Proceedings of the Nutrition Society (2012), **71**, 456–462 doi:10.1017/S0029665112000705
 First published online 21 August 2012

The Winter meeting of the Nutrition Society was held at the Royal College of Physicians, London on 6–7 December 2011

70th Anniversary Conference on 'Body weight regulation – food, gut and brain signalling'
Symposium I: Food–gut interactions

The gut endocrine system as a coordinator of postprandial nutrient homoeostasis

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Hormones from the gastrointestinal (GI) tract are released following food ingestion and trigger a range of physiological responses including the coordination of appetite and glucose homoeostasis. The aim of this review is to discuss the pathways by which food ingestion triggers secretion of cholecystokinin (CCK), glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) and the altered patterns of gut hormone release observed following gastric bypass surgery. Our understanding of how ingested nutrients trigger secretion of these gut hormones has increased dramatically, as a result of physiological studies in human subjects and animal models and *in vitro* studies on cell lines and primary intestinal cultures. Specialised enteroendocrine cells located within the gut epithelium are capable of directly detecting a range of nutrient stimuli through a range of receptors and transporters. It is concluded that the arrival of nutrients at the apical surface of enteroendocrine cells is a major stimulus for gut hormone release, thereby coupling these endocrine signals to the arrival of absorbed nutrients in the bloodstream.

Glucagon-like peptide-1: Cholecystokinin: Glucose-dependent insulinotropic polypeptide: Enteroendocrine: Diabetes: Obesity

Physiological responses to food ingestion include the regulation of appetite and glucose homoeostasis as well as the control of gastric motility and secretion. Although rising circulating nutrient concentrations act as a sign of recent food intake, however, they do not indicate whether the nutrients are of alimentary origin and therefore do not convey sufficient information to enable the body to handle them appropriately. This role is fulfilled by neurohormonal signals from the gut, which indicate the volume and content of ingested food. A number of enteric peptides have been implicated in signalling from the gut to the brain and the pancreas. These include cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP) and peptide YY (PYY), which target receptors in the pancreas and enteric and central nervous systems.

Interest in gut peptides has increased in recent decades, with the finding that they have profound and sustained physiological effects on appetite and insulin release[1–4]. GLP-1, an incretin hormone that stimulates insulin release and reduces food intake, has been very successfully exploited for the treatment of type-2 diabetes. Injectable GLP-1 mimetics and orally available inhibitors of GLP-1 degradation (DPP4 inhibitors) are now widely prescribed and match the effectiveness of other oral therapies on glycaemic control, but are additionally weight-lowering, or at least weight-neutral, and are associated with a low incidence of hypoglycaemic side effects[5].

Recent excitement in the gut peptide field has been triggered by the results of using gastric bypass surgery as a treatment for morbid obesity. Somewhat unexpectedly, it was observed that a number of bariatric procedures have effects on blood glucose control over and above that predicted from the loss of body weight. Roux-en-Y gastric bypass surgery and sleeve gastrectomy are two of the most successful operations, resulting in 'cure' rates for type-2

Abbreviations: CCK, cholecystokinin; GI, gastrointestinal; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; PYY, peptide YY.

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diabetes of >80% in some cohorts[6,7]. The underlying physiological mechanisms are yet to be fully elucidated, but altered secretion of one or more gut peptides almost certainly plays a critical role[8]. It is hoped that understanding which hormones underlie the metabolic improvement in these subjects may lead to the development of novel pharmaceutical strategies for treating type-2 diabetes.

Enteroendocrine cell populations in the small and large intestine

CCK, GIP and GLP-1 are secreted from enteroendocrine I, K and L cells, respectively, located in the epithelial layer of the gastrointestinal (GI) tract[9]. These cells have apical surfaces opening into the gut lumen and basolateral poles containing the secretory vesicles[10]. They are formed, along with other epithelial cell types, in the crypts of the small and large intestine, and differentiate into mature secretory cells as they migrate along the crypt–villus axis, before being shed into the gut lumen after a lifespan of about 5 d.

Each enteroendocrine cell type exhibits a characteristic distribution along the length of the GI tract, with GIP typically found in the duodenum, CCK in the duodenum and jejunum and GLP-1 in the jejunum, ileum and colon[9]. PYY expression is restricted to a relatively small number of L cells in the upper small intestine, but the proportion of L cells producing both hormones increases to almost 100% in the distal ileum and colon[11]. Recent evidence shows that I, K and L cells, typically considered as discrete cell types, exhibit an unexpectedly high degree of transcriptomic overlap, suggesting that they may be variants of a single cell population also incorporating the S cells that produce secretin, and N cells producing neurotensin[11]. Interestingly, although the factors underlying enteroendocrine cell development from the multipotent crypt stem cells are relatively well defined[12,13], less is known about how the gradient of endocrine cells is established and maintained along the longitudinal axis of the GI tract. It would seem likely that the profile of hormones produced by any single enteroendocrine cell may be determined both by its position in the GI tract and its exposure to dietary nutrients.

Physiological profiles of gut hormone secretion and the importance of digestion

Secretion of GLP-1, GIP, CCK and PYY is triggered by the ingestion of carbohydrates, proteins and lipids, with only relatively modest differences in nutrient-responsiveness being reported between the I, K and L cells. GIP and GLP-1 release are particularly strongly stimulated by glucose and fat[14–17], whereas CCK is released by fat and protein[18,19]. Evidence that proteins directly trigger GLP-1 release or that glucose stimulates CCK secretion is more variable between studies, perhaps reflecting differences in nutrient sensing or exposure along the length of the GI tract, or a role for indirect signalling pathways that are not activated under all experimental conditions.

The time courses of gut hormone appearance in the bloodstream after a meal are broadly mirrored by the location of their respective secretory cell types along the GI tract length. Thus, it is generally reported that GIP and CCK appear in the bloodstream as soon as nutrients enter the duodenum, whereas GLP-1 and PYY release is delayed until the food has been shifted lower down the GI tract[14,15]. This is interpreted as indicating a need for nutrients to make direct contact with individual enteroendocrine cells to trigger secretion. However, plasma GLP-1 and PYY levels can rise very rapidly following food ingestion, perhaps even before it could be predicted that nutrients would reach the jejunum. This must indicate either that gastric emptying initially exceeds the maximum absorptive capacity of the duodenum, with the result that small nutrient loads really do reach the jejunum very early after food ingestion, or that there exists an indirect proximal–distal loop resulting in secretion from distal L cells when nutrients enter the duodenum.

Evidence for a proximal–distal loop is quite compelling, although its contribution to normal post-ingestive physiology is unclear. Instillation of oil or protein hydrolysate into a spatially restricted segment of the mouse duodenum triggered GLP-1 release from a site distal to that exposed to nutrient, as demonstrated by selective blood sampling from different regions of the small intestine or by resection of the distal gut[20,21]. Sectioning the vagus or applying pharmacological inhibitors suggested that the response depended on a neural loop, potentially involving gastrin-releasing peptide[21,22]. A hormonal link between the duodenum and distal gut has also been proposed, with GIP being a potential candidate owing to its ability to stimulate GLP-1 release in rodents[23]. Studies in perfused pig intestine, however, did not identify any duodenal peptide capable of stimulating GLP-1 release and in human subjects intravenous GIP infusion does not trigger GLP-1 secretion[24]. Furthermore, low-dose duodenal glucose infusion was an effective stimulus of GIP secretion in human volunteers, but did not increase GLP-1 release[14,25]. Interestingly, duodenal infusion of glucose, at rates too low to stimulate GLP-1 secretion directly, appeared to enhance the GLP-1 response to glucose delivered lower down the GI tract, suggesting that some form of signal from the human duodenum modulates distal L cells[26,27]. Low-dose duodenal lipid infusion also triggered a small GLP-1 response that was prevented by a CCK1 receptor antagonist, suggesting that this may not have involved direct lipid sensing by L cells[28]. Although these data could suggest that the afferent limb of a neural circuit in human subjects involves CCK from the duodenum acting on local vagal nerve endings, there may be a more prosaic explanation such as that CCK-dependent gall bladder contraction provides the bile components necessary for efficient lipid delivery to the distal L cells.

Considerable evidence supports the idea that digestion is a prerequisite for intestinal sensing of most macromolecules. Carbohydrates seem largely to be sensed in the form of glucose, lipids in the form of fatty acids and monoacylglycerols and proteins as small peptides and amino acids. Linking gut hormone release to the luminal liberation of transportable digestion products may have

physiologically important consequences, as the plasma hormone levels would increase in parallel with nutrient absorption. This provides a temporally linked gut signal, indicating to the rest of the body that the elevated circulating nutrient concentrations have arisen from intestinal absorption.

Inhibition of carbohydrate digestion by oral α-glucosidase inhibitors is used therapeutically in patients with type-2 diabetes to slow carbohydrate absorption and reduce circulating glucose concentrations. In physiological studies, α-glucosidase inhibitors are reported to impair GIP secretion, but have inconsistent effects on GLP-1 levels[29–31]. Their effects on GIP release are compatible with the view that liberation of glucose in the duodenal lumen acts as an important stimulus of K cells. The inconsistent effects on GLP-1 secretion may be the result of two opposing actions: on the one hand, the slowed carbohydrate digestion results in reduced duodenal absorption and increased carbohydrate delivery to the lower GI tract where L cells are more prevalent, but at the same time, glucose liberation would also be inhibited in the jejunum and ileum, thereby reducing the stimulation of the distal L cells. Which of these processes is dominant will be influenced both by the degree of α-glucosidase inhibition and the quantity of carbohydrate ingested. Greater delivery of undigested carbohydrate to the colon would also act as an energy source for colonic bacteria, potentially releasing additional modulators of enteroendocrine cell number and function. A similar picture has been observed with lipase inhibitors such as orlistat, which prevent luminal TAG digestion to fatty acids and monoacylglycerols. Orlistat has been reported to abolish fat-triggered GIP, CCK and GLP-1 release, indicating the importance of luminal TAG breakdown for enteroendocrine cell lipid detection[28,32].

Our understanding of how proteins trigger gut hormone secretion is perhaps less well established than that of carbohydrates and lipids. Protein is a strong stimulus of CCK release and has also been found to trigger GIP and GLP-1 secretion, although not in all studies[16,19,20,33]. Although PYY and GLP-1 levels rise in the plasma following ingestion of a protein-rich meal, however, direct instillation of a protein hydrolysate into the human ileum did not trigger GLP-1 secretion[33]. Whether the GLP-1 response to oral protein intake therefore reflects a greater protein-responsiveness of more proximal L cells in the jejunum, or indirect stimulation, e.g. through a CCK dependent mechanism, remains to be determined. The effectiveness of protein as an enteroendocrine stimulus has been variously attributed to large and small peptides as well as amino acids, not only suggesting that luminal digestion may be important, but also that there may exist a range of sensors for protein products.

Direct nutrient sensing by enteroendocrine cells

As discussed earlier, there are a number of studies in human subjects showing that CCK and GIP secretion are triggered by very low rates of energy infusion into the duodenum, but that GLP-1 and PYY release are only triggered when the infusion rate is increased sufficiently to exceed the maximal absorption capacity of the duodenum[14,15]. The simplest interpretation of these findings is that I, K and L cells are all stimulated when nutrients contact their luminal faces and that the pattern of hormonal release reflects the distribution along the longitudinal intestinal axis of different cell types. Most of the data in human subjects are consistent with this view that the profile of gut hormone release after a meal can be explained by such direct nutrient sensing by enteroendocrine cells.

Carbohydrate sensing

Glucose is a robust trigger of GIP and GLP-1 release, but is less effective as a stimulus of CCK secretion in human subjects. Comparisons between the effects of oral and intravenous glucose infusion showed that sugars were only effective when presented from the luminal direction, suggesting the existence of a sugar sensor located on the brush border membrane[34]. There is still considerable argument, however, about whether it is the mere luminal presence of sugar that triggers GLP-1 release, or whether the enteroendocrine response depends on local absorption and/or metabolism. Further controversy is centred around the importance of sweet taste and the question of whether all sweet tasting molecules, including artificial sweeteners, trigger gut hormone secretion.

It has been proposed that the intestine contains cells capable of detecting sweet taste, similar to those found in the tongue where the sensory machinery involves the heterodimeric taste receptor Tas1R2/Tas1R3 coupled to α-gustducin, phospholipase Cβ2 and the calcium-sensitive channel Trpm5. Individual components of this signalling pathway have been detected in the intestine by immunostaining, in some cases overlapping with the expression of gut hormones such as GLP-1[35]. However, although sweet tasting molecules indirectly stimulate translocation of the sodium glucose cotransporter SGLT1 to the enterocyte brush border[36], there is little evidence that the primary intestinal detection of sweet taste occurs in either the K or the L cells[37]. A multitude of recent studies in human subjects and animal models has also resulted in little support for the idea that ingestion of sweet tasting molecules targeting the lingual Tas1R2/Tas1R3 receptor pathway results in detectable elevated plasma levels of gut hormones[38,39].

Earlier studies examining the sugar specificity of gut peptide responses in the intact intestine concluded that sugar absorption was important for hormone stimulation. Glucose-triggered secretion exhibited a requirement for luminal Na^+ ions and was mimicked by metabolisable as well as non-metabolisable substrates of the brush border monosaccharide transporter system[40–42]. The results indicated that glucose uptake rather than metabolism was critical for GLP-1 and GIP secretion. A body of recent evidence supports the idea that the apical uptake pathway, mediated by the sodium coupled GLUT, SGLT1, acts itself as the glucose sensor underlying GLP-1 and GIP release. Glucose triggers small SGLT1-dependent currents and calcium elevation in L cells[37,43], and mice deficient in SGLT1 exhibit a loss of GLP-1 and GIP responsiveness to glucose both *in vitro* and *in vivo*[44]. A working model for

K and L cell glucose sensing would therefore place SGLT1 on the apical membrane of the enteroendocrine cell, generating small sugar-dependent currents that are capable of triggering electrical activity, voltage gated Ca^{2+} entry and release of basolateral secretory vesicles. The low K_m of SGLT1 for glucose transport (about 0·5 mM) makes this an exquisitely sensitive sensor, explaining how GLP-1 release can be initiated when only small glucose loads enter the distal small intestine. Coupling GIP and GLP-1 release with the process of glucose absorption also ensures that the magnitude of the incretin hormone stimulus to pancreatic β-cells coincides with the appearance of glucose in the bloodstream.

Despite the metabolism-independent action of SGLT1, an additional role for sugar metabolism in enteroendocrine cells should not be excluded. Physiological levels of hyperglycaemia increased the GIP response to a luminal glucose load in human volunteers and in the perfused pig ileum, elevating the vascular glucose concentration enhanced GLP-1 secretion in the presence of a luminal glucose infusion[45,46]. Glucose entry via basolateral facilitative GLUT such as GLUT2 may underlie this minor responsiveness to plasma glucose levels, as the concentration of glucose inside L cells seems to be determined predominantly by GLUT-mediated uptake, despite the importance of SGLT1 as an electrically coupled apical nutrient sensor[47]. Consistent with this idea, intestinal GLP-1 content and secretion were found to be impaired in GLUT2 knockout mice[48]. The observed small GLP-1 response to oral fructose might also be attributable to metabolism[41], as apical fructose uptake is mediated by GLUT5, whose activity does not generate an electrical signal. A modulatory role for glucokinase-dependent metabolism on GLP-1 release was suggested by recent experiments in the model cell line GLUTag[47], but neither the downstream signalling pathway nor its importance for physiological incretin release has been established.

Lipid sensing

Fat ingestion is a robust stimulus of GIP, GLP-1 and CCK release, acting through a mechanism that requires lipase-dependent TAG hydrolysis in the intestinal lumen. A comparison between the effectiveness of intravenous *v*. oral lipid delivery revealed that GIP and GLP-1 plasma levels were only increased when the stimulus was provided luminally, despite matched circulating TAG and NEFA concentrations[49]. By infusing lipids at different rates into the duodenum it was shown that the profile of gut hormone appearance in the bloodstream reflected the length of gut that was directly exposed to the luminal stimulus, together with its associated complement of enteroendocrine cells[15]. Whereas, low lipid loads were effective stimuli for CCK release, PYY secretion was triggered with a longer time delay and required higher infusion rates, presumably because of the more distal location of the majority of L cells[15,18].

A number of candidate lipid sensors have been postulated to underlie enteroendocrine response to oral lipids, but whether one or more of these underlie physiological lipid sensing remains incompletely established. Among the likely candidates are the G-protein coupled receptors FFAR1, GPR120 and GPR119 and the atypical protein kinase Cζ[50–53]. Bile components also deserve consideration in the context of fat sensing, since they play a fundamental role in the emulsification, digestion and epithelial delivery of dietary lipids. G-protein-coupled receptors for bile acids (GPBAR1), for example, almost certainly contribute to the enteroendocrine response that follows fat ingestion[54].

FFAR1 and GPR120 are Gq-coupled receptors, responsive to unsaturated NEFA of longer chain length. Their localisation to enteroendocrine cells in the GI tract makes them prime candidates for underlying gut hormone response to lipid ingestion, especially in view of reports that unsaturated long-chain fatty acids are more effective stimuli for GLP-1 and CCK secretion *in vivo* than their saturated or shorter chain-length counterparts[55,56]. FFAR1 deficient mice exhibited impaired GIP and GLP-1 responses to a high-fat meal and reduced long-chain fatty acid responsiveness of I cells *in vitro*, suggesting a physiological role for this receptor in oral fat detection[57,58]. Additional involvement of GPR120, however, is suggested by the finding that siRNA mediated receptor knockdown impairs responses to NEFA in enteroendocrine cell lines[51]. Activation of protein kinase Cζ by long-chain fatty acids has been proposed as an alternative signalling pathway underlying fat sensing by L cells, as demonstrated by the inhibitory effect of protein kinase Cζ siRNA on fatty acid triggered GLP-1 release *in vitro* and *in vivo*[53,59]. As for the G-protein coupled receptors, however, its relative physiological importance is uncertain. As it seems unlikely that L cell protein kinase Cζ would distinguish apical from basolateral long-chain fatty acids, it is not clear that this pathway could account for the specific responsiveness of gut hormone secretion to luminally delivered fatty acids.

GPR119 is a Gs-coupled receptor for oleoylethanolamide and oleoylglycerol [52,60]. Fat ingestion triggers a rise in local oleoylethanolamide concentrations, probably as a result of metabolism in enterocytes and/or other intestinal cell types[61]. It is postulated that this acts as a signalling molecule whose targets include GPR119 on enteroendocrine cells, although it is not certain that local levels rise sufficiently under physiological conditions, particularly if the receptor is apically located. Perhaps, a more likely natural agonist of GPR119 is oleoylglycerol, formed by the luminal hydrolysis of TAG[60]. The bile acid receptor GBBAR1 is also Gs-coupled and enriched in L cells from the distal gut, although whether it is located apically or basolaterally remains to be established[37,54]. Activation of GPR119 by oleoylglycerol, or of GPBAR1 by bile acids, could potentially trigger elevation of the cAMP concentration in enteroendocrine cells, enhancing hormone secretion by a mechanism distinct from either the depolarising effect of glucose or Gq-coupled response to FFAR1 and GPR120 activation. Rising cAMP levels in enteroendocrine cells have been linked to cytosolic Ca^{2+} elevation, enhanced rates of secretion and increased gene transcription, via pathways including the recruitment of protein kinase A and Epac2[54,62–64].

Protein sensing

It is well established that enteroendocrine cells respond to amino acids and peptides in the duodenum, but less so in the ileum. Candidate sensors for ingested protein include receptors and transporters for amino acids, small peptides and proteins. Which of these are expressed and are active in enteroendocrine cells is, however, poorly defined. There are a number of identified amino acid-responsive G-protein coupled receptors, including the calcium sensing receptor, metabotropic glutamate receptors, the umami taste receptor (Tas1R1/Tas1R3 heterodimer) and GPRC6A, which have variously been postulated to play a role in the gut. Purified I cells express high levels of calcium sensing receptor and exhibit Ca^{2+} responses to aromatic amino acids, as predicted from the known amino acid preference of this receptor[65]. Although knockout or pharmacological inhibition of the calcium sensing receptor resulted in impaired CCK and GLP-1 response to aromatic amino acids and protein hydrolysate *in vitro*[65,66], the effect of receptor knockout on the physiological response to ingested protein *in vivo* is not yet reported. Evidence linking the other amino acid receptors to intestinal protein sensing is currently weak.

Uptake of amino acids has also been linked to stimulation of GLP-1 release *in vitro*, by a pathway involving a sodium-coupled transporter system. Similar to the responsiveness of L cells to SGLT1-mediated glucose transport, electrogenic uptake of glutamine and other amino acids via ATA2 (SLC38A2) and B0AT1 (SLC6A19) appears to trigger membrane depolarisation via the small associated inward Na^+ current carried by the transporter[67,68]. Proton uptake via the peptide transporter PEPT1 may also contribute to the detection of small di- and tripeptides[69,70], although evidence supporting a role for this pathway *in vivo* is currently lacking.

Therapeutic modulation of gut hormone secretion

In the field of diabetes and obesity, therapeutic strategies are under development to modulate endogenous gut hormone secretion. The potent incretin action of GLP-1 and GIP makes these interesting targets for blood glucose control, and the anorexic peptides, GLP-1, PYY and CCK, are of interest for the treatment of obesity. Small molecules are currently under evaluation in preclinical and clinical trials, targeting enteroendocrine specific receptors such as GPR119, GPBAR1, FFAR1 and GPR120. Whether any of these will exert therapeutically beneficial effects on the human population remains to be determined.

Bariatric surgery reduces appetite and improves blood glucose control in a majority of subjects, although it is associated with a significant surgical and anaesthetic mortality rate, and a risk of delayed hypoglycaemia requiring strict dietary control, medication or enteral feeding. It was initially reported that procedures that bypassed the foregut, such as Roux-en-Y gastric bypass, were more effective than gastric banding, leading to the idea that the duodenum physiologically secretes an anti-incretin hormone, whose levels fall after surgery[8]. This idea was supported by preliminary results showing the effectiveness of an endoluminal sleeve, that is anchored in the duodenum and prevents food from making direct contact with the duodenal epithelium[71]. However, relatively large patient cohorts are required to distinguish which surgical procedures have metabolic benefits over and above that due to the associated weight loss, and a clearer picture is now starting to emerge. It seems evident that the success of Roux-en-Y gastric bypass is, in fact, mirrored by that of sleeve gastrectomy, a procedure that removes the greater curvature of the stomach, converting the remainder into a small proximal stomach pouch and a distal sleeve carrying food to the duodenum[72]. With this procedure, the foregut is not bypassed, making it unlikely that a duodenal anti-incretin is predominantly responsible for the observed improvement in diabetes control.

Both Roux-en-Y gastric bypass and sleeve gastrectomy result in a rapid rate of food delivery to the jejunum and lower small intestine and dramatically elevated plasma concentrations of GLP-1 and PYY[72]. A likely factor contributing to the improved blood glucose control following these procedures is therefore the enhanced stimulation of insulin release from pancreatic β-cells by GLP-1. It is argued that this is unlikely to be the only explanation for the beneficial effect of bariatric surgery, as therapy with injectable GLP-1 mimetics has not matched the effectiveness of some surgical procedures. Whether this is due to the different routes of GLP-1 delivery, or the associated energy restriction achieved with bariatric surgery, will be interesting topics for future study.

Conclusions

The gut endocrine system provides critical physiological signals indicating the quantity and quality of ingested food and enabling the body to direct nutrients arriving in the circulation to appropriate target tissues and metabolic pathways. The success of GLP-1-based therapies and bariatric surgery for the treatment of diabetes and obesity has heralded a new wave of research interest in this field, with the hope that this will identify novel physiologically active peptides or new roles for hormones that were not previously evaluated for their antidiabetic or anorexigenic properties in human subjects. If the therapeutic benefits of bariatric procedures can be reproduced medically, this will provide a quantum leap forward for the future treatment of diabetes and obesity.

Acknowledgements

F. M. G. is funded by the Wellcome Trust (no. WT088357) and EU (FP7/2007-2013; grant agreement no. 266408). The author declares no conflict of interest.

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