, Phillips RJ. Gastric satiation is volumetric, intestinal satiation is nutritive. *Physiol Behav* 2004; **82**: 69-74.
- 53 Grundy D. Neuroanatomy of visceral nociception: Vagal and splanchnic afferent. *Gut* 2002; **51**: 2-5.
- 54 Jones KL, Doran SM, Hveem K, Bartholomeusz FD, Morley JE, Sun WM, Chatterton BE, Horowitz M. Relation between postprandial satiation and antral area in normal subjects. *Am J Clin Nutr* 1997; **66**: 127-132.
- 55 Santangelo A, Peracchi M, Conte D, Fraquelli M, Porrini M. Physical state of meal affects gastric emptying, cholecystokinin release and satiety. *Br J Nutr* 1998; **80**: 521-527.
- 56 Beckoff K, MacIntosh CG, Chapman IM, Wishart JM, Morris HA, Horowitz M, Jones KL. Effects of glucose supplementation on gastric emptying, blood glucose homeostasis, and appetite in the elderly. *Am J Physiol Regul Integr Comp Physiol* 2001; **280**: 570-576.
- 57 Read N, French S, Cunningham K. The role of the gut in regulating food intake in man. *Nutr Rev* 1994; **52**: 1-10.

- 58 Savastano DM, Covasa M. Intestinal nutrients elicit satiation through concomitant activation of CCK1 and 5-HT3 receptors. *Physiol Behav* 2007; **92**: 434-442.
- 59 Cummings DE, Overduin J. Gastrointestinal regulation of food intake. *J Clin Invest* 2007; **117**: 13-23.
- 60 Buchan AM, Polak JM, Solcia E, Capella C, Hudson D, Pearse AG. Electron immunohistochemical evidence for the human intestinal I cell as the source of CCK. *Gut* 1978; **19**: 403-407.
- 61 Pilichiewicz AN, Chaikomin R, Brennan IM, Wishart JM, Rayner CK, Jones KL, Smout AJ, Horowitz M, Feinle-Bisset C. Load-dependent effects of duodenal glucose on glycemia, gastrointestinal hormones, antropyloroduodenal motility, and energy intake in healthy men. *Am J Physiol Endocrinol Metab* 2007; **293**: 743-753.
- 62 Schirra J, Katschinski M, Weidmann C, Schafer T, Wank U, Arnold R, Goke B. Gastric emptying and release of incretin hormones after glucose ingestion in humans. *J Clin Invest* 1996; **97**: 92-103.
- 63 Rudnicki M, Kuvshinoff BW, McFadden DW. Extrinsic neural contribution to ileal peptide YY (PYY) release. *J Surg Res* 1992; **52**: 591-595.
- 64 McFadden DW, Rudnicki M, Kuvshinoff B, Fischer JE. Postprandial peptide YY release is mediated by cholecystokinin. *Surg Gynecol Obstet* 1992; **175**: 145-150.
- 65 Lin HC, Taylor IL. Release of peptide YY by fat in the proximal but not distal gut depends on an atropine-sensitive cholinergic pathway. *Regul Pept* 2004; **117**: 73-76.
- 66 French SJ, Murray B, Rumsey RDE, Sepple CP, Read NW. Is cholecystokinin a satiety hormone? Correlations of plasma cholecystokinin with hunger, satiety and gastric emptying in normal volunteers. *Appetite* 1993; **21**: 95-104.
- 67 Nguyen NQ, Fraser RJ, Bryant LK, Chapman MJ, Wishart J, Holloway RH, Butler R, Horowitz M. The relationship between gastric emptying, plasma cholecystokinin, and peptide YY in critically ill patients. *Crit Care* 2007; **11**: R132.
- 68 Vazquez Roque MI, Camilleri M, Stephens DA, Jensen MD, Burton DD, Baxter KL, Zinsmeister AR. Gastric sensorimotor functions and hormone profile in normal weight, overweight, and obese people. *Gastroenterology* 2006; **131**: 1717-1724.
- 69 Camilleri M. Peripheral mechanisms in the control of appetite and related experimental therapies in obesity. *Regul Pept* 2009; **156**: 24-27.
- 70 Ritter RC. Gastrointestinal mechanisms of satiation for food. *Physiol Behav* 2004; **81**: 249-273.
- 71 Maljaars PWJ, Peters HPF, Mela DJ, Masclee AAM. Ileal brake: A sensible food target for appetite control. A review. *Physiol Behav* 2008; **95**: 271-281.
- 72 Levin F, Edholm T, Schmidt PT, Gryback P, Jacobsson H, Degerblad M, Hoybye C, Holst JJ, Rehfeld JF, Hällstrom PM, Näslund E. Ghrelin stimulates gastric emptying and hunger in normal-weight humans. *J Clin Endocrinol Metab* 2006; **91**: 3296-3302.
- 73 Heath R, Jones R, Frayn K, Robertson M. Vagal stimulation exaggerates the inhibitory ghrelin response to oral fat in humans. *J Endocrinol* 2004; **180**: 273-281.

- 74 Blom WAM, Lluch A, Vinoy S, Stafleu A, van den Berg R, Holst JJ, Kok FJ, Hendriks HFJ. Effects of gastric emptying on the postprandial ghrelin response. *Am J Physiol Endocrinol Metab* 2006; **290**: 389-395.
- 75 Näslund E, Hellström PM. Appetite signaling: From gut peptides and enteric nerves to brain. *Physiol Behav* 2007; **92**: 256-262.
- 76 Kissileff HR, Carretta JC, Geliebter A, Pi-Sunyer FX. Cholecystokinin and stomach distension combine to reduce food intake in humans. *Am J Physiol Regul Integr Comp Physiol* 2003; **285**: 992-998.
- 77 Oesch S, Ruegg C, Fischer B, Degen L, Beglinger C. Effect of gastric distension prior to eating on food intake and feelings of satiety in humans. *Physiol Behav* 2006; **87**: 903-910.
- 78 Shide D, Caballero B, Reidelberger R, Rolls B. Accurate energy compensation for intragastric and oral nutrients in lean males. *Am J Clin Nutr* 1995; **61**: 754-764.
- 79 Little TJ, Russo A, Meyer JH, Horowitz M, Smyth DR, Bellon M, Wishart JM, Jones KL, Feinle-Bisset C. Free fatty acids have more potent effects on gastric emptying, gut hormones, and appetite than triacylglycerides. *Gastroenterology* 2007; **133**: 1124-1131.
- 80 Rolls BJ, Kim S, McNelis AL, Fischman MW, Foltin RW, Moran TH. Time course of effects of preloads high in fat or carbohydrate on food intake and hunger ratings in humans. *Am J Physiol* 1991; **260**: 756-763.
- 81 French S, Read N. Effect of guar gum on hunger and satiety after meals of differing fat content: Relationship with gastric emptying. *Am J Clin Nutr* 1994; **59**: 87-91.
- 82 Liddle RA. Cholecystokinin cells. *Annu Rev Physiol* 1997; **59**: 221-242.
- 83 Foster-Schubert KE, Overduin J, Prudom CE, Liu J, Callahan HS, Gaylann BD, Thorner MO, Cummings DE. Acyl and total ghrelin are suppressed strongly by ingested proteins, weakly by lipids, and biphasically by carbohydrates. *J Clin Endocrinol Metab* 2008; **93**: 1971-1979.
- 84 Boyd KA, O'Donovan DG, Doran S, Wishart J, Chapman IM, Horowitz M, Feinle C. High-fat diet effects on gut motility, hormone, and appetite responses to duodenal lipid in healthy men. *Am J Physiol Gastrointest Liver Physiol* 2003; **284**: G188-196.
- 85 Beglinger C, Degen L. Gastrointestinal satiety signals in humans - physiologic roles for GLP-1 and PYY? *Physiol Behav* 2006; **89**: 460-464.
- 86 Adrian TE, Ferri GL, Bacarese-Hamilton AJ, Fuessl HS, Polak JM, Bloom SR. Human distribution and release of a putative new gut hormone, peptide YY. *Gastroenterology* 1985; **89**: 1070-1077.
- 87 Cummings DE, Overduin J, Foster-Schubert KE. Gastric bypass for obesity: Mechanisms of weight loss and diabetes resolution. *J Clin Endocrinol Metab* 2004; **89**: 2608-2615.
- 88 Näslund I, Beckman K-W. Gastric emptying rate after gastric bypass and gastroplasty. *Scand J Gastroenterol* 1987; **22**: 193 - 201.
- 89 Horowitz M, Cook DJ, Collins PJ, Harding PE, Hooper MJ, Walsh JF, Shearman DJ. Measurement of gastric emptying after gastric bypass surgery using radionuclides. *Br J Surg* 1982; **69**: 655-657.

- 90 Horowitz M, Collins PJ, Harding PE, Shearman DJ. Gastric emptying after gastric bypass. *Int J Obes* 1986; **10**: 117-121.
- 91 Näslund E, Gryback P, Backman L, Jacobsson H, Juul J, Theodorsson HE, Hällstrom PM. Distal small bowel hormones: Correlation with fasting antroduodenal motility and gastric emptying. *Dig Dis Sci* 1998; **43**: 945-952.
- 92 Näslund E, Gryback P, Hällstrom PM, Jacobsson H, Holst JJ, Theodorsson E, Backman L. Gastrointestinal hormones and gastric emptying 20 years after jejunoileal bypass for massive obesity. *Int J Obes Relat Metab Disord* 1997; **21**: 387-392.
- 93 Kral JG, Näslund E. Surgical treatment of obesity. *Nat Clin Pract End Met* 2007; **3**: 574-583.
- 94 Tice JA, Karliner L, Walsh J, Petersen AJ, Feldman MD. Gastric banding or bypass? A systematic review comparing the two most popular bariatric procedures. *Am J Med* 2008; **121**: 885-893.
- 95 Buchwald H, Avidor Y, Braunwald E, Jensen MD, Pories W, Fahrenbach K, Schoelles K. Bariatric surgery: A systematic review and meta-analysis. *JAMA* 2004; **292**: 1724-1737.
- 96 le Roux CW, Aylwin SJ, Batterham RL, Borg CM, Coyle F, Prasad V, Shurey S, Gbatei MA, Patel AG, Bloom SR. Gut hormone profiles following bariatric surgery favor an anorectic state, facilitate weight loss, and improve metabolic parameters. *Ann Surg* 2006; **243**: 108-114.
- 97 Bose M, Machineni S, Olivan B, Teixeira J, McGinty JJ, Bawa B, Koshy N, Colarusso A, Laferrere B. Superior appetite hormone profile after equivalent weight loss by gastric bypass compared to gastric banding. *Obesity* 2010; **18**: 1085-1091.
- 98 de Jong JR, van Ramshorst B, Gooszen HG, Smout AJ, Tiel-Van Buul MM. Weight loss after laparoscopic adjustable gastric banding is not caused by altered gastric emptying. *Obes Surg* 2009; **19**: 287-292.
- 99 Burton PR, Yap K, Brown WA, Laurie C, O'Donnell M, Hebbard G, Kalff V, O'Brien PE. Effects of adjustable gastric bands on gastric emptying, supra- and infraband transit and satiety: A randomized double-blind crossover trial using a new technique of band visualization. *Obes Surg* 2010; **20**: 1690-1697.
- 100 Usinger L, Hansen KB, Kristiansen VB, Larsen S, Holst JJ, Knop FK. Gastric emptying of orally administered glucose solutions and incretin hormone responses are unaffected by laparoscopic adjustable gastric banding. *Obes Surg* 2011; **21**: 625-632.
- 101 Braghetto I, Davanzo C, Korn O, Csendes A, Valladares H, Herrera E, Gonzalez P, Papapietro K. Scintigraphic evaluation of gastric emptying in obese patients submitted to sleeve gastrectomy compared to normal subjects. *Obes Surg* 2009; **19**: 1515-1521.
- 102 Bernstine H, Tzioni-Yehoshua R, Groshar D, Beglaibter N, Shikora S, Rosenthal RJ, Rubin M. Gastric emptying is not affected by sleeve gastrectomy - scintigraphic evaluation of gastric emptying after sleeve gastrectomy without removal of the gastric antrum. *Obes Surg* 2009; **19**: 293-298.
- 103 Hasler WL. Methods of gastric electrical stimulation and pacing: A review of their benefits and mechanisms of action in gastroparesis and obesity. *Neurogastroenterol Motil* 2009; **21**: 229-243.

- 104 Liu J, Hou X, Song G, Cha H, Yang B, Chen JDZ. Gastric electrical stimulation using endoscopically placed mucosal electrodes reduces food intake in humans. *Am J Gastroenterol* 2006; **101**: 798-803.
- 105 Sanmiguel C, Haddad W, Aviv R, Cunneen S, Phillips E, Kapella W, Soffer E. The TANTALUS™ system for obesity: Effect on gastric emptying of solids and ghrelin plasma levels. *Obes Surg* 2007; **17**: 1503-1509.
- 106 Bohdjalian A, Prager G, Aviv R, Policker S, Schindler K, Kretschmer S, Riener R, Zacherl J, Ludvik B. One-year experience with TANTALUS™: A new surgical approach to treat morbid obesity. *Obes Surg* 2006; **16**: 627-634.
- 107 Vazquez Roque MI, Camilleri M, Clark MM, Tepoel DA, Jensen MD, Graszer KM, Kalsy SA, Burton DD, Baxter KL, Zinsmeister AR. Alteration of gastric functions and candidate genes associated with weight reduction in response to sibutramine. *Clin Gastroenterol Hepatol* 2007; **5**: 829-837.
- 108 Näslund E, King N, Mansten S, Adner N, Holst JJ, Gutniak M, Hellström PM. Prandial subcutaneous injections of glucagon-like peptide-1 cause weight loss in obese human subjects. *Br J Nutr* 2004; **91**: 439-446.
- 109 Linnebjerg H, Park S, Kothare PA, Trautmann ME, Mace K, Fineman M, Wilding I, Nauck M, Horowitz M. Effect of exenatide on gastric emptying and relationship to postprandial glycemia in type 2 diabetes. *Regul Pept* 2008; **151**: 123-129.
- 110 DeFronzo RA, Okerson T, Viswanathan P, Guan X, Holcombe JH, MacConell L. Effects of exenatide versus sitagliptin on postprandial glucose, insulin and glucagon secretion, gastric emptying, and caloric intake: A randomized, cross-over study. *Curr Med Res Opin* 2008; **24**: 2943-2952.
- 111 Samsom M, Szarka LA, Camilleri M, Vella A, Zinsmeister AR, Rizza RA. Pramlintide, an amylin analog, selectively delays gastric emptying: Potential role of vagal inhibition. *Am J Physiol Gastrointest Liver Physiol* 2000; **278**: G946-951.
- 112 Samsom M, Bharucha A, Gerich JE, Herrmann K, Limmer J, Linke R, Maggs D, Schirra J, Vella A, Wörle H-J, Göke B. Diabetes mellitus and gastric emptying: Questions and issues in clinical practice. *Diabetes Metab Res Rev* 2009; **25**: 502-514.
- 113 Witte AB, Grybäck P, Holst JJ, Hilsted L, Hellström PM, Jacobsson H, Schmidt PT. Differential effect of PYY1-36 and PYY3-36 on gastric emptying in man. *Regul Pept* 2009; **158**: 57-62.
- 114 Smith SR, Blundell JE, Burns C, Ellero C, Schroeder BE, Kesty NC, Chen KS, Halseth AE, Lush CW, Weyer C. Pramlintide treatment reduces 24-h caloric intake and meal sizes and improves control of eating in obese subjects: A 6-wk translational research study. *Am J Physiol Endocrinol Metab* 2007; **293**: 620-627.
- 115 Näslund E, Bogefors J, Skogar S, Grybäck P, Jacobsson H, Holst JJ, Hellström PM. GLP-1 slows solid gastric emptying and inhibits insulin, glucagon, and PYY release in humans. *Am J Physiol Regul Integr Comp Physiol* 1999; **277**: 910-916.
- 116 Juhl CB, Hollingdal M, Sturis J, Jakobsen G, Agersø H, Veldhuis J, Pørksen N, Schmitz O. Bedtime administration of nn2211, a long-acting GLP-1 derivative, substantially reduces fasting and postprandial glycemia in type 2 diabetes. *Diabetes* 2002; **51**: 424-429.

- 117 Esfandyari T, Camilleri M, Ferber I, Burton D, Baxter K, Zinsmeister A. Effect of a cannabinoid agonist on gastrointestinal transit and postprandial satiation in healthy human subjects: A randomized, placebo-controlled study. *Neurogastroenterol Motil* 2006; **18**: 831-838.
- 118 Torra S, Ilzarbe L, Malagelada JR, Negre M, Mestre-Fusco A, Aguade-Bruix S, Florensa E, Sune P, Gras B, Hernandez JJ, Casamitjana R, Garcia MA, Ros FB, Delgado-Aros S. Meal size can be decreased in obese subjects through pharmacological acceleration of gastric emptying (the oberyth trial). *Int J Obes* 2010: [Epub ahead of print].
- 119 Delgado-Aros S, Camilleri M, Castillo EJ, Cremonini F, Stephens D, Ferber I, Baxter K, Burton D, Zinsmeister AR. Effect of gastric volume or emptying on meal-related symptoms after liquid nutrients in obesity: A pharmacologic study. *Clin Gastroenterol Hepatol* 2005; **3**: 997-1006.
- 120 Smith DS, Ferris CD. Current concepts in diabetic gastroparesis. *Drugs* 2003; **63**: 1339-1358.
- 121 MacIntosh CG, Morley JE, Wishart J, Morris H, Jansen JBMJ, Horowitz M, Chapman IM. Effect of exogenous cholecystokinin (CCK)-8 on food intake and plasma CCK, leptin, and insulin concentrations in older and young adults: Evidence for increased CCK activity as a cause of the anorexia of aging. *J Clin Endocrinol Metab* 2001; **86**: 5830-5837.
- 122 Chapman I, Parker B, Doran S, Feinle-Bisset C, Wishart J, Lush CW, Chen K, LaCerte C, Burns C, McKay R, Weyer C, Horowitz M. Low-dose pramlintide reduced food intake and meal duration in healthy, normal-weight subjects. *Obesity* 2007; **15**: 1179-1186.
- 123 Edwards CMB, Stanley SA, Davis R, Brynes AE, Frost GS, Seal LJ, Ghatei MA, Bloom SR. Exendin-4 reduces fasting and postprandial glucose and decreases energy intake in healthy volunteers. *Am J Physiol Endocrinol Metab* 2001; **281**: E155-161.
- 124 Verdich C, Madsen JL, Toubro S, Buemann B, Holst JJ, Astrup A. Effect of obesity and major weight reduction on gastric emptying. *Int J Obes Relat Metab Disord* 2000; **24**: 899-905.
- 125 Tosetti C, Corinaldesi R, Stanghellini V, Pasquali R, Corbelli C, Zoccoli G, Di Febo G, Monetti N, Barbara L. Gastric emptying of solids in morbid obesity. *Int J Obes Relat Metab Disord* 1996; **20**: 200-205.
- 126 Corvilain B, Abramowicz M, Fery F, Schoutens A, Verlinden M, Balasse E, Horowitz M. Effect of short-term starvation on gastric emptying in humans: Relationship to oral glucose tolerance. *Am J Physiol* 1995; **269**: G512-517.
- 127 Hutson WR, Wald A. Obesity and weight reduction do not influence gastric emptying and antral motility. *Am J Gastroenterol* 1993; **88**: 1405-1409.
- 128 Shimamoto C, Hirata I, Hiraike Y, Takeuchi N, Nomura T, Katsu K-I. Evaluation of gastric motor activity in the elderly by electrogastrography and the [13]C-acetate breath test. *Gerontology* 2002; **48**: 381-386.
- 129 Carrio I, Estorch M, Serra-Grima R, Ginjaume M, Notivol R, Calabuig R, Vilardell F. Gastric emptying in marathon runners. *Gut* 1989; **30**: 152-155.
- 130 Horner K, Harrington D, Donnelly AE, Shafat A. The association of body mass index with gastric emptying and effect of an exercise intervention on gastric emptying and appetite in adolescent girls. *Journal of Physiology Proceedings of the Physiological Society* 2010; **18** PC29.

- 131 MATHUS-VLIEGEN EM, VAN IERLAND-VAN LEEUWEN ML, BENNINK RJ. Influences of fat restriction and lipase inhibition on gastric emptying in obesity. *Int J Obes* 2006; **30**: 1203-1210.
- 132 WRIGHT RA, KRINSKY S, FLEEMAN C, TRUJILLO J, TEAGUE E. Gastric emptying and obesity. *Gastroenterology* 1983; **84**: 747-751.
- 133 VERDICH C, TOUBRO S, BUEMANN B, LYSRGARD MADSEN J, JUUL HOLST J, ASTRUP A. The role of postprandial releases of insulin and incretin hormones in meal-induced satiety - effect of obesity and weight reduction. *Int J Obes Relat Metab Disord* 2001; **25**: 1206-1214.
- 134 DOUCET E, POMERLEAU M, HARPER M. Pre- and postprandial levels of total PYY are decreased in response to a short-term energy restriction. *Obes Res* 2004; **12**: A114.
- 135 ADAM TC, JOCKEN J, WESTERTEP-PLANTENGA MS. Decreased glucagon-like peptide 1 release after weight loss in overweight/obese subjects. *Obes Res* 2005; **13**: 710-716.
- 136 MORAN LJ, NOAKES M, CLIFTON PM, WITTERT GA, LE ROUX CW, GHATEI MA, BLOOM SR, NORMAN RJ. Postprandial ghrelin, cholecystokinin, peptide YY, and appetite before and after weight loss in overweight women with and without polycystic ovary syndrome. *Am J Clin Nutr* 2007; **86**: 1603-1610.
- 137 ESSAH PA, LEVY JR, SISTRUN SN, KELLY SM, NESTLER JE. Effect of weight loss by a low-fat diet and a low-carbohydrate diet on peptide YY levels. *Int J Obes* 2010; **34**: 1239-1242.
- 138 CHANOINE, JEAN-PIERRE, MACKELVIE, J. K, BARR, I. S, WONG, K. AC, MENEILLY, S. G, ELAHI, H. D. GLP-1 and appetite responses to a meal in lean and overweight adolescents following exercise. *Obesity (Silver Spring)* 2008; **16**: 202-204.
- 139 MACKELVIE KJ, MENEILLY GS, ELAHI D, WONG AC, BARR SI, CHANOINE JP. Regulation of appetite in lean and obese adolescents after exercise: Role of acylated and desacyl ghrelin. *J Clin Endocrinol Metab* 2007; **92**: 648-654.
- 140 HURLEY RS, BOSSETTI BM, O'DORISIO TM, TENISON EB, WELCH MA, RICE RR. The effect of exercise training on body weight and peptide hormone patterns in normal weight college-age men. *J Sports Med Phys Fitness* 1991; **31**: 52-56.
- 141 HOLT S, FORD MJ, GRANT S, HEADING RC. Abnormal gastric emptying in primary anorexia nervosa. *Br J Psychiatry* 1981; **139**: 550-552.
- 142 RIGAUD D, BEDIG G, MERROUCHE M, VULPILLAT M, BONFILS S, APFELBAUM M. Delayed gastric emptying in anorexia nervosa is improved by completion of a renutrition program. *Dig Dis Sci* 1988; **33**: 919-925.
- 143 ROBINSON PH, CLARKE M, BARRETT J. Determinants of delayed gastric emptying in anorexia nervosa and bulimia nervosa. *Gut* 1988; **29**: 458-464.
- 144 DUBOIS A, GROSS HA, EBERT MH, CASTELL DO. Altered gastric emptying and secretion in primary anorexia nervosa. *Gastroenterology* 1979; **77**: 319-323.
- 145 LIEVERSE RJ, VAN SETERS AP, JANSEN JB, LAMERS CB. Relationship between hunger and plasma cholecystokinin during weight reduction with a very low calorie diet. *Int J Obes Relat Metab Disord* 1993; **17**: 177-179.
- 146 MAUGHAN RJ. Fluid and electrolyte loss and replacement in exercise. *J Sports Sci* 1991; **9**: 117-142.

- 147 Hellenbrandt FA, Tepper RH. Studies on the influence of exercise on the digestive work of the stomach. Its effect on emptying time. *Am J Physiol* 1934; **107**: 355-363.
- 148 Fordtran JS, Saltin B. Gastric emptying and intestinal absorption during prolonged severe exercise. *J Appl Physiol* 1967; **23**: 331-335.
- 149 Ramsbottom SJ, Hunt JN. Effect of exercise on gastric emptying and gastric secretion. *Digestion* 1974; **10**: 1-8.
- 150 Neuffer PD, Young AJ, Sawka MN. Gastric emptying during walking and running: Effects of varied exercise intensity. *Eur J Appl Physiol* 1989; **58**: 440-445.
- 151 Marzio L, Formica P, Fabiani F, Lapenna D, Vecchiè L, Cuccurullo F. Influence of physical activity on gastric emptying of liquids in normal human subjects. *Am J Gastroenterol* 1991; **86**: 1433-1436.
- 152 Leiper JB, Broad NP, Maughan RJ. Effect of intermittent high-intensity exercise on gastric emptying in man. *Med Sci Sports Exerc* 2001; **33**: 1270-1278.
- 153 Leiper JB, Nicholas CW, Ali A, Williams C, Maughan RJ. The effect of intermittent high-intensity running on gastric emptying of fluids in man. *Med Sci Sports Exerc* 2005; **37**: 240-247.
- 154 Costill DL, Saltin B. Factors limiting gastric emptying during rest and exercise. *J Appl Physiol* 1974; **37**: 679-683.
- 155 Feldman M, Nixon JV. Effect of exercise on postprandial gastric secretion and emptying in humans. *J Appl Physiol* 1982; **53**: 851-854.
- 156 Cammack J, Read NW, Cann PA, Greenwood B, Holgate AM. Effect of prolonged exercise on the passage of a solid meal through the stomach and small intestine. *Gut* 1982; **23**: 957-961.
- 157 Neuffer PD, Costill DL, Fink WJ, Kirwan JP, Fielding RA, Flynn MG. Effects of exercise and carbohydrate composition on gastric emptying. *Med Sci Sports Exerc* 1986; **18**: 658-662.
- 158 Harris A, Lindeman AK, Martin BJ. Rapid orocecal transit in chronically active persons with high energy intake. *J Appl Physiol* 1991; **70**: 1550-1553.
- 159 Little TJ, Horowitz M, Feinle-Bisset C. Modulation by high-fat diets of gastrointestinal function and hormones associated with the regulation of energy intake: Implications for the pathophysiology of obesity. *Am J Clin Nutr* 2007; **86**: 531-541.
- 160 Long SJ, Hart K, Morgan LM. The ability of habitual exercise to influence appetite and food intake in response to high- and low-energy preloads in man. *Br J Nutr* 2002; **87**: 517-523.
- 161 Van Walleghen EL, Orr JS, Gentile CL, Davy KP, Davy BM. Habitual physical activity differentially affects acute and short-term energy intake regulation in young and older adults. *Int J Obes* 2007; **31**: 1277-1285.
- 162 Duval K, Strychar I, Cyr M-J, Prud'homme D, Rabasa-Lhoret R, Doucet E. Physical activity is a confounding factor of the relation between eating frequency and body composition. *Am J Clin Nutr* 2008; **88**: 1200-1205.
- 163 Koda S, Date Y, Murakami N, Shimbara T, Hanada T, Toshinai K, Nijijima A, Furuya M, Inomata N, Osuye K, Nakazato M. The role of the vagal nerve in peripheral PYY3-36-induced feeding reduction in rats. *Endocrinology* 2005; **146**: 2369-2375.

- 164 Nakabayashi H, Nishizawa M, Nakagawa A, Takeda R, Nijima A. Vagal hepatopancreatic reflex effect evoked by intraportal appearance of GLP-1. *Am J Physiol* 1996; **271**: 808-813.
- 165 Ziessman HA, Bonta DV, Goetze S, Ravich WJ. Experience with a simplified, standardized 4-hour gastric-emptying protocol. *J Nucl Med* 2007; **48**: 568-572.
- 166 Kong F, Singh RP. Disintegration of solid foods in human stomach. *J Food Sci* 2008; **73**: 67-R80.
- 167 Borgström B, Dahlqvist A, Lundh G, Sjövall J. Studies of intestinal digestion and absorption in the human. *J Clin Invest* 1957; **36**: 1521-1536.
- 168 Näslund E, Hellström PM. Drug targets modulating the gut-appetite-metabolism axis. *Drug Discovery Today: Therapeutic Strategies* 2007; **4**: 189-193.
- 169 Wood NJ. Nutrition: Pharmacologically accelerating gastric emptying can reduce the calorie intake of obese individuals. *Nat Rev Gastroenterol Hepatol* 2011; **8**: 1.
- 170 Poortvliet PC, Bérubé-Parent S, Drapeau V, Lamarche B, Blundell JE, Tremblay A. Effects of a healthy meal course on spontaneous energy intake, satiety and palatability. *Br J Nutr* 2007; **97**: 584-590.
- 171 Geraedts MCP, Troost FJ, Saris WHM. Gastrointestinal targets to modulate satiety and food intake. *Obes Rev* 2011; **35**: 829-837.
- 172 Willbond SM, Doucet E. Individually timing high-protein preloads has no effect on daily energy intake, peptide YY and glucagon-like peptide-1. *Eur J Clin Nutr* 2011; **65**: 55-62.
- 173 King NA, Hopkins M, Caudwell P, Stubbs RJ, Blundell JE. Beneficial effects of exercise: Shifting the focus from body weight to other markers of health. *Br J Sports Med* 2009; **43**: 924-927.
- 174 Chaput JP, Klingenberg L, Rosenkilde M, Gilbert JA, Tremblay A, Sjodin A. Physical activity plays an important role in body weight regulation. *J Obes* 2011; **2011**: pii: 360257. Epub 362010.
- 175 Mayer J, Roy P, Mitra KP. Relation between caloric intake, body weight, and physical work: Studies in an industrial male population in west bengal. *Am J Clin Nutr* 1956; **4**: 169-175.
- 176 Blundell JE, Stubbs RJ, Hughes DA, Whybrow S, King NA. Cross talk between physical activity and appetite control: Does physical activity stimulate appetite? *Proc Nutr Soc* 2003; **62**: 651-661.
- 177 Hopkins M, King NA, Blundell JE. Acute and long-term effects of exercise on appetite control: Is there any benefit for weight control? *Curr Opin Clin Nutr Metab Care* 2010; **13**: 635-640.
- 178 Blundell JE, King NA. Physical activity and regulation of food intake: Current evidence. *Med Sci Sports Exerc* 1999; **31**: S573-S583.
- 179 Blundell JE, King NA. Effects of exercise on appetite control: Loose coupling between energy expenditure and energy intake. *Int J Obes Relat Metab Disord* 1998; **22**: 22-29.
- 180 King NA, Hopkins M, Caudwell P, Stubbs RJ, Blundell JE. Individual variability following 12 weeks of supervised exercise: Identification and characterization of compensation for exercise-induced weight loss. *Int J Obes* 2008; **32**: 177-184.
- 181 Caudwell P, Hopkins M, King NA, Stubbs RJ, Blundell JE. Exercise alone is not enough: Weight loss also needs a healthy (mediterranean) diet? *Public Health Nutr* 2009; **12**: 1663-1666.

- 182 Chaput J-P, Pelletier C, Després J-P, Lemieux S, Tremblay A. Metabolic and behavioral vulnerability related to weight regain in reduced-obese men might be prevented by an adequate diet-exercise intervention. *Appetite* 2007; **49**: 691-695.
- 183 Smith GP. Cholecystokinin and treatment of meal size: Proof of principle. *Obesity* 2006; **14**: S168-S170.
- 184 King NA. What processes are involved in the appetite response to moderate increases in exercise-induced energy expenditure? *Proc Nutr Soc* 1999; **58**: 107-113.
- 185 Chan JL, Mun EC, Stoyneva V, Mantzoros CS, Goldfine AB. Peptide YY levels are elevated after gastric bypass surgery. *Obesity (Silver Spring)* 2006; **14**: 194-198.
- 186 Blundell JE. Perspective on the central control of appetite. *Obesity (Silver Spring)* 2006; **14**: 160S-163S.

List of Tables and Figures:

Table 1. A summary of studies examining the effects of bariatric surgeries on gastric emptying

Table 2. A summary of studies examining the effects of lifestyle interventions on gastric emptying

Table 3. A summary of studies examining the effects of lifestyle interventions on fasting and postprandial appetite gut peptides

Figure 1. A hypothetical model of the relative contributions of gastric distension, cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1), peptide YY (PYY) and ghrelin (all episodic signals influenced by gastric emptying) to satiation and satiety.

Figure 2. A model to describe how chronic physical activity could potentially impact on gastric emptying, appetite regulation and energy balance

Table 1 A summary of studies examining the effects of bariatric surgeries on gastric emptying

Procedure	Reference	Weight Loss*	Study design/intervention	Initial GE (outcome)	Overall GE (outcome)
Gastric Bypass	Horowitz et al. (1982) (89)	23 ± 3kg	Cross section of patients (n = 12) 12 months after bypass compared to non-operated controls (n = 11)	faster liquid (t_{lag} , % remaining at 5min, 10min), solid slower except faster in 4 subjects(t_{lag})	faster liquid ($t_{1/2}$). solid slower except faster in 4 subjects ($t_{1/2}$, % remaining at 50, 100min)
Jejunioileal Bypass	Näslund et al. (1997) (92)	44 ± 4 to 31 ± 4 kg/m ²	Cross section of JIB operated subjects 20 +/- 3 yrs ago (n = 7) compared to non-operated obese controls (n = 7)	unchanged (t_{lag})	unchanged ($t_{1/2}$, % remaining at 60, 90, 120 min)
	Näslund et al. (1998) (91)	42 ± 4 to 31 ± 4 kg/m ²	GE measured pre and 9 months post surgery (n = 9)	slower (t_{lag})	slower ($t_{1/2}$)
Roux-en-Y Gastric Bypass	Morignio et al. (2006) (11)	15.4 ± 6.3kg	GE measured pre and 6 weeks post RYGB (n = 9)	faster (AUC ₀₋₆₀)	faster (AUC ₀₋₆₀)
	Akkary et al. (2008) (9)	50.6kg weight loss in those with faster initial GE compared to 47.3kg in those with slower	Comparison of weight loss in those with slower (n = 116) and faster initial (n = 188) emptying at 1 day postoperative at 1 year follow up	faster initial GE (30min) 1 day postoperatively associated with greater weight loss at 1 year	-
	Falkén et al. (2011) (12)	45.5 ± 1.9 (preoperative) to 38.6 ± 1.8 (at 2 months) to 30.3 ± 1.8 (at 1 year) kg/m ² .	GE measured pre and 3 days, 2 months and 1 yr post RYGB (n = 12)	Faster (acetaminophen absorption peak time)	Faster (acetaminophen absorption $t_{1/2}$)
Sleeve Gastrectomy	Shah et al. (2010) (14)	-	Cross section of morbidly obese non operated type 2 diabetics (n = 20), morbidly obese type 2 diabetics operated with SG (n = 23), lean controls (n = 24)	-	faster ($t_{1/2}$) in operated
	Melissas (2008) (10)	Mean group weight: 140 (preoperative) to 101 (at 6 months) to 89 (at 24 months) kg.	GE measured pre surgery, 6 and 24 months after SG (n = 9)	faster (t_{lag}) at 6 and 24months compared to pre-surgery	faster ($t_{1/2}$, % GE rate) at 6 and 24months compared to pre-surgery
	Braghetto et al (2009) (101)	-	Cross section of obese subjects 3 months after SG (n = 20) compared to normal controls (n = 18)	faster (% remaining at 20, 30, 60 min) in operated	faster ($t_{1/2}$) in operated

	Bernstine et al. (2009) (102)	125 ± 25 to 99 ± 22 kg	GE measured pre surgery and 3 months post SG (n = 21)	faster (% remaining at 30min)	unchanged ($t_{1/2}$, % remaining at 1,2,3,4h)
Gastric Banding	de Jong et al. (2008) (98)	47.8 to 41.7 kg/m ²	GE measured pre surgery and 16 months post gastric banding (n = 16)	unchanged (t_{lag})	unchanged (GE rate (%/h))
	Burton et al. (2010) (99)	143.3 ± 25.5 to 96.3 ± 18.2 kg	Cross over design. 2 GE studies: One with the LAGB at its optimal volume and another with 1 ml within the LAGB (n = 14 patients who had achieved >50% weight loss > 12 months post surgery).	not tested	unchanged ($t_{1/2}$)
	Usinger et al. (2011) (100)	125 ± 8 to 121 ± 8 kg	GE measured pre and 6 weeks post LAGB (n = 8 obese with and without impaired glucose tolerance).	unchanged (acetaminophen absorption peak time)	unchanged (acetaminophen absorption AUC).
BPD-DS	Hedberg et al. (2011) (15)	51.7 to 31.1 kg/m ²	20 patients having undergone BPD-DS in median 3.5 yrs previously compared to previous normal GE data in the same lab	faster (t_{lag}) in operated	faster ($t_{1/2}$) in operated

* Weight Loss in units reported in original paper. AUC: area under curve; BPDS: biliopancreatic diversion with duodenal switch; GE: gastric emptying; LAGB: laparoscopic gastric band; JIB: Jejunioileal bypass; SG: sleeve gastrectomy; t_{lag} : lag time; $t_{1/2}$: half time.

Table 2 A summary of studies examining the effects of lifestyle interventions on gastric emptying

Lifestyle Factor	Reference	Weight Loss*	Study design/intervention	Initial GE (outcome)	Overall GE (outcome)
Diet	Verdich et al. (2000) (124)	18.8kg, 14.8%	8 wks formula (4.2 MJ p/d), 8 wks restriction (6.3 MJ p/d) followed by 8 wks weight maintenance (n = 19 obese)	slower (t_{lag})	unchanged (total 4h emptying time)
	Tosetti et al. (1996) (125)	10%	parallel study of 4 month energy restriction with or without intragastric balloon (n = 20 obese)	slower	slower (overall emptying rate)
	Corvilain et al. (1995) (126)	-	GE measured after 12hour and 4day fast (n = 12 normal weight, n = 11 obese)	faster (t_{lag})	slower ($t_{1/2}$, in both groups)
	Hutson et al. (1993) (127)	13.7kg, 8.3%	3-4 wks of a 100kcal p/d diet. GE tested 2 days after the normal diet had been reinstated (n = 8 obese)	unchanged (t_{lag})	unchanged ($t_{1/2}$)
Exercise	Shimamoto et al. (2002) (128)	-	cross section of active (n = 7) and inactive (n = 7) elderly individuals	faster in active (time of peak $^{13}CO_2$ concentration)	faster in active (time of peak $^{13}CO_2$ concentration)
	Carrio et al. (1989) (129)	-	cross section of marathon runners (n = 9) and sedentary (n = 9) males	faster in marathon runners (t_{lag})	faster in marathon runners ($t_{1/2}$)
	Horner et al. (2010) (130)	↔	intervention of 3x40 min moderate intensity exercise classes p/wk (n = 9 adolescent girls) compared to a control group (n = 10).	unchanged (t_{lag} , t_{lat})	unchanged ($t_{1/2}$, t_{asc})
Combined Diet and Exercise	Mathus Vliegen et al. (2006) (131)	10.4kg, 9.9%	1 year of daily energy deficit of 2.3MJ (an energy- and fat-restricted diet), exercise (advice on increasing leisure activity and optional aerobics classes), behavioral modification and placebo tablets (n = 9)	unchanged (t_{lag})	slower (emptying rate (%/h)), unchanged ($t_{1/2}$)
	Mathus Vliegen et al. (2006)	3.5kg	2 months of same intervention above (n = 14)	unchanged (t_{lag})	unchanged ($t_{1/2}$), (%/h)
	Mathus Vliegen et al. (2006)	2.3kg	4 weeks of same intervention above (n = 42)	unchanged (t_{lag})	unchanged ($t_{1/2}$), (%/h)
	Wright et al. (1983) (132)	-	undefined intervention - subjects who lost weight during the 18 month study period underwent a second GE test (n = 4 obese)	unchanged (% remaining in the stomach)	unchanged ($t_{1/2}$, % remaining in the stomach)

* Weight Loss in units reported in original paper. GE: gastric emptying; t_{lat} : latency time; t_{asc} : ascension time t_{lag} : lag time; $t_{1/2}$: half time.

Table 3 A summary of studies examining the effects of lifestyle interventions on fasting and postprandial appetite gut peptides

Lifestyle Factor	Reference	Weight Loss*	Study design/intervention	Fasting gut peptides	Postprandial gut peptides
Diet	Verdich et al. (2001) (133)	18.8kg, 14.8%	pre and post 8 wks formula (4.2 MJ p/d), 8 wks restriction (6.3 MJ p/d) followed by 8 wks weight maintenance (n = 19 obese)	GIP ↓, GLP-1 ↔	GIP ↓, GLP-1 ↑
	Cummings et al. (2002) (24)	17.3kg, 17.4%	3 months diet-induced weight loss followed by 3 months maintenance at reduced weight (n = 13 obese)	ghrelin ↑	ghrelin ↑
	Doucet et al. (2004) (134)	-	4 day energy restriction of 25% energy intake	PYY ↓	PYY ↓
	Adam et al. (2005) (135)	6.1kg	pre and post 6 wk very low energy diet (n = 32 obese)	GLP-1 ↔ (trend to ↓),	GLP-1 ↓,
	Moran et al. (2007) (136)	4.2 ± 3.9kg	pre and post 8 wks energy restriction (deficit of ~ 30%, intake), (n = 14 with PCOS, n = 14 controls)	ghrelin, PYY, CCK ↔	PYY, CCK, ghrelin ↔
	Lafferere et al. (2008) (25)	9.8kg	pre and post 55 +/- 9.9 days energy restriction (1000 kcal/d meal replacement plan) (n = 10 obese)	GIP ↔, GLP-1 ↔	GIP ↔, GLP-1 ↔
	Chearskul et al. (2008) (26)	17.9kg, 15%,	pre and post 8wks after restriction of approx 1800kj/d and 1 week of maintenance (n = 12 obese)	CCK ↔	CCK ↓ (30min)
	Olivan et al. (2009) (22)	10kg	Pre and post meal replacement plan 1000 kcal p/d. Post measurements after 10kg weight loss (55.0 ± 9.9 days) (n = 10 obese)	ghrelin ↑, PYY ↔	PYY ↔, ghrelin ↔
Essah et al. (2010) (137)	5.8kg (LF), 1.0kg (LCHO)	Pre and post 8 wks energy restricted (-500kcal p/d) low fat (LF) or low CHO diet (LCHO) (n = 30 obese)	PYY ↓(following both diets)	PYY ↓(following both diets)	
Exercise	Chanoine et al. (2008) (138)	↔	Pre and post 1h p/d aerobic exercise (65-75%HRmax) for 5 days, (n = 34 normal and overweight adolescent boys)	GLP-1 ↔	GLP-1 ↑ (30 min)
	MacKelvie et al. (2007) (139)	↔	Pre and post 1h p/d aerobic exercise (65-75%HRmax) for 5 days, (n = 34 normal and overweight adolescent boys)	total ghrelin ↔, AG ↑, DG ↔	total ghrelin ↔, AG ↑, DG (in normal weight) ↓, DG (in overweight) ↑

	Hurley et al. (1991) (140)	↔	Pre and post 10 wk exercise intervention (20 min at 70% VO ₂ max 3d p/wk) (n = 7 normal weight sedentary)	PP slight ↑, GIP ↔	PP slight ↑, GIP ↔
	Martins et al. (2010) (30)	3.5kg	Pre and post 12 wk aerobic exercise intervention, (5 d p/wk, 500kcal at 75% HR max) (n = 15 overweight)	AG ↑, total ghrelin, GLP-1, PYY ↔	↑ AG suppression, ↑ GLP-1, PYY ↔
	Kelly et al. (2009) (31)	2.8 ± 0.5 kg.	Pre and post 12 wk exercise (5d p/wk at 75%VO ₂ max) intervention combined with a eucaloric diet (n = 10)	PYY ↔, GIP ↔	PYY↑ (0-30min), GIP ↔
Combined Diet and Exercise	Valderas et al. (2010) (13)	16.6 ± 4%	Pre and post a 2month low-calorie diet (1300–1800 kcal/d (20–25 kcal/kg of ideal weight)), behavioral modification and 180 min/wk of aerobic and resistance exercise (n = 8 obese)	PYY ↓	PYY ↓
	Kelly et al. (2009) (31)	8.3 ± 1.1kg	Pre and post 12 wk exercise intervention (5d p/wk at 75%VO ₂ max) combined with a hypocaloric diet. Diet reduced ~700kcal fewer daily, reduced fat intake by 5% (n = 9 obese).	PYY ↔, GIP ↔	PYY↑ (0-30min), GIP ↓
	Leidy et al. (2007) (38)	2.5 ± 0.9kg	Pre and post 13 wk exercise intervention (5 d p/wk at 70-80% HRmax) combined with energy restriction to achieve -30-60% energy deficit, (measured ghrelin profiles over 24h) (n = 8 normal weight)	ghrelin ↑	ghrelin ↓
	Mathus Vliegen et al. (2006) (131)	2.3 (at 1wk) to 10.4 (at 1 year) kg.	Pre and at 4 wks, 8 wks and 1 yr. 1 yr intervention of energy restriction (an energy- and fat-restricted diet), exercise (advice on increasing leisure activity and optional aerobics classes), behavioral modification and placebo tablets (n = 9 obese)	CCK ↔ (at all time points)	CCK ↔ (at all time points but trend to ↓ at 4 weeks)

* Weight Loss in units reported in original paper. AG: acylated ghrelin; DG: deacyl ghrelin; CCK: cholecystokinin; CHO: carbohydrate; GIP: gastric inhibitory polypeptide; GLP-1: glucagon-like peptide-1 PCOS: polycystic ovarian syndrome; PP: pancreatic polypeptide; PYY: peptide YY; HRmax: maximum heart rate; VO₂max: maximal oxygen uptake

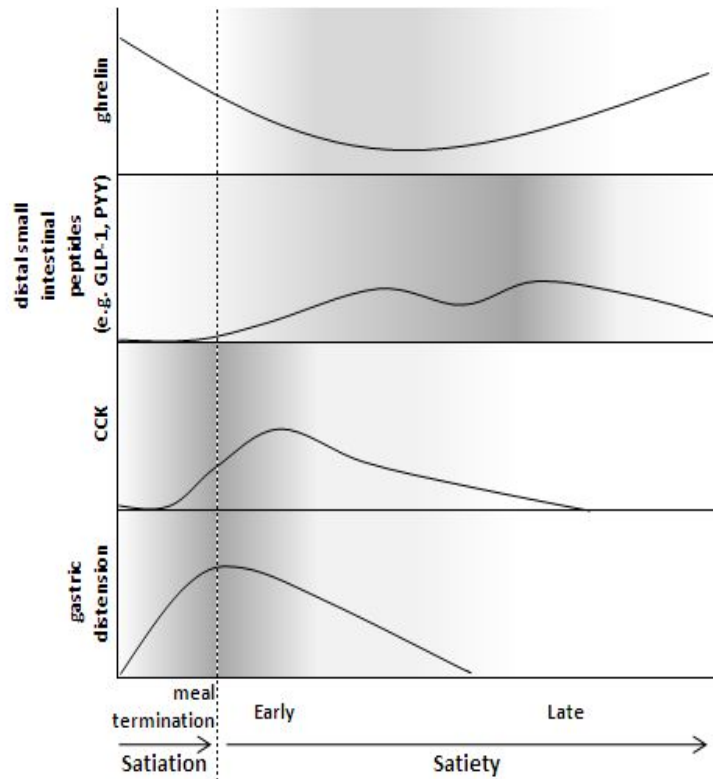


Figure 1. A hypothetical model of the relative contributions of gastric distension, cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1), peptide YY (PYY) and ghrelin (all episodic signals influenced by gastric emptying) to satiation and satiety. Darker shading indicates a greater relative contribution. Time (x axis) and magnitude (y axis) are dependent on the meal characteristics. Gut peptides are particularly sensitive to specific macronutrients (e.g. CCK to fat and protein (82); GLP-1 to carbohydrate and fat (85); PYY primarily to fat (85); ghrelin suppression to protein and carbohydrate (83)) and peak at different time points. Ghrelin is the only peptide implicated in meal initiation, rising before a meal and falling approximately 60min after a meal (35). During a meal and shortly after, gastric distension and CCK (peaking within 15min (84)) are important determinants of satiation. The release of GLP-1 and PYY occurs in a biphasic pattern and can remain elevated for hours after a meal (59, 86). As the stomach continues to empty, it is likely that the exposure of nutrients to the distal small intestine has an increasingly greater contribution to satiety. These episodic signals may also be modulated by tonic signals such as leptin and insulin which are responsive to energy availability and body adiposity.

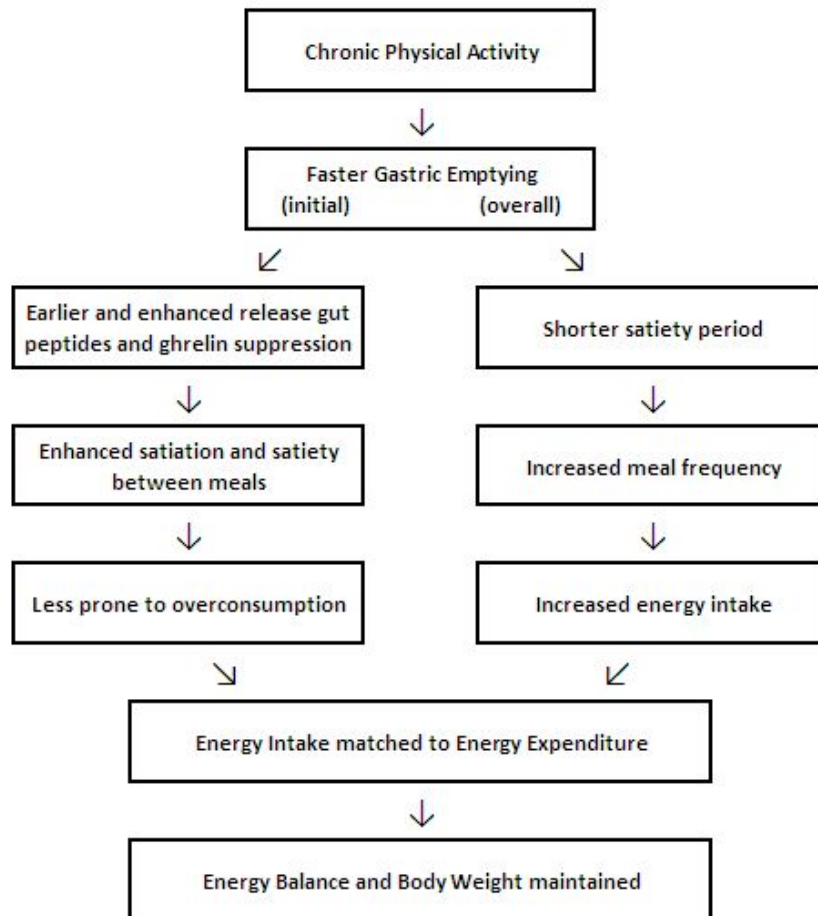


Figure 2. A model to describe how chronic physical activity could potentially impact on gastric emptying, appetite regulation and energy balance