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The role of gut hormones in the pathogenesis and management of obesity

Janine M Makaronidis[1,2,3] and Rachel L Batterham[1,2,3]

The growing obesity epidemic is driving the need for the development of novel, effective therapeutic strategies for obesity and its complications. Increasing our understanding of the processes controlling body weight is therefore imperative. Gut hormones have emerged as essential regulators of energy homeostasis. Dysregulation of gut hormone physiology is increasingly implicated in obesity pathogenesis and the compensatory biological responses driving weight regain following energy restriction. Furthermore, gut hormones are among key mediators of the weight loss following Roux-en-Y gastric bypass and sleeve gastrectomy, the bariatric procedures which remain the most effective treatment for severe obesity. Therapeutic strategies targeting gut hormones and their receptors are driving a new pharmacotherapy era and constitute the most promising approach to addressing the obesity epidemic.

Addresses
[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
[3] National Institute of Health Research, UCLH Biomedical Research Centre, London, UK

Corresponding author: Batterham, Rachel L (r.batterham@ucl.ac.uk)

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Introduction

Obesity is a chronic multifactorial condition, defined as having an unhealthy amount of adipose tissue posing a threat to health. Obesity undoubtedly constitutes a major current public health challenge. Obesity reduces life expectancy by up to 40% and is a major driver for type 2 diabetes (T2D), heart disease, liver disease, and cancer [1]. Prevalence has been exponentially rising in countries across the world, with over 600 million people living with obesity world-wide in 2016 [2].

The management of obesity now poses a global challenge, calling for urgent, effective strategies to prevent and treat obesity and its complications. The lack of understanding about the biological causes and the notion that obesity is a lifestyle choice have led to stigma, blame and poor provision of services for people with obesity. To date, most treatment strategies have been ineffective at producing sustainable weight loss.

The rising prevalence of obesity can be explained by a mismatch between our current environment and the biological systems that control body weight, which evolved in the face of food shortage. Evolutionary adaptations which conferred a survival benefit against famine, provide physiological strategies to render human metabolism efficient at seeking and storing energy from food. Appetite and body weight and are controlled by a complex neuro-metabolic network of physiological pathways, which communicate signals of energy need and availability and influence eating behaviour [3]. Gut hormones are metabolically active polypeptides, secreted along the gastrointestinal (GI) tract, in response to energy deficit and nutrient availability and are key regulators of eating behaviour and energy homeostasis [4]. Here we review emerging evidence of the role of gut hormones in the pathogenesis and management of obesity.

Gut hormones as regulators of energy homeostasis

Energy homeostasis involves inherently complex physiological mechanisms, influenced by a multitude of pathways integrating central and peripheral signals. Gut hormones, secreted from enteroendocrine cells (EECs) along the entire length of the GI tract, act as autocrine, paracrine, and endocrine regulators of energy homeostasis. They act on receptors located on multiple organs and tissues [5]. Table 1 summarises key gut hormones and their actions.

In the central nervous system (CNS), the hypothalamus plays a key role in integrating short-term and long-term peripheral signals to drive orexigenic or anorexigenic responses, in a mutually exclusive manner. Activation of hypothalamic neurons producing neuropeptide Y (NPY) and Agouti-related protein (AgRP) increases energy intake, whereas melanocortin-producing neurons inhibit eating [6]. Melanocortin-4 receptor (MC4R) activation leads to satiety, improved insulin sensitivity and increases energy expenditure [7]. MC4Rs have also been localised on EECs and are thought to act as additional regulators of gut hormone secretion in the GI tract [8].

Table 1

Major gut hormones and their sites of action

Gut hormone	Source	Stimulus	Targets	Molecular mechanisms	Action
Orexigenic					
Ghrelin [9,37]	P/D1-type cells in: • Gastric antrum • Gastric fundus • Duodenum	• Fasting • Regular meal-times • Food cues	Following acylation by ghrelin *O*-acyl-transferase into acyl-ghrelin • Growth hormone secretagogue receptor type 1a (GHSR1a), a G-protein coupled receptor (GPCR) • Hypothalamus • Ventral tegmental area and other CNS reward areas • Vagus nerve	• Hypothalamus: promotes expression of prolyl carboxypeptidase, which results in MC4R inhibition • GHSR1a activation stimulated AgRP and NPY neurons results in increased drive to eat • Stimulates endocannabinoid release	• Increase appetite, promotes nutrient intake • Increases gastric emptying, gastric acid production • Decreases insulin secretion
Anorectic					
Glucagon-like-peptide 1 (GLP-1) [11,37,83]	• Enteroendocrine L-cells • Brainstem neurons	• Exposure to nutrients, including glucose and fatty acids • L-cell stimulation by bile acids	GLP-1 receptors (GLP-1R) (GPCR) are widely distributed on central and peripheral organs and tissues, including: • Hypothalamus • Liver • Skeletal and cardiac muscle	• GLP-1R activation on beta cells activates protein kinase A and exchange protein activated by cAMP2 (EPAC2) thereby stimulating insulin release • GLP1R activation in the nucleus of the solitary tract (NTS), leads to stimulation of GLP-1 afferent fibres in the paraventricular nucleus of the hypothalamus, directly suppressing eating	• Reduces appetite and energy intake • Delays gastric emptying • Promotes insulin secretion • Enhances β-cell proliferation • Suppresses glucagon secretion • Vagus stimulation
Peptide YY 3-36 (PYY) [37,84,85]	• Enteroendocrine L-cells • Pancreas • Brainstem neurons	• Nutrient ingestion, particularly fat and protein	Y2 receptors (GPCR): • Throughout the CNS • Vagus nerve	• Y2 receptor activation on presynaptic hypothalamic NPY/AGRP neurons, leads to inactivation of NPY/AGRP neurons and result in anorexia	• Reduces appetite and energy intake • Delays gastric emptying • Promotes insulin secretion • Vagus stimulation
Oxyntomodulin (OXM) [86]	• Enteroendocrine L-cells	• Co-secreted with GLP-1 following nutrient ingestion	• GLP-1R • Glucagon receptors (GPCR) • Hypothalamus via unknown receptor	• Oxyntomodulin mediated anorectic effects are driven through GLP-1R activation	• Decreases energy intake • Delays gastric emptying, • Glucose-dependent insulin secretion

Table 1 (*Continued*)

Gut hormone	Source	Stimulus	Targets	Molecular mechanisms	Action
Cholecystokinin (CCK) [20]	• Enteroendocrine I-cells and L-cells • Pancreas • CNS	• Nutrient intake in particular lipids and protein	• CCK-1 receptors in periphery (including stomach, pancreas, gallbladder) (GPCR) • CCK-2 receptors in the brain (GPCR)	• Directly stimulates vagal afferents terminating in the NTS, activating ascending pathways • Directly activates paraventricular nucleus of the hypothalamus	• Inhibits energy intake • Delays gastric emptying • Inhibits gastric acid secretion • Stimulates insulin and pancreatic enzyme secretion
Amylin [32•,87]	• Pancreatic beta cells	• Co-secreted with insulin in response to glucose and fatty acid ingestion	Amylin-specific receptors (calcitonin receptor partnered with individual receptor-modifying proteins) (GPCR): • Throughout the CNS • Gastric fundus • Bone	• Receptor activation in the area postrema increases Cyclic guanosine monophosphate (cGMP), activation is then synaptically transmitted to the NTS, inhibiting eating	• Supresses postprandial glucagon secretion • Inhibition of energy intake • Slows gastric emptying
Gastric inhibitory polypeptide (GIP) [88]	• Enteroendocrine K-cells	• Ingestion of glucose and lipids	GIP receptor (GPCR) in: • Pancreatic islet cells • Hypothalamus • Adipose tissue	• Beta cells: stimulates adenylyl cyclase and elevate cAMP levels, resulting in glucose-dependent insulin release • Induces proliferation of hippocampal progenitor cells	• Stimulates insulin secretion • Anti-apoptotic function in pancreatic beta cells • Reduces energy intake
Neurotensin (NT) [14]	• Enteroendocrine cells • CNS [14]	• Nutrient ingestion, particularly lipids	Neurotensin receptors NTR1, NTR2, NTR3 (GPCR): CNS, particularly hypothalamus Pancreas GI tract	• Increases hypothalamic pro-opiomelanocortin expression • Activates midbrain dopaminergic system, suppressing appetite	• Reduces GI motility and gastric secretion • Stimulates pancreatic and biliary secretion • Facilitates fat translocation • Incretin effect
Uroguanylin [89,90]	• Intestinal epithelial cells [89]	• Nutrient ingestion, secreted as prouroguanylin	Guanylyl cyclase 2C (GUCY2C) tyrosine kinase receptors on: • Intestinal epithelial cells • Hypothalamus	• Hypothalamic GUCY2C stimulates cyclic guanosine monophosphate; anorectic effect suggested to result from proopiomelanocortin (POMC) neuron activation	• Promotes satiety and reduces energy intake • Regulates fluid and electrolyte balance and cellular metabolism.
Gastric leptin [16,48]	• Gastric chief cells • Gastric endocrine P cells	• In response to energy intake and hormones such as CCK and insulin	• Leptin receptors (type I cytokine receptor) located on vagal afferents	• Fasted: inhibits vagal afferents, increases energy intake. • Fed state: stimulates vagal afferents, inducing satiety	Regulates energy intake, independent of nutritional status

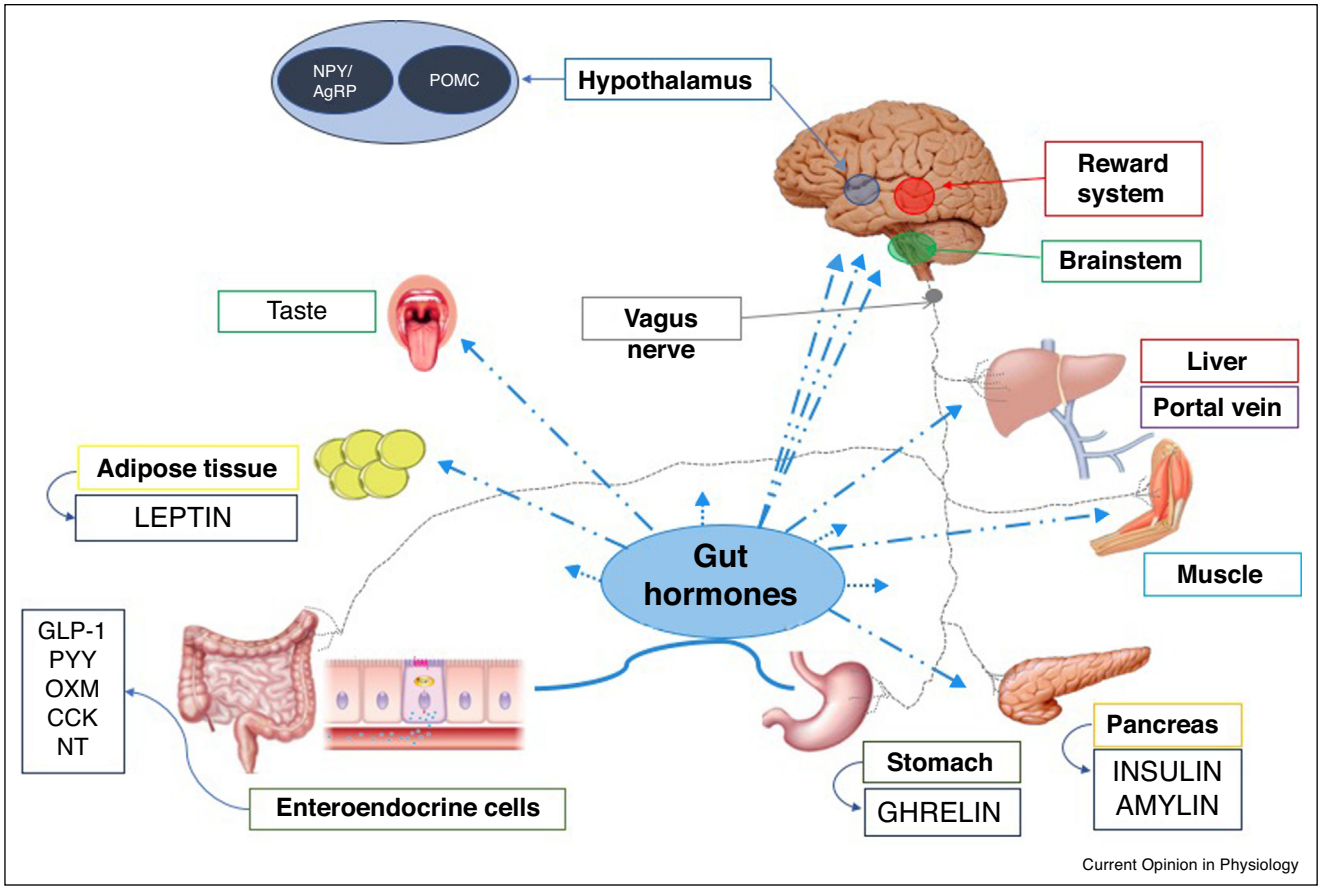
Figure 1 illustrates a summary of the role of gut hormones in the control of energy homeostasis.

Ghrelin, an orexigenic gut hormone and growth hormone secretagogue, is secreted from P/D1 cells predominantly located in the gastric fundus in response to fasting [9]. Ghrelin acts on the hypothalamus and drives eating. This effect is exaggerated following prolonged fasting [10]. In contrast, anorectic hormones peptide YY 36 (PYY), glucagon-like peptide 1 (GLP-1) and oxyntomodulin (OXM), signal nutrient availability to the brain and suppress eating [4].

A key role in modulating energy intake was recently shown for the hypothalamic GLP-1 receptor (GLP1r). Acute knockdown of the receptor in rodents lead to hyperphagia and obesity [11]. In a study by Li *et al.* artificial GLP-1r stimulation resulted in reduced food consumption in fasted mice, whereas inhibition in fed animals led to increased food intake [12].

Importantly, gut hormones act synergistically in their control of eating behaviour [13,14]. Receptors for PYY, GLP-1, CCK and gastric leptin have been located on vagal afferents [15,16]. The vagus nerve has an innate plasticity and sensitivity to the actions of various gut hormone changes dependent on nutrient availability [17]. The expression and sensitivity of different gut hormone receptors is a highly dynamic process, thought to be influenced by acute and chronic changes in energy availability [17]. Vagal plasticity in gut–brain signalling thereby further impacts upon energy intake. Human studies using native peptides have demonstrated that

Figure 1



The role of gut hormones in energy homeostasis.
Schematic diagram illustrating the role of gut hormones in the control of energy homeostasis. Exposure of gastrointestinal enteroendocrine cells to ingested nutrients leads to secretion of gut hormones including GLP-1, PYY, CCK and OXM. Pancreatic polypeptides insulin and amylin are secreted in response to nutrient ingestion. In contrast, fasting leads to secretion of ghrelin from gastric P/D1 cells. Leptin circulates in concentrations proportionate to adiposity. Gut hormones act on multiple organs and tissues, including skeletal muscle and the liver. In the CNS, they act directly and indirectly on nuclei in the brainstem, hypothalamus and reward centres. In the hypothalamus, the gastric hormone ghrelin activates NPY/AgRP-expressing neurons and stimulates appetite. Anorectic peptides, including PYY and GLP-1, inhibit these neurons, suppressing appetite and decreasing energy intake.

GLP-1, PYY and OXM have an additive effect on appetite suppression, whereas gastric inhibitory polypeptide (GIP) and cholecystokinin (CCK) enhance the effects of GLP-1 [13,18–20]. Furthermore, evidence is emerging on the interplay between intestinal EECs and the microbiome and its effect on gut hormone secretion. Certain populations of microbiota have the ability to influence EEC responsiveness, and thereby meal-stimulated secretion of peptides GLP-1 and PYY [21]. Furthermore, short-chain fatty acids, a by-product of intestinal microbial metabolism, constitute and energy source for intestinal epithelial cells but can also directly affect GLP-1 and PYY secretion [21]. The relationship between EECs and the microbiome is complex and dysregulation of these interactions has been associated with obesity; nevertheless, these interactions remain incompletely understood. Evidence is emerging of the impact of gut hormones on energy homeostasis via a number of additional pathways; through interactions with bile acids and through affecting energy expenditure and through interactions with pro-inflammatory immune-mediated pathways; nevertheless, these pathways remain incompletely understood [22,23].

Gut hormones, palatability and hedonic eating

Eating ultimately is a behaviour which is strongly influenced by memory, food cues and social factors. From an evolutionary perspective, the palatability of food as a driver for eating has been crucial to survival [3]. Over the past decade, it has become apparent that in addition to regulating neural activity within homeostatic brain regions, gut hormones also influence the reward-related aspects of eating. Neuronal populations responsive to ghrelin, PYY, GLP-1 and CCK are located within CNS reward centres, and also the olfactory and gustatory cortex [24–26]. Gut hormones therefore influence both the intention and desire to eat, as well as palatability of food, including the perceived hedonic value of food's taste and smell of food. Cognate receptors for a number of gut hormones are present on the olfactory bulb and taste buds, and gut hormones are secreted into saliva, suggesting they have a role in the physiological response to eating, from initial exposure to food [27–29]. Neuroimaging studies have shown that PYY and GLP-1 inversely correlate with reward-responses to food-cues and can suppress reward-responses to food [30,31].

Interestingly, exposure to food cues can result in changes to circulating gut hormone levels in the absence of energy consumption. Li *et al.* demonstrated periventricular hypothalamic GLP1r activation in mice presented with food in fasted conditions, before food consumption; an effect which was not seen in fed conditions [12]. In the absence of subsequent food consumption, GLP1r activation was transient, whereas food consumption resulted in sustained activation. A recent study investigating the role of amylin, a pancreatic polypeptide with anorectic effects, on the mesolimbic reward system in rats demonstrated that activation of the amylin receptor in the ventral tegmental area, a region involved in food reward, suppressed intake of palatable solutions [32•]. A more marked suppression was seen in intake of fat compared to carbohydrate-rich solutions, suggesting a role for amylin signalling in the palatability of high-fat food and motivated eating behaviour [32•]. However, exposure to the sight or smell of food, can trigger ghrelin secretion and drive eating [33–35]. Ghrelin acts upon the dopamine-reward system and can enhance the hedonic response to food both in the fasted and fed state [9]. Thereby, homeostatic signals fail to suppress eating when the reward value of a certain stimulus is too high and energy intake can exceed net energy requirements.

Gut hormones in obesity pathophysiology: cause or consequence?

Obesity develops when energy intake chronically exceeds requirements. A plethora of adaptive changes occur in response to weight gain and several metabolic peptides are moderated by adiposity. In a state of a chronically positive energy balance, eating becomes disjointed from signals of energy availability through consistently overriding homeostatic signals, and consequently also from the sensations of hunger and satiety [36]. Altered gut hormone secretion profiles are seen in obesity [37].

The association between ghrelin and obesity has been a focus of research efforts aimed at understanding the pathogenesis of obesity. In obesity, there is loss of pre-meal ghrelin peaks and reduced post-meal suppression, as well as loss of circadian secretion profiles [9,38]. Increased food cue reactivity is seen in both the fasted and fed state compared to lean individuals [39]. Furthermore, emotional stress and sleep deprivation have been linked to rises in ghrelin levels, which in turn drive eating and food choices [40,41]. The directionality of the relationship between ghrelin secretion and the pathogenesis of obesity remains incompletely understood. However, in a recent study in mice, deletion of the ghrelin receptor on AgRP neurons was shown to prevent diet-induced obesity, suggesting a role for the ghrelin receptor in the pathogenesis of obesity [42]. In addition, sustained exposure to a high-fat diet in mice was shown to lead to an increase in gastric ghrelin-producing cells, implying that the dysregulated ghrelin secretion in obesity, is at least partially a consequence of a positive energy balance [43••].

Blunted responses in meal-stimulated circulating levels of GLP-1 and PYY along with reduced levels of anorectic peptides including neurotensin (NT) and uroguanylin have also been demonstrated in people with obesity [37,44,45]. In addition, a study by Moghadam *et al.* demonstrated that diet-induced obesity in mice results in reduced circulating PYY and GLP-1

concentrations and a loss of circadian secretion profiles of PYY, GLP-1 and amylin [46•]. This further supports that dysregulation of gut hormone secretion profiles may be consequential to weight gain. Interestingly, reduced population numbers and responsivity of gastrointestinal EECs was demonstrated in people with obesity compared to lean individuals using gastric and duodenal biopsies, deregulation of EEC differentiation has been proposed as an underlying mechanism by Wölnerhanssen *et al.* [47••]. Obesity furthermore results in loss of plasticity in areas where gut hormone receptors are located, such as the vagus nerve [17]. Studies from animal models with obesity suggest that gut hormone receptor expression on the vagus nerve and its responsivity to gut hormones are diminished in obesity [17].

Adiposity also impacts upon the interactions between individual gut hormones. Resistance to the effects of certain hormones is also seen. In a process similar to insulin resistance in T2D, leptin levels initially rise with weight gain, but resistance to its effects develops; hence administration of exogenous leptin is ineffective at reducing energy intake and body weight [48]. However, a recent report of a patient with leptin deficiency receiving supplementation, highlights key interactions between gut hormones. Treatment with leptin led to significant rises in meal-stimulated GLP-1, PYY and insulin levels, whereas ghrelin levels decreased [49••]. This effect highlights the regulatory effect of leptin on ghrelin secretion and the interplay between leptin, GLP-1 and PYY. Interestingly, despite the resistance to the effects of insulin and leptin in obesity, sensitivity to the effects of PYY, GLP-1 and OXM during exogenous administration is preserved, hence targeting these hormones and their receptor systems offers a viable therapeutic strategy for obesity [37,50]. Table 2 summarises obesity-associated changes in gut hormones and how these are targeted by various therapeutic approaches.

Reversing the abnormal obesity-related gut hormone changes

Lifestyle interventions and the management of obesity

Conventional lifestyle modification strategies for the management of obesity involve generating a negative energy balance. Whereas weight loss is achievable in the short-term, this results in powerful compensatory physiological changes, aimed at defending the higher body weight, which consequently predispose to weight regain. Investigating the effects of a very low calorie diet (VLCD), Sumithran *et al.* demonstrated significant reductions in PYY, CCK, insulin, leptin and amylin levels at the end of a 10-week VLCD, coupled with increased ghrelin, GIP and pancreatic peptide (PP) levels, which persisted at 52 weeks follow up [51]. More recently, Nymo *et al.* showed increased ghrelin levels and hunger ratings 1 year following VLCD, in a group of participants with obesity who sustained 15% weight loss [52•]. These hormonal adaptations to weight loss are likely to drive the increased appetite, increased food cue responsivity and rebound weight regain commonly seen with dietary energy restriction [53–55].

However, there is individual variability in the response to energy restriction diets as well as weight loss maintenance. Iepsen *et al.* demonstrated that weight loss maintenance following an 8-week VLCD was associated with higher circulating postprandial concentrations of PYY and GLP-1 [56•]. Different strategies among lifestyle intervention regimes have also been shown to differentially impact upon gut hormone levels. Exercise regimes, for instance, have been shown to result in ghrelin level reductions and increase circulating PYY levels [57,58]. Different dietary regimes can also have different effects upon gut hormone profiles; high-protein intake has been linked to reduced ghrelin, whereas low protein intake is thought to have the opposite effect and ketogenic diets have been suggested to reduce appetite and ghrelin levels [59,60]. Furthermore, a recent study comparing the effect of different dietary carbohydrate contents in overweight and obese participants, demonstrated lower ghrelin and leptin levels, as well as higher energy expenditure in participants following a low compared to a high-carbohydrate diet [61]. Whereas significant methodological differences may still underlie the discrepancies in the results from lifestyle intervention studies and highlight the need for further studies; these nevertheless suggest that individualising lifestyle interventions based on their physiological consequences may improve the effectiveness of lifestyle interventions in the management of obesity.

Lessons from bariatric surgery

In contrast to weight loss through energy restriction, which engenders a hormonal milieu favouring weight regain, certain types of bariatric surgery lead to sustained weight loss, resolution of co-morbidities and improved life expectancy [62]. Weight loss following bariatric surgery results from a number of physiological changes which favourably impact upon eating behaviour. These lead to increased satiety and reduced hunger, a reduction in the hedonic value of food and changes in taste and smell, driving food preference away from energy-dense food [63–65]. Gut hormones are among key mediators of these changes, hence studies involving the post-bariatric surgery population constitute a unique research opportunity furthering our understanding of body weight regulation in health and obesity [66].

Importantly, bariatric surgical procedures such as Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG), lead to weight-independent metabolic benefits [67]. It is now established that RYGB engenders elevations in nutrient-stimulated levels of several anorectic hormones including PYY and GLP-1, which is also seen to a lesser extent post-SG. A reduction in ghrelin levels is also seen,

Table 2

Gut hormone profiles in the management of obesity: effects of energy restriction, bariatric surgery and pharmacotherapy targets

Gut hormone	Changes in obesity	Therapeutic Strategies for obesity			
		Changes in dieting	Changes in RYGB	Changes in SG	Pharmacotherapy
Anorexigenic					
GLP-1	Post-prandial levels: ↓ [37]	Unchanged/↓ [53]	Fasting levels: unchanged Post prandial levels: ↑↑↑ [37,68,69,72]	Fasting levels: unchanged Post prandial levels: ↑↑ [68,69]	Once daily: Liraglutide (licenced) [78] Once weekly: Semaglutide [91], Dulaglutide [92], Efpeglenatide [80] (phase 3) Oral semaglutide (Phase 3) [79] Oral semaglutide/PYY combination (Phase 1) [79] Dual GLP-1/glucagon agonist (Phase 1) [80] Dual GLP-1/GIP agonist (Phase 2) [81] GLP-1/ GIP/glucagon triagonist (phase 1) [82]
PYY	Post-prandial levels: ↓ [37]	Unchanged/↓ [51,53]	Fasting levels: ↔ or ↑ Post prandial levels: ↑↑↑[37,68,72,93]	Fasting levels: unchanged or ↑ Post prandial levels: ↑↑ [68,69]	PYY 36 (Phase 1) [79] Oral PYY/GLP-1 (phase 1) [79]
OXM	Unknown	Unknown	↑ [86]	Unknown	OXM analogue [92]
CCK	Satiety effects ↓ Post-oleic acid infusion levels ↓ [70,71]	↓ [51,53]	↑[37,72]	↑↑ [69]	CCK-1 receptor agonist (phase 1) (NCT00600743) GLP-1/CCK fusion peptide (phase 1) [94]
GIP	↑	↑ [51]	Unchanged or ↓[88]	Unchanged or ↓ [95]	GIP analogue (phase 1) [96] Dual GLP-1/GIP agonist (Phase 2) [81]
NT	Levels rise with weight gain in short-term Lower fasted levels in obesity[44]	Unknown	↑↑[97]	Unknown	
Amylin	↑ (may lead to downregulation of amylin receptors and reduce the effect of amylin secretion on satiety and gastric emptying) [87]	↓ [53]	↓[93]	Unknown	Amylin analogue (weekly) (phase 1) [79] Amylin/calcitonin dual agonist (phase 2) [92]
Orexigenic					
Ghrelin	Secretion dysregulated	Ghrelin resistance in hypothalamic neurons Levels ↔ or ↑ Ketogenic diets: ↓ [51,54]	Short-term: ↓ Longer-term: controversial with reports of returning to baseline, ↓ or ↑ [37]	Fasting levels: ↓ Postprandial levels: ↓↓[68,95]	Ghrelin-*O*-acyltransferase (GOAT) inhibitor (phase 1) [98] Unacylated ghrelin analogue (phase 2) (NCT03274856)

Abbreviations: GLP-1, Glucagon-like peptide-1; PYY, peptide YY 36; OXM, oxyntomodulin; CCK, cholecystokinin; GIP, Gastric inhibitory polypeptide; NT, neurotensin; GOAT, Ghrelin-*O*-acyltransferase.

which is more marked post-SG [68,69]. These changes are immediate, occur before weight loss and are sustained in the long-term [70,71]. Importantly, patients with sub-optimal weight loss have lower meal-stimulated GLP-1 and PYY and higher ghrelin levels, compared to those with good weight loss [72]. Furthermore, blocking gut hormone activity, either with somatostatin analogue octreotide, or more selectively blocking the action of GLP-1 and PYY, results in increases in appetite and energy intake, additionally supporting the role of gut hormones as drivers for post-bariatric surgery weight loss [64,73].

The exact mechanism driving the changes in gut hormone secretion remains incompletely understood; however, it is speculated that increased EEC stimulation by ingested nutrients as a consequence of more rapid gastric emptying or GI re-routing plays a key role [66].

Interestingly, a recent study demonstrated an increase in EEC population, which at 3-months post-SG returned to numbers seen in lean individuals [47••]. The authors of the same study suggest that SG reverses the obesity-associated changes in EEC transcription factor expression by 3 months post-surgery.

Bariatric surgery is safe and effective and now has an established role in the management of severe obesity, as well as in the treatment algorithm for people with T2D [74,75]. In a recent trial comparing RYGB and SG in 217 patients over a 5-year follow up period, immediate operative complications occurred in 0.9% of SG and 4.5% of RYGB patients [76]. Late complications including internal herniation, reflux, severe dumping and insufficient weight loss occurred in 14.9% of SG and 17.3% of RYGB patients. Furthermore, it has to be borne in mind, that weight loss following bariatric surgery follows a wide normal distribution, with a proportion experiencing extreme weight loss and up to 20% suboptimal weight loss [77]. Therefore, in light of limited access to surgery, the necessary lifestyle adjustments following surgery and the potential for complications, bariatric surgery should be offered to individuals when deemed appropriate.

The future role of gut hormones in the treatment of obesity

The novel insights gained into the role of gut hormones as regulators of body weight, particularly by studies undertaken in people post-bariatric surgery, have paved the way for a new era of pharmacological management of obesity. GLP-1 analogues are already successfully in use for the management of people with T2D and are increasingly used in people with obesity [78]. Longer-acting GLP-1 analogues with weekly administration are currently in phase 3 trial evaluation [79,80]. Furthermore, analogues and/or receptor agonists of further gut hormones, including PYY, CCK and amylin are currently in development or early phase clinical trials [79,80].

Because of the synergistic nature of gut hormone action in the physiological regulation of energy homeostasis, strategies combining the actions of more than one hormone or receptor are in development. Given the adaptive hormonal changes that occur in response to weight loss, it is anticipated that targeting more than one system of energy balance simultaneously may circumvent these adaptive changes and thus result in improved weight loss outcomes. A dual GIP/GLP-1 receptor agonist was recently used in patients with T2D in a phase 2a trial and demonstrated significant improvements in glycaemic control and weight [81]. Further dual agonist compounds combining PYY, glucagon or CCK with GLP-1 are entering early phase clinical trials. An amylin/calcitonin co-agonist is also in early development. A more recently developed tri-agonist, combining the effects of GLP-1/ GIP/glucagon with equal affinity for each of the three receptors, is showing promising results in rodent studies [82].

Conclusion

Obesity and the consequential metabolic conditions, continue to pose a growing public health challenge. To date, bariatric surgery, remains the only effective treatment for people with severe obesity, engendering weight loss and co-morbidity resolution sustained in the long-term. Research efforts focusing on widening our understanding of the mechanisms mediating the weight loss and change of eating behaviour resulting from bariatric surgery, have improved our understanding of the body's mechanisms controlling energy balance. Gut hormones have emerged as key regulators of energy homeostasis and drivers for eating behaviour and have a fundamental role both in the pathophysiology of obesity, but also in driving weight loss following bariatric surgery. Research efforts are now focussed on targeting the gut hormone system and its receptors to develop more effective therapeutic strategies for obesity and associated diseases.

Conflict of interest statement

Nothing declared.

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- • of special interest
- •• of outstanding interest

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