The Role of Gut Hormones in Obesity

Review Article

Authors: Jessica KW Mok[1,2,3], Janine M Makaronidis[1,2,3], Rachel L Batterham[1,2,3]

Affiliations
1. Centre for Obesity Research, Rayne Institute, Department of Medicine, University College London, London UK
2. University College London Hospital (UCLH) Bariatric Centre for Weight Management and Metabolic Surgery, University College London Hospital, London, UK and
3. National Institute of Health Research, UCLH Biomedical Research Centre, London, UK

Correspondence to:

Professor Rachel L Batterham
Centre for Obesity Research
Division of Medicine
Rayne Building
5 University Street
WC1E 6JF
London
Email: r.batterham@ucl.ac.uk

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Abstract

The worldwide obesity epidemic represents a severe threat to global health and is driving the scientific quest for a greater understanding of the mechanisms that regulate bodyweight, in order to develop effective preventative and therapeutic strategies. These research efforts have identified gut hormones as key regulators of energy and glucose homeostasis and have implicated them in the pathogenesis of obesity, the weight recidivism that frequently plagues dietary interventions and the marked changes in eating behaviour, weight reduction and metabolic benefits that accompany bariatric surgery. Consequently, therapeutic strategies aimed at modulating gut hormone levels or targeting their receptors are now being using to treat people with obesity and obesity-associated diseases, such as type 2 diabetes, and represent the most promising therapeutic avenue to combat the obesity epidemic.

Keywords:

Gut hormones; obesity; obesity treatment; weight loss, PYY, GLP-1

1. Introduction

Obesity, defined by a body mass index (BMI) of ≥30kg/m^2, is a chronic progressive condition that results from excessive adipose tissue accumulation. Obesity-linked diseases, such as type 2 diabetes (T2DM), cardiovascular disease, musculoskeletal disorders, certain cancers and liver disease, impact upon health and reduce life expectancy[1-3]. Conversely, reductions in BMI improve both associated co-morbidity and increase life expectancy. It is estimated that by 2025, the global obesity prevalence will reach 18% in men and 21% in women[2]. Treatments for obesity to date have been limited and unsuccessful in addressing the challenge of the global obesity epidemic.

The key for developing new, effective, treatments for obesity lies in furthering our understanding of the mechanisms regulating bodyweight. The procurement of adequate nutrition is essential for survival and throughout the majority of human evolution food has been scarce, thus it is hardly surprising that multiple systems have evolved to ensure that eating is a priority. Energy homeostasis is controlled by neuronal circuits within the brain, which integrate peripheral signals of energy availability, originating from the gastrointestinal (GI) tract, adipose tissue, muscles, bones, higher cognitive centres and external environmental food cues[4]. Studies employing mouse transgenics, human genetics and human functional brain imaging have provided key insights into the neural pathways underpinning bodyweight regulation. The hypothalamus is recognised as a key region integrating peripheral signals to drive either orexigenic or anorexigenic responses, in a mutually exclusive manner[5]. The melanocortin-4 receptor (MC4R) has been identified as playing a key role in energy homeostasis; see Figure 1 for a more detailed overview[6]. The French philosopher Voltaire stated that "*Nothing would be more tiresome than eating and drinking if God had not made them a pleasure as well as a necessity"* and it is now clear that in addition to signals of net energy requirements and availability, the drive to eat is also strongly influenced by brain reward systems and these in turn are influenced by signals from the GI tract. Hedonic food cues, which are ever present in our obesogenic environment, drive the desire to eat and even in the absence of an energy requirement, can result in excess energy consumption, weight gain and ultimately obesity[5]. Thus, effective weight management strategies need to target both the homeostatic and hedonic regulation of eating and gut hormones have emerged as prime candidates. Here we review our current understanding of the role of gut hormones in the development and management of obesity.

2. The role of gut hormones in energy homeostasis, the pathogenesis and treatment of obesity

2.1. Gut hormones: role in energy homeostasis

The GI tract is the body's first point of contact with ingested nutrients and is metabolically highly active. Enteroendocrine cells (EECs) are distributed across the entire length of the GI tract. Following a meal, EECs sense nutrients and release a panoply of gut hormones, which act as autocrine, paracrine, and endocrine regulators of energy and glucose homeostasis[7]. For instance, peptide YY 36 (PYY), glucagon-like peptide 1 (GLP-1) and oxyntomodulin (OXM) are released from L-cells; they signal nutrient availability to the brain and have appetite-suppressing effects[7]. GLP-1 also has a profound incretin effect, enhancing glucose-dependent insulin release and inhibiting glucagon secretion[8].

In the absence of nutrient intake, ghrelin, an orexigenic hormone, is secreted by P/D1 cells located primarily in the gastric fundus, leading to increased appetite and energy intake[9]. Circulating ghrelin levels peak prior to nutrient ingestion and decrease rapidly post-meal. Administration of ghrelin to humans promotes a feeling of hunger and stimulates energy intake[10]. The adipokine leptin acts as a signal of long term energy availability and promotes satiety, by modulating orexigenic neurons in the arcuate nucleus of the hypothalamus in an opposing manner to ghrelin[11]. Interestingly, MC4Rs have been localised on P/D1 and L-cells and are thought to regulate ghrelin, GLP-1 and PYY secretion, adding an additional layer of complexity[12]. Table 1 summarises the main known gut hormones, their sites and mechanisms of action.

Importantly, gut hormones act synergistically; GLP-1 and PYY in combination, for instance, have a more potent effect on reducing energy intake, compared to either of the two hormones alone[13, 14]. OXM, GIP and cholecystokinin (CCK) act synergistically with GLP-1 to enhance its effects[14-17]. Furthermore, gut hormones additionally influence energy homeostasis through interactions with the microbiome and bile acids; GLP-1, PYY and leptin act upon vagal signals; and OXM and amylin increase energy expenditure, though the mechanisms underlying these effects remain incompletely understood[18-21].

2.2 Gut hormones: influence on hedonic pathways

Hedonic factors are able to generate powerful physiological responses and override homeostatic signals of energy availability, leading to excess energy intake and weight gain. Brain functional imaging studies in humans have shown that gut hormones such as ghrelin, GLP-1 and PYY, modulate neural activity in brain reward regions altering the reward value of food[22-24]. Eating behavior is also strongly influenced by food cues, memory and social factors[5]. Exposure to food-related stimuli can

stimulate changes in circulating gut hormone levels which in turn act upon brain reward pathways, either increasing in the case of ghrelin, or decreasing in the case of PYY, the reward value of food[25, 26]. Furthermore, the taste and smell of food, which are key contributors toward food choice, are also under the influence of gut hormone action. Gut hormones are present in saliva and their cognate receptors are present on taste buds and the olfactory bulb[27, 28].

2.3. Gut hormones and the pathogenesis of obesity

Obesity occurs when energy intake chronically exceeds energy expenditure. By consistently overriding homeostatic signals of energy availability, eating becomes disjointed from energy requirements, and results in dysregulation of the metabolic mechanisms controlling energy homeostasis, including impaired gut hormone secretion[29]. Abnormal gut hormone responses have been demonstrated in adults and children with obesity. Individuals with obesity have blunted ghrelin reductions post-meal, together with reduced circulating baseline and meal-stimulated levels of the anorectic peptides PYY, GLP-1 and neurotensin (NT), compared to individuals with normal weight[29-31].

The directionality of the relationship between weight gain and dysregulated gut hormone responses remains to be fully elucidated. However, a recent study in rats with diet-induced obesity, akin to a western diet, showed reduced circulating PYY and GLP-1 concentrations and a loss of circadian secretion profiles of PYY, GLP-1 and amylin[32]. In addition, sustained exposure to a high-fat diet in mice has been shown to lead to an increase in ghrelin-producing cells[33]. These findings suggest that high energy intake *per se* may chronically impair gut hormone responsiveness to ingested nutrients. Studies investigating the role of ghrelin in obesity, have shown blunted post-meal ghrelin suppression, loss of pre-meal peaks, along with reduced diurnal variability; these changes are thought to contribute to the lack of a regular meals and the frequent snacking behaviour often observed in individuals with obesity[9, 34]. In addition, the population and responsivity of intestinal EECs is reduced in people with obesity. A study using biopsied tissue from individuals with obesity also suggests that deregulation of intestinal cell differentiation underlies blunted gut hormone secretion[35].

A recent report of a patient with leptin deficiency, highlights key interactions between gut hormones. Leptin supplementation resulted in significant rises in meal-stimulated insulin and GLP-1, as well as PYY levels[36]. In the same study, ghrelin levels were decreased, highlighting the regulatory effect of leptin on ghrelin secretion and the interplay between leptin, GLP-1 and PYY. Interestingly, while resistance to the effects of insulin and leptin are seen in obesity, sensitivity to the effects of PYY, GLP-1 and OXM during exogenous administration is preserved, suggesting these hormones and their receptor systems offer a viable therapeutic target for obesity[17, 30].

2.4. Gut hormone response to an energy deficit diet

Several lifestyle interventions aimed at engendering weight loss involve restricting energy intake and increasing physical activity to generate a negative energy balance. Although these are successful in the short-term, weight regain is common. Sumithran *et al*. undertook a study that offered key insights into the biology underlying weight regain. They studied 50 individuals with severe obesity at baseline, after a 10-week very low energy diet (VLED) and 52 weeks after the end of the VLED[37]. Mean weight loss was 13.5±0.5kg and 7.9±1.1kg after 10 and 52 weeks respectively. Participants reported increased hunger and increased desire and urge to eat. After the 10-week VLED a significant reduction in PYY, cholecystokinin (CCK), insulin, leptin and amylin levels were seen, whilst ghrelin, GIP and pancreatic polypeptide (PP) increased. These unfavourable gut hormone changes coupled with increased hunger persisted at 52 weeks[37]. Other authors have reported weight regain, with participants regaining a third or half of the weight loss within 1 year and returning to baseline weight within 3-5 years post-intervention[38, 39]. Similar compensatory findings of reduced circulating GLP-1, PYY, CCK, amylin, leptin, increased ghrelin levels and hunger, enhanced food-cue reactivity and increased drive to consume energy-dense food are also reported[40-42]. These compensatory changes may account for the poor long-term efficacy of lifestyle interventions at engendering sustained weight loss. A study comparing a comparable energy deficit induced by either energy restriction or by exercise reported that appetite and acyl-ghrelin levels were increased, whilst PYY was reduced with energy restriction but that exercise led to a reduction in acyl-ghrelin levels and an increase in circulating PYY levels[43]. Other studies also found suppression in appetite and ghrelin following exercise both in low volume sprint interval exercise and endurance exercise[44]. Iepsen et al showed a 13% weight loss induced by 8 weeks of VLED, followed by a 52-week weight-maintenance programme and demonstrated that weight loss maintenance was associated with increased circulating postprandial concentrations of PYY and GLP-1[45]. It is likely that methodological differences underlie these discrepancies and additional studies are warranted.

2.5. Gut hormones as mediators of the success of bariatric surgery

Bariatric surgery is currently the most effective treatment for people with severe obesity leading to marked and sustained weight reduction, improvement or resolution of obesity-associated diseases and increased life expectancy[46]. Importantly, bariatric surgical procedures such as Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG), lead to weight-independent metabolic benefits[47]. Following bariatric surgery, patients report a marked change in eating behaviour, with reduced appetite, changes in taste and food preference away from energy dense foods[48-50]. Thus, bariatric surgery offers a valuable research platform for furthering our understanding of the role of gut hormones in the regulation of energy and glucose homeostasis.

It is now established that lifestyle-induced weight loss and bariatric surgery differentially impact upon circulating gut hormone levels. Multiple studies have shown that bariatric surgery engenders elevations in nutrient-stimulated levels of several anorectic hormones including PYY and GLP-1 and a reduction in ghrelin levels is seen post-RYGB, with more marked reductions post-SG[51, 52]. These changes are present immediately post-surgery and sustained in the longer term[53, 54]. Table 2 summarises gut hormone changes following RYGB and SG and contrasts these with the changes following diet-induced weight loss. Furthermore, cross-sectional studies undertaken in patients with poor versus good weight loss post-surgery revealed that individuals with poor weight loss have increased appetite coupled with lower meal-stimulated GLP-1 and PYY and higher ghrelin levels, compared to those with good weight loss[55]. These studies provide observational evidence for a role of gut hormones in mediating the appetite-reducing effects of bariatric surgery[56]. This hypothesis is further supported by the finding that administration of the somatostatin analogue, octreotide, following bariatric surgery promotes appetite and weight gain[57]. More recently, blockade of GLP-1 and PYY in patients post-RYGB have been shown to lead to a 20% increase in energy intake, further implicating a key role for GLP-1 and PYY in mediating the appetite reduction observed post-surgery[58].

The mechanisms underlying the post-surgery changes in gut hormones remain incompletely understood, however, increased exposure of EECs to ingested nutrients is thought to play a key role[59]. There is also emerging evidence that following bariatric surgery the number of EEC changes. A recent study reported a reduction in total number of EECs and EECs containing gut hormones in the stomach and duodenum of people with obesity compared to lean individuals[35]. Importantly, 3 months post-SG, there was an increase in EECs normalising numbers to those seen in lean subjects. Furthermore, the expression levels of transcription factors required for differentiation of absorptive and secretory cell lineages were altered, suggesting that the reduction in L-cell gut hormone secretion seen in obesity may be secondary to deregulation in differentiation of intestinal epithelial cell lineages, which is restored post-SG.

3. Harnessing the gut for the prevention and treatment of obesity and metabolic diseases

The gut hormone system offers the most tractable therapeutic option for the treatment of obesity and obesity-associated diseases. Intravenous administration of supra-physiological levels of native gut hormones PYY, GLP-1, amylin and OXM leads to reduced appetite and decreased energy intake[18, 26, 60, 61]. In the past, a short half-life and pharmacokinetic stability have proven barriers for the

development of gut hormone-based preparations. However, a multitude of compounds mimicking gut hormone actions are currently under development, heralding a new era of pharmacotherapy for obesity.

Indeed, GLP-1 analogues already have an established role in the management of people with T2DM and people with obesity[62]. The longer acting GLP-1 analogue, semaglutide, has shown promising results in terms of weight loss in early phase studies; a weekly subcutaneous and an oral compound are undergoing phase 3 evaluation[63]. Analogue preparations of GIP and amylin are also being trialled in clinical studies. Strategies aimed at reducing acyl-ghrelin and/or increasing des-acyl-ghrelin are also being developed and show promise. In rodents, inhibition of ghrelin-O-acyltransferase (GOAT), the enzyme required for generating acyl-ghrelin, has been shown to reduce energy intake and bodyweight. Furthermore, administration of des-acylated ghrelin analogue, AZP-531, to people with Prader-Willi syndrome, a genetic syndrome characterised by hyperphagia and increased acylated ghrelin levels, has been reported to decrease hunger, fat mass and weight circumference[64] . Table 3 summarises current pharmacotherapy efforts in different stages of development targeting gut hormones as therapeutic strategies for obesity.

In an attempt to mimic the post-bariatric surgery hormone changes and circumvent compensatory adaptive changes associated with energy restriction, studies combining different gut hormones or targeting multiple systems are in progress. In a study by Tan *et al*., GLP-1, PYY and OXM were co-infused in participants with obesity, aiming to replicate post-RYGB levels and demonstrated a 32% reduction in energy intake compare to placebo[65]. Similarly, rodent studies suggest a potential role of CCK as an adjunct to GLP-1 based therapies as well as with amylin and leptin[66]. Other preclinical studies have focused on monomeric GLP-1/GIP/glucagon triagonism with balanced agonism at the GLP-1, GIP, and glucagon receptors which have shown improvement in bodyweight in obese mice[67].

4. Conclusion

Obesity and its associated diseases represent a major threat to global health. Research efforts aimed at furthering our understanding of energy homeostasis have identified gut hormones as key regulators of bodyweight acting upon homeostatic and hedonic brain circuits to modify eating behaviour. Changes in circulating gut hormones are implicated in contributing to the development of obesity, the failure of lifestyle intervention and in mediating the profound beneficial effects of bariatric surgery. Consequently, major research efforts are focused on harnessing the body's gut hormone system to treat obesity and obesity-associated diseases. Single agent approaches are already licensed for the

treatment of people with T2DM or obesity with more efficacious combination approaches in development.

Tables

Table 1: The main gut hormones involved in energy homeostasis

Gut hormone	Source	Targets	Function	Changes seen in obesity
Anorexigenic				
Glucagon-like-peptide 1 (GLP-1)	Enteroendocrine L-cells and brainstem neurons. GI-derived GLP-1 is secreted in response to nutrient sensing and through EEC stimulation by bile acids[8, 68]	GLP-1 receptors (GLP-1R) are widely distributed on central and peripheral organs and tissues, including the hypothalamus, liver, skeletal and muscle[30]	Reduces appetite and energy intake, delays gastric emptying, promotes insulin secretion, enhance β-cell proliferation, suppresses glucagon secretion, vagus stimulation[30]	Individuals with obesity have attenuated nutrient-stimulated GLP-1 circulating levels compared to normal weight individuals [30].
Peptide YY 3-36 (PYY)	Enteroendocrine L-cells, pancreas and brainstem [68]	PYY exerts its anorectic effect through Y2R in the hypothalamic arcuate nucleus [26]	Reduces appetite and energy intake, delays gastric emptying, promotes insulin secretion, vagus stimulation[15, 30]	Individuals with obesity have attenuated nutrient-stimulated circulating levels of PYY compared to normal weight individuals [30]
Oxyntomodulin (OXM)	Enteroendocrine L-cells co-secreted with GLP-1[69]	GLP-1R, glucagon receptors, hypothalamus via unknown receptor[69]	Decreases energy intake, delays gastric emptying, causes glucose-dependent insulin secretion	Effect of obesity on endogenous OXM is largely unknown, however exogenous administration is associated with weight loss[18]
Cholecystokinin (CCK)	Enteroendocrine I- and L-cells, pancreas and certain enteric and central neurons, in response to nutrient intake in particular lipids and protein[68]	CCK-1 receptors in periphery and CCK-2 receptors in the brain [70]	Inhibit energy intake, via CCK1R on vagal afferents, inhibit gastric secretion, stimulate insulin secretion [70]	Satiety effect of CCK attenuated in obesity and CCK response to oleic acid infusion is reduced in people with overweight or obesity compared to normal weight subjects [70, 71]
Glucose-dependent insulinotropic polypeptide (GIP)	Enteroendocrine K-cells in response to dietary lipids[68]	GIP receptor in pancreatic islet cells, hypothalamus, adipose tissue[72]	Stimulates insulin secretion, anti-apoptotic function in pancreatic beta cells, reduces energy intake[72]	Some studies suggest GIP hypersecretion in people with obesity[72]
Neurotensin (NT)	Enteroendocrine L-cells, CNS , released in response to nutrient intake, in particular fat[73]	NT receptors: NTR1, NTR2, NTR3 widely distributed in the brain and periphery[73]	Reduces GI motility and gastric secretion, stimulates pancreatic and biliary secretion, facilitates fat translocation, act as an incretin.[73]	People with severe obesity have lower circulating NT levels in the fasted state that normal weight people[31]
Uroguanylin	Intestinal epithelial cells, released in response to nutrient ingestion. Secreted as prouroguanylin, enzymatic	Activates guanylyl cyclase 2C (GUCY2C) receptors on intestinal epithelial cells and the hypothalamus [74]	Promotes satiety and reduces energy intake. At intestinal level regulates fluid and electrolyte balance and cellular metabolism.[74]	Circulating levels are suppressed in adolescents with obesity and Intestinal expression of uroguanylin is diminished in female paediatric patients with obesity.[75]

	conversion to uroguanylin.[74]			
Gastric leptin	Gastric chief cells and gastric endocrine P cells in response to energy intake and peptide hormones suck as CCK and insulin[11]	Leptin receptors located in vagal afferents[76]	Regulates energy intake; effect is dependent on nutritional status. In the fasted state, it inhibits vagal afferents, facilitating increased energy intake. In the fed state, stimulates vagal afferents with satiety-inducing effect.[11]	Suggestion of reduce responses to gastric distension following energy intake.[76]
Amylin	Pancreatic beta cells, co-secreted with insulin, in response to nutrient ingestion and incretin hormones[61]	Amylin-specific receptors (composed of the calcitonin receptor partnered with individual receptor-modifying proteins) in nucleus accumbens, the dorsal raphe, and the hindbrain area postrema [19]	Supresses postprandial glucagon secretion, inhibition of energy intake and slows gastric emptying[61]	Elevated in people with obesity, which may lead to down-regulation of amylin receptors and lessen the impact of postprandial amylin secretion on satiety and gastric emptying [61]
FGF19	Terminal Ileum following FXR signalling from activation by bile acids[77]	FGF receptors 1, 2, 3 and 4, located in hepatocytes, cardiac and skeletal muscle, kidneys, blood vessels and the CNS [77]	Regulates glucose and lipid metabolism, stimulates hepatic protein and glycogen synthesis, increases energy expenditure and reduces energy intake.[77]	Decreased FGF19 levels reported in people with obesity and insulin-resistance compared to normal weight people[77]
Bile acids	Liver hepatocytes[78]	Farnesoid X Receptor (FXR) in the distal ileum and G protein-coupled TGR5 receptor on surface of L-cells [78]	Stimulates glycogen synthesis, increases glycolysis and decreases gluconeogenesis, increasing insulin sensitive and improve glucose tolerance[78]	Conflicting results, some studies show that people with obesity have lower postprandial BA levels than normal weight people
Orexigenic				
Ghrelin	P/D1-type cells in the gastric antrum and fundus and duodenum[30]	Growth hormone secretagogue receptor type 1a (GHSR1a), after acylation by ghrelin O-acyl-transferase (GOAT) into acyl-ghrelin, hypothalamus, vagus nerve[9]	Increase appetite, promotes nutrient intake, increases gastric emptying, gastric acid production, decreases insulin secretion[9].	Ghrelin secretion is dysregulated in people with obesity. Diet induced obesity causes resistance to the effects of ghrelin in hypothalamic appetite regulating neurones. Decrease in ghrelin following energy ingestion is blunted in individuals with obesity. However, weight loss is associated with increases in ghrelin levels. [30]

Table 2: Changes in circulating gut hormones following RYGB, SG and diet induced weight loss

Gut hormone	Changes in RYGB	Changes in SG	Changes in Dieting
Anorexigenic			
GLP-1	Fasting levels: ↔ Post prandial levels: ↑↑↑ [30, 51, 52, 55]	Fasting levels: ↔ Post prandial levels: ↑↑ [51, 52]	↔ or ↓ [40]
PYY	Fasting levels: ↔ or ↑ Post prandial levels: ↑↑↑ [30, 51, 55, 79]	Fasting levels: ↔ or ↑ Post prandial levels: ↑↑ [51, 52]	↔ or ↓ [37, 40]
Oxyntomodulin	↑ [69]		
CCK	↑[30, 55]	↑↑ [52]	↓ [37, 40]
GIP	↔ or ↓ [72]	↔ or ↓ [80]	↑ [37]
Neurotensin	↑↑[81]		
Gastrin	↔ or ↓[82]	↔ or ↓[82]	
Amylin	↓[79]		↓ [40]
FGF19	↑ [83, 84]	↑[83]	↔ [84]
Bile acids	Conflicting data: ↔ or ↑↑[83, 85]	Conflicting data: ↔ or ↑[83, 85]	↓ [86]
Orexigenic			
Ghrelin	↓ in the first weeks longer-term effects are controversial: ↔, ↓ or ↑ [30]	Fasting levels: ↓ Postprandial levels: ↓↓[51, 80]	↔ or ↑, VLCD or ketogenic diet: ↓ [37, 41]

↑ = increase intervention

↓ = decrease intervention

↔ = no significant change

Table 3: Summary of current pharmacotherapy in development targeting gut hormones for obesity

Target	Compound	Phase of Study		Effects from early phase/animal studies
GLP-1	Semaglutide weekly SC	Phase 3 (NCT03548935)	Novo Nordisk	Weight loss HbA1c reduction
	Efpeglenatide Weekly SC	Phase 2 (NCT03353350)	Sanofi	Weight loss HbA1c reduction
	Dulaglutide Weekly SC	Phase 3 (NCT01558271)	Lilly	Weight loss HbA1c reduction
	Oral Semaglutide[87]	Phase 3	Novo Nordisk	Weight reduction Glucose lowering
PYY	PYY 3-36 [87]	Phase 1	Novo Nordisk	Reduced appetite Reduced energy intake
Ghrelin	ghrelin-O-acyltransferase (GOAT) inhibitor [88]	Phase 1	Takeda	Reduced energy intake and reduced meal frequency in mice
	Unacylated ghrelin analogue (AZP-531)	Phase 2 (NCT02040012)	Alize Pharma	Appetite reduction and weight loss in mice Reduced appetite scores, reduced waist circumference and fat mass but weight neutral in Prader-Willi patients
	GLWL-01	Phase 2 (NCT03274856)	GLWL/ Eli Lilly	Under evaluation in Prader-Willi patients and participants with obesity
CCK	CCK-1 receptor agonist	Phase 1 (NCT00600743)	GSK	Appetite and bodyweight reduction in mice Conflicting reports of efficacy in early human studies
Amylin	Long-acting amylin analogue[87]	Phase 1 (NCT02958085)	Novo Nordisk	Weight loss Reduction in energy intake Improved glucose tolerance

			Boehringer-Ingelheim	
GIP	GIP analogue [89]	Phase 1	Zealand Pharma	Insulinotropic effects Weight neutral in mice
Glucagon	Glucagon analogue [87]	Phase 1	Novo Nordisk	
FGF 21	Long-acting FGF 21 analogue	Phase 1 (NCT01923389)		Reduced triglycerides, weight neutral in early human study
Combination therapies				
GLP-1/PYY	Oral PYY and oral GLP-1	Phase 1 (NCT00822705)		Appetite suppression Reduced energy intake
PYY/ Semaglutide	PYY/Semaglutide combination [87]	Phase 1	Novo Nordisk	Appetite suppression Reduced energy intake
Glucagon/ GLP-1	Glucagon-GLP-1 co-agonist	Phase 1	Zealand Pharma/ Boehringer Ingelheim	Energy intake reduction Appetite suppression Increased energy expenditure
	Dual glucagon/GLP-1 agonist	Phase 1 (NCT03376802)	Sanofi AstraZeneca	
GLP-1/GIP	Dual GLP-1/GIP agonist [90]	Phase 1	Sanofi	Appetite suppression
	Dual GIP/GLP-1 Receptor Agonist [87]	Phase 2	Novo Nordisk	Decreased bodyweight and total cholesterol, improved glycemic control in T2DM patients
Amylin/ Calcitonin	Dual agonist [91]	Phase 1	Lilly/Nordic	Sustained weight loss, improved glucose homeostasis in rodents
GLP-1/ GIP/glucagon	Tri-agonist [87]	Phase 1	Novo Nordisk	Inhibits energy intake and decreases bodyweight in mice
GLP-1/CCK	GLP-1:CCK fusion peptide [92]	Phase 1		Reduced energy intake and weight reduction in obese mice

Figure Legends

Figure 1: Hormones that control eating

Leptin and insulin circulate in concentrations proportionate to body fat mass and decrease appetite by inhibiting neurons that produce the neuropeptides NPY and AgRP, while stimulating melanocortin-producing neurons in the arcuate-nucleus region of the hypothalamus, near the third ventricle of the brain. NPY and AgRP stimulate eating, and melanocortins inhibit eating, via other neurons. Activation of NPY/AgRP-expressing neurons inhibits melanocortin-producing neurons. The gastric hormone ghrelin stimulates appetite by activating the NPY/AgRP-expressing neurons. Gut hormones released from the GI tract in response to eating, including PYY, inhibit these neurons and thereby suppress appetite and decrease energy intake. Reprinted with permission from Nature Publishing Group, Schwartz, M.W. and G.J. Morton, *Obesity: keeping hunger at bay.* Nature, 2002. **418**(6898): p. 595.

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