Molecular mechanisms of incretin hormone secretion
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Incretin peptides (glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP)) are secreted from enteroendocrine cells in the intestinal epithelium, and help to coordinate metabolic responses to food ingestion. A number of molecular mechanisms have recently been defined that underline carbohydrate, lipid and protein sensing in gut endocrine cells. Knockout mice lacking sodium glucose transporter-1 (SGLT-1) or the short chain fatty acid sensing receptor FFAR2 (GPR43), for example, have highlighted the importance of these molecules in incretin secretion. This review outlines our current understanding of sensory pathways in incretin secreting cells and highlights the therapeutic potential of targeting them for the development of novel therapies for obesity and diabetes.

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Introduction
The gastrointestinal (GI) tract, in addition to digesting food and absorbing the available nutrients, releases hormones with important physiological roles in regulating plasma glucose levels, gut motility and satiety. Amongst these, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are known as incretins, based on their ability to enhance glucose-stimulated insulin secretion. The possibility of stimulating the release of endogenous incretins as a therapeutic strategy for the treatment of type 2 diabetes (T2DM) and obesity has led to heightened interest in the physiology of enteroendocrine cells and the gut-brain-pancreatic axis. This review will focus on our current understanding of the enteroendocrine cell populations known as K-cells and L-cells, which primarily secrete GIP and GLP-1, respectively.

Enterendocrine cells have historically been difficult to study as they are found scattered within the intestinal epithelium, but recent advances in labelling specific cell populations in transgenic mice with fluorescent reporters have enabled live cell identification and purification. As a consequence, there are increasing numbers of published studies analysing the molecular events underlying stimulus secretion coupling in enteroendocrine cell types. An unexpected outcome of these investigations has been the observation that enteroendocrine cells are more plurihormonal than previously thought. Although L-cells have long been known to produce peptideYY (PYY) in addition to the products of proglucagon processing (GLP-1, GLP-2 and oxyntomodulin), it was surprising to find that most K-cells and L-cells also produce cholecystokinin (CCK) [1,2]. Many mechanisms described here might also therefore play a role in the secretion of other enteroendocrine hormones, although the relative contributions of different signalling pathways likely differ between cells and along the length of the GI tract. Thus, whereas GIP secreting K-cells are predominantly located in the duodenum and are exposed to nutrients soon after food ingestion, GLP-1 is also produced more distally where its secretion may be influenced by slowly digested macronutrients and products of bacterial fermentation (Figure 1).

L-cells and K-cells, like many of the enteroendocrine family, consist of an apical pole with microvilli facing the gut lumen and a broader base where peptides are released, and it is believed that peptide secretion is a result of direct sensing of nutrients in the lumen [3]. Recent work has begun to elucidate the mechanisms underlying nutrient sensing and peptide release, and in vitro studies suggest that L-cells are electrically active, exhibiting action potentials and calcium transients in response to glucose [4]. Whilst minor differences in glucose sensing by K-cells have been described [5], many molecular mechanisms described below are active in GIP and GLP-1 secreting cells and are likely also to be involved in the release of other enteroendocrine hormones. However, to what extent the different identified sensory pathways contribute to nutrient detection in vivo remains to be fully established.

Nutrient signalling
Carbohydrate sensing
Glucose is a robust stimulant of incretin release and several pathways of carbohydrate sensing have been
proposed. In the upper small intestine, there is good evidence that GLP-1 and GIP release are triggered by Na⁺ coupled glucose uptake mediated by the brush border sodium glucose cotransporter (SGLT1). Small transporter-associated currents appear sufficient to drive membrane depolarisation, in turn triggering electrical activity, voltage-gated calcium entry and peptide release [6*]. This idea is supported by the demonstration that glucose-dependent GLP-1 and GIP secretion in vitro are prevented by pharmacological SGLT1 inhibitors [7*] and that SGLT1 knockout mice have impaired GIP and GLP-1 release early after glucose gavage [8]. By contrast, plasma GLP-1 levels measured later after glucose administration appeared markedly elevated in mice lacking SGLT1, suggesting that attenuated glucose absorption in the upper small intestine results in increased delivery to the L-cell richer distal gut, where alternative sensing pathways may be recruited [9]. One hypothesis is that an increased distal glucose load facilitates microbial fermentation and the production of short chain fatty acids, which in turn activate L-cells via alternative signalling pathways [10]. SGLT1 independent glucose-sensing pathways have, however, been identified in enteroendocrine cells, and may contribute to the delayed elevation of GLP-1 levels in SGLT1 knockout mice. L-cells and K-cells express glucokinase and ATP sensitive potassium (K\textsubscript{ATP}) channel subunits, providing the machinery to couple electrical activity to glucose metabolism. This pathway seems not to be responsible for the peak incretin levels detected early after glucose ingestion, which were unaffected in humans treated with K\textsubscript{ATP} channel inhibitors [11]. Measurement of L-cell glucose concentrations suggests that although the SGLT1-mediated Na⁺ flux is large enough to drive membrane depolarisation, the accompanying monosaccharide flux is insufficient to alter intracellular glucose concentrations. L-cells have a high
phloretin-sensitive glucose flux, however, suggesting that facilitative glucose transporters could equilibrate cytoplasmic with basolateral glucose levels, and that L-cell metabolism would predominantly be influenced by glucose arriving from the plasma rather than luminal glucose direction [77]. The interplay between plasma glucose, metabolism and GLP-1 secretion remains, however, an enigma. A third, and highly controversial pathway links enteroendocrine secretion to activation of sweet taste receptors. This pathway utilises a G protein coupled receptor heterodimer (T1R2/T1R3) as the detector of glucose and other sweeteners and couples through the G protein α-gustducin. α-gustducin and T1R3 have been detected in the gut, and in some studies were found colocalised with GLP-1 and GIP [12–14], but several findings suggest they may not themselves act as the L-cell glucose sensor. Convincing arguments against an important role of sweet taste receptors are the multiple demonstrations that ingestion of glucose, but not artificial sweeteners, triggers elevation of plasma incretin levels in rodents [15] and humans [16].

Lipid sensing

Products of fat ingestion have not been reported to alter L-cell electrical activity, but are rather thought to be sensed by G protein coupled receptors (GPCRs). In L-cells, several GPCRs have been implicated in lipid signalling, such as GPR120 [17], GPR119 [18,19] and FFAR1 (GPR40) [20]. FFAR1 and GPR120 respond to long-chain and medium-chain fatty acids, and are thought to be Gq-coupled, activating phospholipase C and thereby triggering IP3 mediated Ca2+ release and secretion of peptides [21]. Other lipids that rise in concentration in the intestine postprandially include 2-monocacylglycerols, which are produced from triglycerides by lipases and act as ligands for GPR119 [22], which is expressed both in K-cells and L-cells [4,5,19]. GPR119 is preferentially Gq-coupled and ligand binding results in activation of adenylyl cyclase, an increase in cAMP levels and enhanced L-cell secretion [19,23]. Alternative lipid sensing pathways underlying GLP-1 secretion, involving uptake by fatty-acid transport protein (FATP4) [24] and activation of atypical protein kinase C [25] have also been described.

SCFA are produced in the colon during bacterial fermentation of dietary fibre or, less usually, of non-absorbed carbohydrate. They may provide one link between fibre content, the gut microbiome and L-cells [26,27], acting through two GPCRs, FFAR2 and FFAR3. FFAR2 can couple to Gq/signalling pathway and Gs-signalling pathway, whilst FFAR3 seems to lack a Gq component [28]. A role for FFAR2 in GLP-1 secretion was suggested by the findings that SCFA triggered Ca2+ transients in primary L-cells and that circulating GLP-1 levels and SCFA-dependent GLP-1 release in vitro were impaired in mice lacking FFAR2 [29].

Protein sensing

Although protein digestion is an effective stimulus of GLP-1 release, the optimal size of the digestion products for triggering secretion remains uncertain. Several amino acids have been shown to stimulate GLP-1 release in vitro [30,31]. The effectiveness of L-Gln has been attributed to its ability both to trigger membrane depolarisation via electrogenic Na+-dependent amino acid uptake, and to elevate cytoplasmic cAMP concentrations, perhaps though activation of an unidentified Gs-coupled GPCR [30,31]. Ingestion of L-Gln also stimulates GLP-1 release in healthy and obese and diabetic humans [32]. GPCRs have been linked to the sensing of other luminal amino acids by enteroendocrine cells; GPRC6A to ornithine [33] and the CaSR to phenylalanine [34]. The sensing of larger protein digestion products simulated by, for example meat hydrolysate has been linked to activation of mitogen-activated protein (MAP) kinases, but the receptors involved are less clear [35,36].

Non-nutrient pathways

GLP-1 secretion is not only stimulated by nutrients, but also by other luminal components. Enteral progesterone has been implicated in incretin secretion through activation of plasma membrane receptors [37]. Bile acids are also involved in the integration of metabolic signals and have been implicated in fibroblast growth factor 15/19 secretion from the distal gut downstream of the well-characterised nuclear hormone receptor FXR [38]. In L-cells, however, bile acids appear to stimulate GLP-1 secretion through activation of the predominantly Gs coupled receptor TGR5 (GPRAR) [39,40]. Recently, administration of bile acids has been shown to have positive effects on glucose homeostasis and plasma GLP-1 levels in human volunteers [41,42]. Interestingly plasma bile acid levels increase after bariatric surgery, and bile acid stimulated GLP-1 secretion might contribute to the associated improvements in metabolic control [43].

Inhibitory pathways

In addition to stimulatory pathways enhancing incretin secretion, enteroendocrine cells also express GPCRs coupled to Gi proteins with inhibitory functions. K-cells and L-cells, for example, express Gi-coupled somatostatin receptors. Somatostatin impairs the release of GLP-1 and GIP, and in enteroendocrine cell lines inhibits forskolin-stimulated cAMP transients, consistent with the recruitment of a Gi coupled signalling pathway [44,45]. Enhanced somatostatin release is a likely pathway underlying the observed inhibition of GLP-1 secretion in patients treated with GLP-1 mimetics [46]. The Gi-coupled endocannabinoid receptor Cnr1 has also been linked to modulation of incretin hormone secretion. Cnr1 is expressed at higher levels in K-cells than L-cells and preferentially inhibits secretion of GIP rather than GLP-1 [44].
It is becoming clear that enteroendocrine cells receive signals from multiple inputs, both from ingested nutrients and components in the gut lumen, and also from other enteroendocrine cells and tissues. These inputs involve on the one hand electrogenic pathways, through co-transport of Na⁺, and the other hand GPCRs and classical downstream G protein coupled pathways. It is hoped that a greater understanding of the physiological signalling pathways employed by enteroendocrine cells in vivo could be exploited to target the cells for the treatment of T2DM and obesity.

**Therapeutic potential and future possibilities**

On the basis of the fundamental importance of incretins for glucose homeostasis, therapies based on activating the incretin axis have proved highly effective in treating T2DM. Stable injectable GLP-1 mimetics and inhibitors of dipeptidyl peptidase 4 (DPP4), which rapidly inactivates circulating GLP-1, are licensed for the treatment of T2DM and, in the case of GLP-1 mimetics, offer additional benefits such as weight loss and cardioprotection [47,48]. Therapies based on targeting endogenous enteroendocrine cells, however, could potentially offer the benefits of releasing more than one peptide, thus activating appetite suppressants as well as insulino tropic pathways. Several candidate enteroendocrine targets, including FFAR1, GPR119 and GPR120, are currently under investigation. Amongst these, the FFAR1 agonist TAK-875 targets pancreatic β-cells as well as L-cells and exhibits favourable glycaemic effects in patients with the T2DM [49], although the relative contribution of GLP-1 may be minor. Agonists for GPR119 showed encouraging efficacy in animal models, but had limited glucose lowering and incretin activity in humans, for reasons that remain to be established [50,51]. Somewhat surprisingly, a dual acting SGLT1/2 inhibitor has recently been shown to cause elevation in GLP-1 and PYY levels in rodents and human patients with type 2 diabetes [9,52], thus mimicking the effect of SGLT1 knockout, perhaps by feeding the gut microbiome and enhancing SCFA production in the L-cell rich distal gut [10]. It seems likely that the markedly elevated post-prandial GLP-1 and PYY levels that follow some forms of bariatric surgery [53] are similarly linked to increased delivery of nutrients to the distal gut, and have dramatic effects on appetite and T2DM resolution [54,55,56**,57,58]. Mimicking the effects of bariatric surgery by medical interventions would be a major therapeutic breakthrough.

**Conclusion**

The enteroendocrine system plays a fundamental role in orchestrating post-prandial physiology, and is central to the regulation of glucose homeostasis and satiety. The success of current GLP-1-based therapies and the dramatic effects of bariatric surgery on insulin secretion and appetite greatly support the future development of therapeutic strategies that exploit targets upstream of enteroendocrine secretion as novel treatments for T2DM and obesity. Despite the notable progress made to date in dissecting the mechanisms of stimulation-coupled enteroendocrine secretion, there are currently no drugs clinically approved that directly target endogenous enteroendocrine cells. The unexpected success of bariatric surgery in treating T2DM, however, highlights the benefits that could be achieved through a gut-based therapeutic approach.

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