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Appetite, the enteroendocrine system, gastrointestinal disease and obesity

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The enteroendocrine system is located in the gastrointestinal (GI) tract, and makes up the largest endocrine system in the human body. Despite that, its roles and functions remain incompletely understood. Gut regulatory peptides are the main products of enteroendocrine cells, and play an integral role in the digestion and absorption of nutrients through their effect on intestinal secretions and gut motility. Several peptides, such as cholecystokinin, polypeptide YY and glucagon-like peptide-1, have traditionally been reported to suppress appetite following food intake, so-called satiety hormones. In this review, we propose that, in the healthy individual, this system to regulate appetite does not play a dominant role in normal food intake regulation, and that there is insufficient evidence to wholly link postprandial endogenous gut peptides with appetite-related behaviours. Instead, or additionally, top-down, hedonic drive and neurocognitive factors may have more of an impact on food intake. In GI disease however, supraphysiological levels of these hormones may have more of an impact on appetite regulation as well as contributing to other unpleasant abdominal symptoms, potentially as part of an innate response to injury. Further work is required to better understand the mechanisms involved in appetite control and unlock the therapeutic potential offered by the enteroendocrine system in GI disease and obesity.

Appetite regulation: Enteroendocrine: Digestive disease: Obesity

The enteroendocrine system

Enteroendocrine cells (EEC) make up approximately 1 % of the gastrointestinal (GI) epithelial cell population, being dispersed, as single cells, throughout the gut epithelium[1,2]. Despite collectively forming the largest endocrine system in human subjects, relatively little is understood regarding their complex and multi-faceted role, particularly in GI disease. EEC are luminal chemosensors in the GI tract. Nutrient-sensing receptors are expressed on the apical pole of the cells which are open to sense luminal contents, responding to nutrients by basolaterally secreting multiple regulatory peptides (gut hormones) which, in turn, control intestinal secretion and motility. In doing so, EEC act as transepithelial signal transducers and are fundamental in regulating digestion, motility and intestinal absorption and, frequently, are reported as playing a part in appetite regulation[1,3]. There is also an emerging role for EEC in intestinal immune regulation, as well as other chemosensory mechanisms detecting non-nutrient stimuli, which will not be discussed in this appetite-focused review[1,2].

A growing number of recognised peptide hormones, as well as the non-peptide bioactive amine 5-hydroxytryptamine or serotonin, which is synthesised and secreted by enterochromaffin cells, are secreted by EEC in their response to luminal stimuli[4]. Historically, it was reported that distinct differentiated EEC subsets secreted

Abbreviations: CCK, cholecystokinin; CD, Crohn's disease; EEC, enteroendocrine cell; GI, gastrointestinal; GLP-1, glucagon-like peptide 1; IBS, irritable bowel syndrome; PYY, polypeptide YY.

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individual hormones, leading to classification by immunohistochemical methods. However, it has more recently emerged that individual EEC actually co-express and co-secrete a mixture of peptide hormones, probably depending on their location within the GI tract[5–7]. These biological mediators can act in a typical endocrine fashion or a more local paracrine fashion, most notably on neighbouring cells and vagal afferent fibres[1].

During food intake, mechanical gastric distension is sensed via vagal afferent fibres to the hindbrain whilst EEC release regulatory peptide hormones[1,8]. Cholecystokinin (CCK) is released by the I cells of the duodenum and jejunum particularly in response to lipids and proteins[1,9]. CCK delays gastric emptying, thus potentiating mechanical gastric distension, and stimulates bile and pancreatic enzyme release[10–12]. CCK also transmits satiety signals centrally, via vagal afferents, to the nucleus of the solitary tract. However, the complex central neurological processes involved in appetite regulation will not be reviewed further here[13].

The regulatory gut hormones, glucagon-like peptide 1 (GLP-1) and polypeptide YY (PYY), are released more distally by L cells of the ileum and colon in response to ingested fat and carbohydrate signalling[1,4]. Following nutrient ingestion, GLP-1 delays gastric emptying and stimulates glucose-dependent insulin secretion[4,10]. PYY similarly delays gastric emptying and gastric acid release as well as reducing intestinal motility and pancreatic exocrine function[10]. PYY secretion increases colonic water and ion absorption whilst decreasing their secretion[14].

The overall effect of these regulatory gut hormones is therefore to delay gastric emptying and, as such, slow GI transit thus allowing for optimisation of digestion and small bowel absorption of nutrients[4]. Although a good deal of experimentation in animal models has supported their role in satiety and appetite regulation, the situation in normal physiological terms is somewhat less clear, and the evidence for physiological effects of endogenously secreted regulatory peptides on food intake in free-living human subjects is remarkably scarce.

Appetite regulation in health

The role of gut satiety hormones

CCK, GLP-1 and PYY are frequently referred to as satiety hormones, playing a crucial role in appetite regulation and limiting nutrient intake following a meal. Human dietary preload studies yield variable results when measuring the association between post-prandial changes in circulating levels of these gut peptides and subsequent changes in appetite and satiety[15–21]. Those reporting a correlation between increased plasma satiety hormone levels and post-prandial suppression of appetite, or increased satiety, do not provide sufficient evidence to conclude a causal link with increasing circulating peptides actually driving appetite-related behaviours[22].

Further discrepant results are demonstrated in studies infusing fatty acids into the upper GI tracts of healthy human volunteers. Whilst these studies show equivalent increases in plasma CCK levels with 12- (C12) and 18-carbon (C18) chain lengths, subsequent energy intake and food consumption are significantly decreased following C12 infusion but not C18 infusion despite significantly greater PYY increases following C18[9,23]. As such, the observed endogenous gut hormone responses following intraduodenal fatty acid infusion do not appear to consistently explain subsequent appetite-related behaviour[23]. Of note, it has been demonstrated that the infusion of SCFA directly into the human colon results in significant increases in plasma PYY and GLP-1 concentrations whilst decreasing subsequent energy intake[24]. The real-world significance of this is not immediately clear as few other major nutrients typically arrive in the colon in health and consequent effects on gut hormones and appetite are likely to have complex underlying mechanisms involving the gut microbiota[25]. However, this does suggest that strategies to recruit the colonic EEC responses may have utility by manipulating SCFA levels in the colon. Small bowel EEC responses are rather transient as meals are episodic and transit relatively quickly (orocaecal transit is about 90 min on average) whilst nutrients have much longer dwell times in the colon, where interactions with the microbiome are further considerations[26,27].

Intravenous peptide infusion studies have attempted to demonstrate a causal relationship between increased plasma concentrations of satiety hormones and appetite suppression in human subjects. This is unavoidably problematic as infusions are peripheral rather than into the visceral compartment. Again, the results are variable with some studies reporting no significant changes in appetite outcomes following infusion of CCK, PYY or GLP-1[28–30]. The majority of peptide infusion studies, however, do report significant effects in appetite outcomes, frequently in a dose-dependent manner[31–34]. The difficulty when extrapolating these data in order to draw conclusions regarding the role of satiety hormones in appetite regulation in healthy human subjects is that the majority of infusion studies result in a rapid increase of the relevant gut peptide, reaching supra-physiological plasma concentrations[22,35].

In a recent carefully crafted review, Lim and Poppitt compared fold changes from baseline in gut hormone concentrations between dietary preload studies and peptide infusion studies[22]. The relationship between peptide concentrations and appetite behaviours in both groups were also explored. They demonstrated that postprandial fold changes of all of the three satiety hormones (CCK, PYY and GLP-1) were consistently lower following food intake than with exogenous peptide infusion. In order to decrease *ad libitum* energy intake in the infusion studies, minimum fold changes of 3·6 (CCK), 4·0 (GLP-1) and 3·1 (PYY) were required, and in the dietary studies, only 29 % (CCK), 0 % (GLP-1) and 8 % (PYY) met this threshold fold change. Furthermore, any increase in gut peptides reported in the dietary preload studies was not consistent with appetite outcomes. Taken together, the authors concluded that it is very difficult to reach these threshold changes in gut peptides through dietary manipulation alone and thus the role of endogenously released satiety hormones in appetite regulation following a meal remains unclear[22].

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This suggestion that postprandial, physiological, levels of gut hormones do not, in fact, play a strong role in appetite suppression may explain the lack of success in attempting to develop satiety-enhancing foods which can be used for therapeutic benefit to reduce overconsumption in the longer term[22,36]. The use of potent nutrients or drugs however, which result in supra-physiological levels of these regulatory peptides, may be of more benefit in modulating long-term appetite and energy intake. Further evidence for the limited effect of endogenous GLP-1 in appetite control is provided through GLP-1 antagonist studies which show no effect on subsequent food intake[37]. However, the use of exogenous long-acting GLP-1 agonists can lead to significant weight loss. Liraglutide, a GLP-1 analogue, is efficacious in mediating weight loss in obese individuals and those with type 2 diabetes through reducing appetite and energy intake[38,39]. Therefore, gut peptides may still have a therapeutic role if given exogenously and supra-physiologically, alone or perhaps in combination. However, targeting the release of endogenous mediators by small bowel EEC has shown little promise for manipulating energy homeostasis.

The afore-mentioned observations inevitably place into question the prominence given to the role of the so-called satiety hormones in appetite suppression in health. This needs to be placed in a wider biological context rather than viewed through a 21st century human prism. Eating, digestion and absorption are essential, highly evolved and closely regulated, taking place within a digestive system which has adapted to absorb nutrients with maximal efficiency, usually in the face of scarcity. Certainly, from an evolutionary perspective, it does not immediately make sense to develop an enteroendocrine system which functions to suppress appetite and eating after modest consumption when, for so much of human existence (and many other species), access to adequate nutritional intake has been scarce. Moreover, food was not cooked or processed when these systems evolved. In the modern day, many of us now have access to surplus food supplies, clearly well in excess of our energy requirements, and overconsumption is common, meaning the proposed physiological mechanisms are overridden or ignored. The rise in domestic pet obesity also fits this concept that eating is not simply switched off physiologically. Appetite and energy intake regulation is clearly highly complex, not just on-off bottom-up switches alone, and must also involve significant top-down control to be limited. The interplay between current metabolic state and deliberate choices to eat, which can be clearly overridden by the hedonic drive and further modulated through neurocognitive factors, such as attentional bias towards food cues at any one time, must be considered. These aspects of appetite control are further discussed in the following section.

The interaction between homeostatic, hedonic and cognitive mechanisms on appetite

The human appetite system has homeostatic and non-homeostatic aspects, and it is now well established that these systems act together under a common neurochemical network to influence when and how much food will be consumed[40,41].

Traditionally, the homeostatic and hedonic pathways were considered to act in parallel to control energy balance. Homeostatic signals increase motivation to eat following depletion of energy stores through circulating metabolites, hormones and nutrients to define periods of hunger and satiety. The hypothalamus and brainstem are thought to be the main homeostatic brain areas driving ingestive behaviour. The hedonic mechanisms, mainly processed in the corticolimbic system, focus on the influence of reward on motivated behaviours (eating) and how cues associated with the pleasure of consumption can elicit food-seeking behaviour and intake. The high prevalence of overweight and obesity suggests that hedonic-based regulation can override repletion signals during periods of satiety in situations where food is in abundance[41,42]. In human evolutionary terms, this scenario is rather new. Current evidence suggests that there is cross-talk between metabolic, reward and cognitive processes in appetite control, with the brain receiving a great deal of external and internal cues, integration of which allows adjustment of appropriate ingestive behaviour[40]. However, it is clear that there is great variation in signal integration between individuals, and also between males and females, resulting in differences in appetite-related behaviour which may account for, at least in part, the observed sex differences in disordered eating and obesity[43,44]. The impact of sexual dimorphism and the potential mechanisms including potential differences in the gut and extra-GI hormone (especially sex hormones) responses have been reviewed in detail[45].

Metabolic state can modulate food attractiveness and motivation to eat. In the fed state, the incentive value of food decreases in healthy human volunteers[46], whereas in the fasted state increases[47]. This has been proposed to be mediated by signals of circulating hormones such as insulin[48,49], PYY[50], ghrelin[51] and leptin[52]. However, in some cases, visual food cues have been shown to induce a strong response in reward and cognitive control brain regions in non-obese subjects, not diminished by postprandial metabolic signals, such as elevated insulin levels[53], showing that the hedonic pathway can also override homeostatic signals. Exposure to visual food cues before a meal can also affect metabolic and endocrine responses, such as an increase in the levels of the orexigenic hormone ghrelin[54], cephalic-phase insulin release[55] and decrease in postprandial glucose levels[56].

Moreover, metabolic signals can also influence cognitive responses involved in responses to food cues, such as attention. In the fasted state, attention allocation to palatable food cues has been shown to enhance; healthy volunteers attend to food cues more when they are fasted compared to when they are fed[57]. Attentional bias to food cues, which is the tendency to focus attention to salient information (food) over neutral information, has been associated with increased food intake and hunger[58]. Although some studies have shown an altered cue-reactivity system in individuals with obesity[59,60],

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in a recent study by our group, it was shown that participants with overweight and obesity show a decreased attentional bias to food cues in the fed state compared to a fasted state similarly to subjects with normal weight[57]. It remains unexplored whether this modulation of attentional processing of food cues between hunger and satiety is altered in GI disease as a result of a change in the balance between homeostatic and hedonic mechanisms of appetite regulation.

In order to objectively map and measure the aspects of food hedonics and food reward, either neuroimaging techniques or neurocognitive tasks can be used. At the leading edge of non-invasive and most commonly used brain imaging technology is the functional MRI, which allows human brain mapping of the neurocognitive mechanisms behind differentiated internal signals or cognitive processing[61]. Using neurocognitive tasks, more implicit aspects of 'wanting', which refers to the drive to eat triggered by a food cue, can be measured. These tasks require a physical effort, such as a mouse click or a button press to a presentation of a food stimuli (picture of food, smell of food, actual presence of food, etc.), where the effort or the reaction time is measured[62]. Although these methodologies are widely used in health, studies in GI disease are lacking.

Appetite involves complex interactions between homeostatic, hedonic and cognitive processes, which remain quite unexplored. Current technologies allow the investigation of how homeostatic and higher brain functions are integrated and the use of these methodologies should be encouraged for future studies exploring the aspects of appetite in health and disease.

Appetite regulation in digestive disease

Given the role of gut peptides in motility and secretion, as well as their role in appetite suppression at least at supraphysiological levels, it seems inferential that, in digestive disease, with associated symptoms of anorexia, nausea, abdominal pain and diarrhoea, EEC dysfunction may play a role[10]. In the following section, the limited available literature regarding appetite regulation and EEC function in GI disease is reviewed.

Gastrointestinal infection and inflammation

GI infection and inflammation typically cause symptoms of nausea, loss of appetite, diarrhoea and abdominal pain frequently associated with weight loss[63,64]. Early evidence for EEC dysfunction in intestinal infection comes from studies demonstrating improvement in food intake following administration of a specific CCK antagonist, loxiglumide, to lambs infected with the parasite *Trichostrongylus colubriformis*[65]. Similarly, in human subjects, infection with the parasite *Giardia lamblia* causes an increased plasma CCK which correlates with anorectic symptoms upon feeding[66].

Studies using a mouse model of enteritis, induced by *Trichinella spiralis*, demonstrate hypophagia in association with the up-regulation of CCK expressing EEC and subsequently increased plasma CCK levels[67]. These findings were most marked on day 9 post-infection corresponding with the timing of peak intestinal inflammation. Again, administration of loxiglumide significantly improved eating behaviour. Importantly, when treated with CD4+ T-cell neutralising antibodies, the parasite-induced hypophagia resolved and the CCK cell hyperplasia lessened highlighting a pivotal link between the immune system and EEC function[67]. IL-4 and IL-13 were also implicated in the EEC hyperplasia and hypophagia.

Furthermore, GM mice lacking CCK, infected with *T. spiralis*, do not demonstrate hypophagia or lose weight despite comparably severe active enteritis[68]. Again, the importance of the immune system in EEC function is demonstrated by the lack of hypophagia and EEC hyperplasia in infected mice with severe combined immunodeficiency, which lack B and T cells. Adoptive transfer of CD4+ T cells from infected immunocompetent mice into infected severe combined immunodeficiency mice restores EEC hyperplasia and hypophagia[68].

This adaptive EEC response to infection is potentially beneficial as the CCK-induced hypophagia and subsequent weight loss leads to a reduction in the inflammatory adipokine, leptin, resulting in enhanced parasite expulsion[68]. Conversely, the CCK null mice display delayed parasite expulsion and a different cytokine response. These data support a hypothesis that increases in CCK during intestinal infection and inflammation may contribute to the symptoms of anorexia and weight loss but that the mechanisms involved are dependent on complex interactions between EEC and the immune system, and maybe part of an adaptive mechanism. Anorexia may be considered appropriate in the acute phase after infection, limiting further ingestion and resting the gut.

In human studies, the main disease area studied to date is inflammatory bowel disease. Patients with active Crohn's disease (CD) have significantly reduced appetite, both before and after eating, compared to healthy controls[69,70]. Terminal ileal biopsies from patients with active small bowel CD demonstrate significant up-regulation of EEC, with increased GLP-1 expression but unchanged PYY expression. This is not the case in ileal biopsies from patients with isolated Crohn's colitis in which no significant changes are observed[71]. Furthermore, patients with active CD affecting the small bowel have significantly elevated fasting and postprandial plasma levels of PYY which correlate with subjective ratings of nausea and bloating[69]. Again, these findings are not demonstrated in the patients with colonic CD, perhaps explained by the increased density of L cells in the distal ileum and hence small bowel CD being more likely to promote EEC up-regulation[69]. Although not studied to date, L cells co-secrete GLP-2 with GLP-1. This is a trophic hormone and may contribute to intestinal homoeostasis and repair.

Both symptoms and EEC peptide expression are shown to normalise when the disease is in remission[69]. In one study, mean postprandial plasma CCK levels have also been shown to increase 3-fold in CD patients compared to healthy controls[72].

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In a more recent study, participants with active CD involving the terminal ileum have been shown to have significantly higher fasting GLP-1 and PYY plasma concentrations compared to healthy controls with no significant postprandial responses following a test meal[73]. Postprandial levels of both PYY and GLP-1 remained significantly elevated in CD patients compared to controls. No significant differences in CCK were observed. Patients with CD reported significantly higher levels of both fasting and postprandial aversive abdominal symptoms when compared to healthy controls[73]. These findings suggest that increased fasting gut peptide concentrations may account for at least some of the appetite suppression and weight loss observed in patients with active small bowel CD. In reality, however, the underlying mechanisms are likely to be highly complex involving an interaction between unpleasant abdominal symptoms, EEC dysfunction, psychosocial factors[74], disordered eating patterns[75] and neurocognitive influences[57].

Post-infectious irritable bowel syndrome

The earlier section concentrated on appetite dysregulation in conditions with overt GI inflammation. A large proportion of patients with significant GI symptoms and associated reduced appetite, however, do not present with an overtly diseased gut and many of these are subsequently diagnosed with the so-called irritable bowel syndrome (IBS)[76,77]. IBS-type symptoms can persist in about 10–20 % of patients following an acute bacterial, protozoal or viral gastroenteritis, termed post-infectious IBS[76,78,79]. Intestinal biopsies are conventionally reported as normal in IBS; however, reports suggest that more rigorous analysis yields evidence of subtle inflammatory abnormalities[80]. In post-infectious IBS, raised T-lymphocyte counts can be demonstrated in the biopsies of some patients more than one year following the initial infection[80]. Similarly, EEC counts are found to remain increased in a number of patients with post-infectious IBS, at one year following acute *Campylobacter* infection, again implicating an intimate relationship between gut inflammation, the immune system and EEC function[80,81]. Conversely, in IBS which is not preceded by GI infection, there appears to be a general depletion in gut EEC[82,83].

The finding of increased EEC in patients with post-infectious IBS raises the question of whether increases in gut satiety peptides could contribute to some of the appetite-related symptoms observed in this cohort of patients. Interestingly, the relative risk of developing post-infectious IBS increases as the EEC count increases[81]. In particular, cells expressing PYY and serotonin have been shown to increase in the colon and rectum of patients following acute *Campylobacter* and *Shigella* infection and, as such, it is speculated that increases in PYY may thus contribute to suppressed appetite in some patients[80,84,85].

Likewise, post-infectious IBS and dyspepsia, associated with food-related bloating and abdominal pain which can last for many months, has been described following *Giardia* infection[86]. As mentioned previously, in the acute phase, it has been demonstrated that infection with *Giardia* results in increased plasma CCK levels which correlate with the anorectic symptoms[66]. In patients who develop chronic abdominal symptoms, following successful treatment of *Giardia* infection, duodenal EEC containing CCK are significantly increased compared to controls 6 months after *Giardia* infection; however, plasma CCK is not significantly increased. Plasma CCK levels are, however, significantly correlated with fullness and bloating scores in those with post-infectious IBS and functional dyspepsia[87]. Perhaps an increase in CCK could contribute to the symptoms of post-prandial fullness and appetite suppression and, whilst plasma CCK levels are not found to be significantly raised, there is the possibility that the increased numbers of CCK producing EEC could act at a more local, paracrine level, in suppressing appetite by over-stimulated vagal afferent receptor pathways.

Coeliac disease

As with other digestive diseases, there is a relative paucity of data with regard to the regulation of appetite in coeliac disease. Coeliac disease results from an immune reaction to gluten and results in symptoms of bloating, abdominal pain, diarrhoea, weight loss and lethargy, frequently associated with alterations in appetite[88].

In a recent study, whilst no difference was observed between hunger levels at baseline between patients with coeliac disease and healthy controls, those with recently diagnosed coeliac disease, not yet on a gluten-free diet, remained significantly more hungry postprandially than healthy controls and coeliac patients already on a gluten-free diet. This was associated with a lower GLP-1 and glucose-dependent insulinotropic polypeptide response[89]. The significance of this is however unclear as, as documented earlier, the effect of a potent GLP-1 antagonist yields little effect on subsequent food intake, so lower physiological GLP-1 levels would not necessarily be expected to increase hunger[37]. Likewise, whilst coeliac patients, already on a gluten-free diet, had similarly low postprandial GLP-1 levels to those who were not yet on a gluten-free diet, their hunger was no different from that of controls[89]. Further studies are needed.

Elevated plasma levels of PYY are found in patients with untreated coeliac disease and these subsequently normalise following the commencement of a gluten-free diet[90,91]. The studies do not attempt to correlate these findings with the assessments of appetite or food intake but do hypothesise that increased plasma PYY may contribute abnormalities in upper GI motor and secretory function in coeliac disease and, as such, could impact upon appetite. Conversely, plasma CCK levels are reduced in coeliac disease and, as such, are unlikely to contribute towards appetite regulation[92,93].

Overall, there is currently a lack of credible evidence to draw robust conclusions regarding any role for EEC dysfunction in the regulation of appetite in coeliac disease. Clearly, as with CD, the alterations in appetite

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experienced by patients with coeliac disease are complex and multifactorial and further research is required in this area.

Obesity, enteroendocrine cells and bariatric surgery

Obesity is increasing worldwide with almost a third of the world's population being classified as overweight or obese[94]. The exact mechanisms underpinning the development of obesity remain incompletely understood. As with some of the GI diseases discussed earlier, there is evidence for potential disordered crosstalk between the gut microbiota, innate immunity, systemic inflammation and EEC with subsequent interactions between homeostatic and hedonic factors[95]. This is an important area for future research.

Altered gut hormones do however appear to play a key role following bariatric surgery. This is currently the most effective treatment for severe obesity and its associated complications[96,97]. Traditionally, it was reported that weight loss and metabolic consequences of bariatric surgery were a consequence of gastric restriction and nutrient malabsorption; however, more recently, perceptions have shifted to a more neuro-hormonal mechanistic explanation involving changes in EEC function[96]. The finding that improved glycaemic control precedes significant weight loss following bariatric surgery is suggestive of a mechanistic role for post-surgical hormonal and metabolic adaptations[98].

Le Roux *et al.* demonstrated that, following Roux-en-Y gastric bypass, postprandial plasma PYY and GLP-1 were significantly increased in patients compared to controls[97]. This was associated with an exaggerated insulin response in the Roux-en-Y gastric bypass patients. These findings were not observed in patients undergoing purely restrictive surgery with a gastric band. It is therefore suggested that the supraphysiological plasma levels of PYY and GLP-1 are likely to contribute to increased satiety, weight loss and improved glycaemic control in those undergoing metabolic bariatric surgery[97]. Similar findings, with increased postprandial PYY and GLP-1, have been replicated in a number of studies of patients following different bariatric procedures including Roux-en-Y gastric bypass and sleeve gastrectomy[99–101].

Postprandial plasma CCK levels have also been shown to be increased, compared to controls, in patients following Roux-en-Y gastric bypass [100,101]. It is possible that supraphysiological CCK levels contribute to appetite suppression and weight loss following bariatric surgery; however, the role of CCK has not been as widely studied as that of PYY and GLP-1. One study demonstrated that postprandial CCK levels were most elevated in those who had the poorest weight loss response to bariatric surgery whereas GLP-1 was most elevated in the good responders[100]. Overall, the evidence suggests that changes in EEC function are highly likely to play a mechanistic role in the metabolic consequences following bariatric surgery but more research is required to understand exactly how these changes come about and whether they can be used to predict and optimise post-operative outcomes.

What about primary or autoimmune enteroendocrine cell dysfunction?

Unexplained GI symptoms make up a significant proportion of gastroenterology referrals to secondary care. As alluded to earlier, many of these patients end up being labelled with IBS but it is clear that there is great heterogeneity within this group of patients[76]. Furthermore, a large number of patients are informed that they have functional GI syndromes with unexplained symptoms including nausea, cyclical vomiting, dyspepsia and abdominal pain, all of which may be associated with reduced appetite[102].

Few studies have focused on the role of EEC function in these functional GI conditions but it remains conceivable that under- or over-activity of particular EEC subsets and subsequent alterations in gut peptide expression may play a role. Could cyclical vomiting or functional nausea, with associated early satiety and suppressed appetite, actually be secondary to EEC dysfunction resulting in 'hyper-CCKism' or 'hyper-PYYism'? In all other endocrine systems, we are able to describe autoimmune disease resulting in hypo- or hyper-function of the organ in question. Yet, in the largest endocrine system in the human body, we have almost no data on primary or autoimmune disorders of the EEC. This reflects a lack of tools to study this system. For example, the utility of measuring plasma levels in peripheral blood is debatable if subtle changes at a paracrine level in the visceral compartment are what matter. New pharmacological tools to probe this system are needed.

Few case reports of EEC dysgenesis describe the intestinal failure associated with an almost complete lack of EEC but there are few data on whether abnormal EEC function in health can actually cause unexplained GI symptoms including those associated with appetite alterations[103–105]. More work is required in this complex, yet neglected area of enteroendocrinology[1].

Conclusion

Appetite regulation is a highly complex process involving interactions between, amongst others, EEC, microbiome, vagal afferent fibres, central processing, biological sex, neurocognitive factors, hedonic drive, psychosocial influences and deliberate choice. In health, whilst EEC play a fundamental role in regulating nutrient absorption through modulating intestinal secretions and motility, it remains unclear whether the hormones secreted by EEC play a significant role in appetite regulation. In GI disease, there is some evidence of EEC dysfunction with supraphysiological levels of satiety hormones potentially contributing to appetite suppression as well as other unpleasant abdominal symptoms. However, the true role of gut peptides remains underexplored. Clearly, further basic science and clinical research is required in this relatively neglected area of the literature in order to better understand the complex mechanisms of appetite regulation and uncover any potential therapeutic role for EEC manipulation in GI disease and obesity.

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Conflicts of Interest

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