SYMPOSIUM REPORT

Nutritional regulation of glucagon-like peptide-1 secretion

Gwen Tolhurst, Frank Reimann and Fiona M. Gribble

Cambridge Institute for Medical Research and Department of Clinical Biochemistry, Addenbrooke's Hospital, Hills Road, Cambridge CB2 0XY, UK

Glucagon-like peptide-1 (GLP-1), released from L-cells in the intestinal epithelium, plays an important role in postprandial glucose homeostasis and appetite control. Following the recent therapeutic successes of antidiabetic drugs aimed at either mimicking GLP-1 or preventing its degradation, attention is now turning towards the L-cell, and addressing whether it would be both possible and beneficial to stimulate the endogenous release of GLP-1 *in vivo*. Understanding the mechanisms underlying GLP-1 release from L-cells is key to this type of approach, and the use of cell line models has led to the identification of a variety of pathways that may underlie the physiological responses of L-cells to food ingestion. This review focuses on our current understanding of the signalling mechanisms that underlie L-cell nutrient responsiveness.

(Received 26 September 2008; accepted after revision 3 November 2008; first published online 10 November 2008)
Corresponding author F. M. Gribble: Wellcome Trust/MRC Building, Addenbrooke's Hospital, Hills Road, Cambridge CB2 0XY, UK. Email: fmg23@cam.ac.uk

It is widely recognized that the oral ingestion of glucose triggers more insulin release than a similar plasma glucose profile delivered intravenously – a phenomenon known as the 'incretin effect'. It is largely attributable to two hormones, glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1), which are released from the intestine in response to food ingestion, and have direct stimulatory effects on the pancreatic β-cell. The combined action of GLP-1 and GIP is believed to account for up to 70% of the total insulin secretory response after a meal.

Recent years have witnessed the development and licensing of a number of antidiabetic agents targeted towards the GLP-1 axis, both in the form of GLP-1 mimetics and inhibitors of dipeptidyl peptidase-IV (DPP-IV) (Drucker & Nauck, 2006), the enzyme responsible for the rapid inactivation of GLP-1 in the circulation. These agents improve blood glucose control because they increase insulin release, reduce glucagon secretion and slow gastric emptying, and as the stimulation of insulin secretion is glucose dependent they carry a lower risk of provoking hypoglycaemic side-effects than many of the existing oral therapies. With prolonged treatment, GLP-1 mimetics also have beneficial effects on appetite and body weight, and have been shown to enhance β-cell mass as a consequence of promoting β-cell growth and preventing β-cell apoptosis (Brubaker & Drucker, 2004; Edwards, 2004). In view of the therapeutic success of the current GLP-1-based strategies, attention is now shifting towards the L-cells that naturally produce GLP-1, and whether it would be possible to harness the endogenous stores of GLP-1 in the gut using a targeted therapeutic approach.

Regulation of secretion

GIP and GLP-1 are secreted from open-type intestinal endocrine cells that make direct contact with the gut lumen (Eissele *et al.* 1992) and are therefore believed to sense the arrival and passage of nutrients along the gastrointestinal tract. Like other enteroendocrine cells, the K-cells that produce GIP and L-cells that produce GLP-1 lie scattered along the length of the intestinal epithelium. The highest density of K-cells is found in the duodenum, whereas L-cells increase in density along the length of the gastrointestinal tract, with the highest numbers being found in the distal ileum and colon. The cells form part of a larger enteroendocrine system, secreting a range of hormones including cholecystokinin, serotonin and secretin. Whilst enteroendocrine cells have been classified according to their hormonal content, it is now apparent that many cells produce more than one hormone. L-cells, for example, produce glucagon-like peptide-2 (GLP-2) and peptide YY, in addition to GLP-1.

Unfortunately, studies into the cellular physiology of enteroendocrine cells have been held back by difficulties

This report was presented at a Physiological Society Themed Meeting on *Orchestration of metabolism in health and disease*, which took place at the University of Oxford, UK, 9–11 September 2008.

© 2009 The Authors. Journal compilation © 2009 The Physiological Society
DOI: 10.1113/jphysiol.2008.164012

The Journal of Physiology

in culturing primary intestinal cells, and the inability to distinguish the different cell types morphologically for single cell analysis. Experiments on GLP-1 release have therefore been largely confined to work on model cell lines, immunohistochemical analysis of fixed tissue and dynamic studies on the intact intestine either *in vivo* or *ex vivo*. This review focuses on what is currently known about the mechanisms of GLP-1 release from *in vitro* models, and the potential future developments on the horizon.

(i) A proximal–distal loop

Plasma GLP-1 levels rise within 10–15 min of food ingestion and reach peak levels of 15–50 pmol l^{-1} by 40 min (Holst, 2007). As the L-cell density is low in the upper intestine, it was originally believed that the direct stimulation of L-cells by nutrients could not account for the observed early postprandial rise in plasma GLP-1. To explain this phenomenon a proximal–distal loop was proposed, involving nutrient detectors located in upper regions of the GI tract which would control the release of GLP-1 from distal L-cells by neural or hormonal circuitry (reviewed in Holst, 2007). Whilst this type of pathway almost certainly contributes to the global profile of postprandial GLP-1 release, it is now recognized that the density of L-cells in the human duodenum may be sufficiently high to account for the early phase of GLP-1 secretion (Theodorakis *et al.* 2006).

(ii) The glucose sensor

Evidence that L-cells are themselves nutrient sensitive comes from the study of model GLP-1-secreting cell lines: GLUTag, STC-1 and NCI-H716 (Drucker *et al.* 1994; Abello *et al.* 1994; Reimer *et al.* 2001). Whilst GLUTag cells appear to be a good model for murine GLP-1 release, NCI-H716 cells have the advantage of being of human origin, and STC-1 cells are probably a less specific model for the L-cell, as they also secrete a range of other intestinal hormones, including cholecystokinin and secretin. As these cell lines have different origins and properties, it is perhaps not surprising that they are not identical in their responsiveness to nutrient stimuli. The consensus view from all three lines, however, is that hormone secretion is dependent on a rise in the cytoplasmic calcium concentration ($[Ca^{2+}]_i$), which could arise either by Ca^{2+} release from intracellular stores or by influx across the plasma membrane. At least in GLUTag and STC-1 cells, the Ca^{2+} influx pathway can be attributed to the activation of voltage-gated calcium channels, suggesting in turn a role for membrane depolarization in the initiation of GLP-1 secretion.

Although GLP-1 release *in vivo* is strongly stimulated by glucose ingestion, the underlying mechanism is still debated, both in terms of the relative contributions of direct *versus* indirect glucose-sensing pathways, and the identity of the signalling pathways within the L-cells. The finding that GLUTag and NCI-H716 cells are themselves glucose sensitive (Reimann & Gribble, 2002; Jang *et al.* 2007) supports the idea that at least a component of oral glucose-stimulated GLP-1 release arises from the direct stimulation of L-cells by luminal sugars. However, a variety of signalling mechanisms have been proposed to explain how L-cells might sense glucose, including ATP-sensitive potassium (K_{ATP}) channel closure, sodium glucose cotransporter (SGLT) activity and activation of sweet taste receptors. These different alternatives are illustrated in Fig. 1, and discussed in more detail below.

K_{ATP} channel-dependent glucose sensing. K_{ATP} channels are perhaps the best characterized glucose sensors, having been described originally as metabolism-dependent ion channels in cardiac muscle and pancreatic β-cells, but subsequently found in a number of glucose-responsive tissues, including the brain and other islet cell types. Closure of K_{ATP} channels in β-cells is brought about by the increasing ATP and falling MgADP concentrations that accompany an elevated rate of glucose metabolism. The consequent reduction of the background K^+ flux enables small inward currents to drive membrane depolarization, which in turn triggers action potentials, entry of Ca^{2+} via voltage-gated Ca^{2+} channels and the stimulation of insulin secretion (Rorsman, 1997). GLUTag cells are similarly electrically active, exhibiting an enhanced rate of action potential firing, Ca^{2+} entry and secretion of GLP-1 in response to glucose and the K_{ATP} channel inhibitor, tolbutamide (Reimann & Gribble, 2002). Whereas in β-cells, glycolytic flux under the control of glucokinase is believed to fix the set-point of the cell close to the plasma glucose concentration, the glucose sensitivity of GLUTag cells is comparatively left-shifted, raising questions about whether it is similarly glucokinase dependent. It also remains to be established whether the glucose dependence of GLUTag cells faithfully reflects the behaviour of L-cells *in situ*.

Despite the clear expression and functional demonstration of K_{ATP} channels in GLUTag cells, the role of K_{ATP} channels in GLP-1 secretion *in vivo* has been questioned, largely because sulphonylureas, which stimulate insulin release in type 2 diabetes as a consequence of their inhibitory action on K_{ATP} channels, have not been shown to trigger GLP-1 secretion in humans. In support of a role for K_{ATP} channels in L-cells, however, it was recently demonstrated that Kir6.2, which forms the pore of the K_{ATP} channel, can be identified in human L-cells by immunohistochemistry (Nielsen *et al.* 2007). Furthermore, we have also demonstrated

© 2009 The Authors. Journal compilation © 2009 The Physiological Society

high expression levels of K_{ATP} channel subunits and glucokinase in murine L-cell populations separated by flow cytometry from transgenic mice with fluorescently tagged L-cells (Habib *et al.* 2007).

Sodium–glucose cotransporter activity. It has been known for some years that non-metabolizable, as well as metabolizable, sugars can stimulate GLP-1 release, provided that they are substrates of the intestinal glucose uptake pathway and applied in the presence of sodium (Herrmann *et al.* 1995; Ritzel *et al.* 1997). In support of this finding, we identified an additional glucose-sensing pathway in GLUTag cells, whereby sugars trigger membrane depolarization and GLP-1 secretion via the electrogenic action of SGLT1 (Gribble *et al.* 2003). SGLT1 is the principal sugar transporter responsible for glucose absorption at the luminal surface of the intestinal epithelium, and uses the inwardly directed sodium gradient to drive glucose uptake into cells, even at low luminal glucose concentrations. In GLUTag cells, we showed that the electrogenic activity of SGLT1 was itself sufficient to drive membrane depolarization and GLP-1 release. Indeed, the EC_{50} of glucose-induced GLP-1 secretion from GLUTag cells (0.2–0.5 mM) is closer to the half-maximally effective substrate concentration of SGLT1 ($K_M = 0.2$ mM; Díez-Sampedro *et al.* 2000) than to that of glucokinase ($S_{0.5} \sim 8$ mM; Matschinsky, 2002), raising the possibility that SGLT1 activity itself determines the concentration dependence of glucose-stimulated GLP-1 release.

It is generally agreed that the facilitative glucose transporter GLUT2 plays a role in basolateral glucose flux in small intestinal epithelial cells, and if similarly expressed in L-cells could provide both a glucose efflux pathway and a potential means of responding to blood glucose levels. Although GLP-1 release is generally considered to be insensitive to plasma glucose levels, $GLUT2^{-/-}$ mice were found to display impaired GLP-1 responses to oral glucose (Cani *et al.* 2007). Furthermore, GLP-1 release from porcine intestine, perfused both via the lumen and the vasculature, was shown to be responsive to physiological changes in the vascular glucose concentration (Hansen *et al.* 2004). These findings raise the possibility that a metabolism-dependent pathway, responding to the plasma glucose concentration via GLUT2, glucokinase and K_{ATP} channels, could set the responsiveness of the L-cell to luminal nutrients. As the inward currents generated by electrogenic nutrient

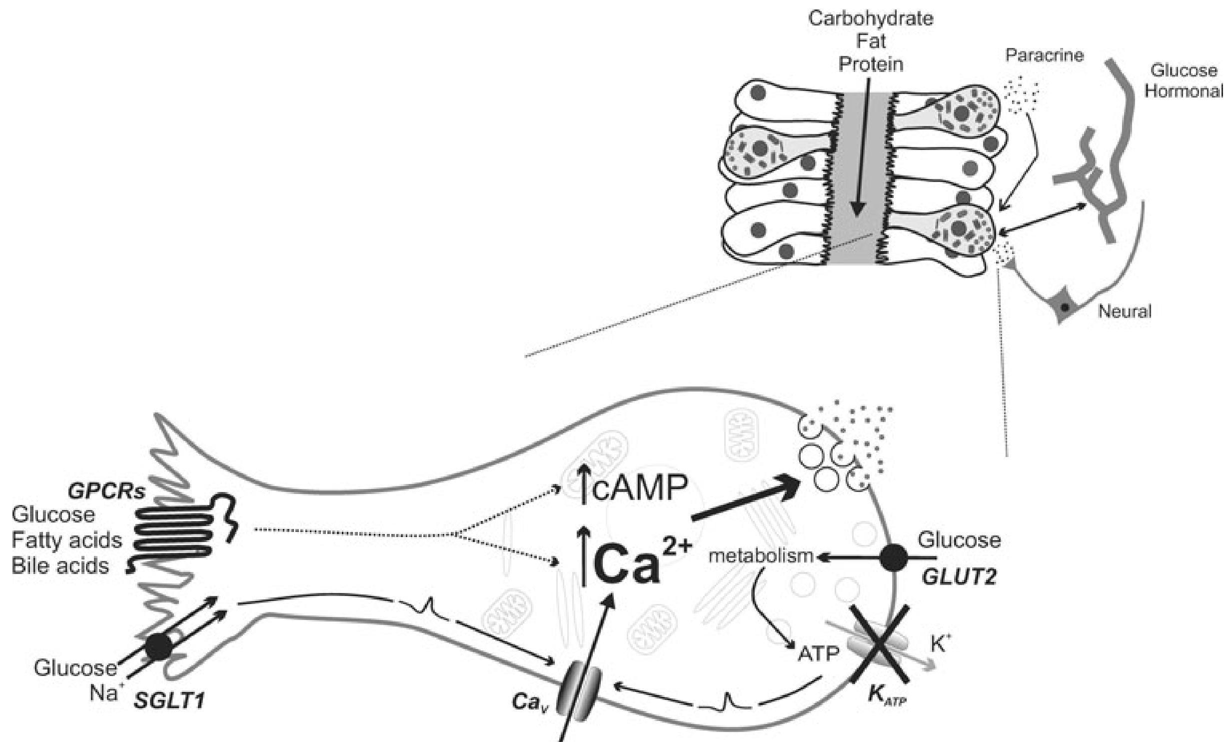

Figure 1. A working model for nutrient-stimulated GLP-1 release
Upper panel: enteroendocrine cells in the intestinal epithelium (grey) detect nutrients passing in the lumen, but also respond to paracrine, neural and hormonal stimuli. Lower panel: potential nutrient-sensing pathways in an individual L-cell include electrogenic uptake pathways, such as SGLT1, metabolic closure of K_{ATP} channels and activation of G protein-coupled receptors (GPCRs). Downstream signalling pathways include elevated cAMP and [Ca^{2+}], which stimulate vesicle fusion and the consequent release of GLP-1.

© 2009 The Authors. Journal compilation © 2009 The Physiological Society

transporters are very small, their ability to stimulate electrical activity would be strongly influenced by the magnitude of background currents like K_{ATP}.

Sweet taste receptor pathways. The sweet taste receptor found in lingual taste buds is a heteromer of Tas1R2 and Tas1R3 subunits, acting through signalling pathways coupled to α-gustducin and cAMP changes as well as to activation of phospholipase-Cβ2 and TRPM5 channels (Rozengurt & Sternini, 2007). Recent reports have proposed that sweet taste receptors might similarly act as the glucose sensors in enteroendocrine cells. This is based partly on immunohistochemical studies, which showed that components of the sweet taste machinery were found in scattered enteroendocrine cells (Rozengurt & Sternini, 2007). Furthermore, mice with targeted knockdown of Tas1R3 or α-gustducin exhibited impaired glucose-stimulated GLP-1 secretion *in vivo*, and did not show the characteristic increase in intestinal SGLT1 expression normally triggered by a high carbohydrate diet (Margolskee *et al.* 2007). Taken together with the finding that artificial sweeteners triggered GLP-1 release from cell lines, the data have been interpreted as indicating that sweet taste receptors in L-cells underlie the glucose responsiveness of GLP-1 release, and that this has downstream effects on SGLT1 expression. Although potentially exciting, it remains to be demonstrated that artificial sweeteners can substitute for glucose as an acute stimulus for GLP-1 release in humans or animals.

(iii) Other stimuli

Fats and protein are other well-known stimuli of GLP-1 release *in vivo* (Elliott *et al.* 1993; Herrmann *et al.* 1995; Hall *et al.* 2003). The mechanism of protein-triggered GLP-1 release remains unclear, but it has been reproduced by peptones in humans (Layer *et al.* 1995), rodents (Dumoulin *et al.* 1998) and cell models (Cordier-Bussat *et al.* 1998), as well as by amino acids (Herrmann *et al.* 1995; Reimann *et al.* 2004). In GLUTag cells, we found that glutamine was a potent trigger of GLP-1 release, acting in part via the sodium-dependent amino acid transporter SLC38A2 (Reimann *et al.* 2004). This supports the idea that small inward currents carried by electrogenic nutrient transporters can trigger L-cell excitability, and raises the possibility that other electrogenic transporters might have similar depolarizing effects. An interesting candidate is the proton-coupled di- and tri-peptide transporting system (PEPT1 or PEPT2; SLC15A1,2), the activity of which could potentially account for the stimulation of GLP-1 release by peptones. Although this remains to be demonstrated experimentally, STC-1 cells with enhanced expression of PEPT1 brought about by heterologous transfection, indeed exhibited membrane depolarization and secretion triggered by dipeptides (Matsumura *et al.* 2005).

G protein-coupled receptors (GPCRs) are regarded as potentially important components of the signalling pathways in L-cells, as they may underlie the regulation of L-cells by certain neurotransmitters and hormones (Abello *et al.* 1994; Herrmann-Rinke *et al.* 1995; Balks *et al.* 1997), as well as by some luminal nutrients. Studies in a variety of incretin-releasing models have shown the importance of $G_{\alpha s}$-coupled pathways that elevate cyclic AMP (cAMP), as well as $G_{\alpha q}$, which triggers cascades leading to IP_3-mediated Ca^{2+} release from intracellular stores and activation of protein kinase C (Brubaker, 1988; Damholt *et al.* 1998; Reimer *et al.* 2001; Reimann *et al.* 2006). Studies in cell lines have shown that cAMP not only stimulates GLP-1 secretion, but also enhances proglucagon biosynthesis (Brubaker *et al.* 1998). Interestingly, elevated cAMP has a direct depolarizing action on GLUTag cells, resulting from the modulation of membrane ion channels, which enables $G_{\alpha s}$-coupled receptor activation to stimulate GLP-1 release even in the absence of an alternative depolarizing stimulus (Simpson *et al.* 2007).

Although yet to be demonstrated definitively, one potential mechanism by which lipids, fatty acids and bile acids might stimulate GLP-1 release is via activation of specific GPCRs on L-cells, such as GPR40, GPR120, GPR119 and TGR5. GPRs 40 and 120 are $G_{\alpha q}$ coupled and responsive to long chain unsaturated fatty acids (Hirasawa *et al.* 2005; Edfalk *et al.* 2008). GPR119 and TGR5 are believed to be $G_{\alpha s}$ coupled and responsive to oleoylethanolamide and bile acids, respectively (Katsuma *et al.* 2005; Overton *et al.* 2006). There is also convincing evidence, however, that other fatty acid-responsive pathways, such as activation of PKCζ, may contribute to the stimulatory action of fatty acids on GLP-1 release (Iakoubov *et al.* 2007). Nevertheless, these G protein-coupled receptors have raised particular interest, because if expressed specifically in the L-cells, they would provide potential therapeutic targets for novel antidiabetic agents. Indeed, the first agents targeting GPR119 have been shown to stimulate beneficial metabolic effects *in vivo* (Chu *et al.* 2008).

The future

The use of model cell lines and fetal rat intestinal cultures (FRICs) has undoubtedly progressed research into the stimulus–secretory pathways in enteroendocrine cells. However, cell lines commonly differ in their genetic makeup and regulation, and may have undergone functional changes during the immortalization process. Although FRIC cultures contain primary L-cells, they are necessarily derived from fetal gut that has not yet been exposed to alimentation, perhaps accounting for

© 2009 The Authors. Journal compilation © 2009 The Physiological Society

their reported lack of responsiveness to glucose (Brubaker & Vranic, 1987). As the existing models are few in number and variable in their nutrient responsiveness, their validity for studying the adult incretin system needs to be addressed. In addition, L-cells *in situ* are polarized and integrated within an epithelial cell layer, and are therefore differentially exposed to luminal and plasma constituents at their apical and basolateral membrane surfaces. This environment almost certainly has profound effects on L-cell function but will be very difficult to replicate *in vitro*. To try to overcome some of these problems, and to provide standards against which to assess the existing models, we are currently working with transgenic mice expressing fluorescent markers in specific enteroendocrine cell types, in combination with studies on adult murine primary intestinal cultures (Parker *et al.* in press; Reimann *et al.* in press). These techniques allow the identification and purification of primary L-cells for single cell functional studies and gene expression analysis, and may enable the characterization of L-cells in a polarized environment. In the light of the emerging importance of the enteroendocrine system in the control of basic processes such as appetite and blood glucose homeostasis, and the probability that novel pharmacological tools will be developed to target specific pathways in L-cells, this field promises exciting new developments over the next few years.

References

Abello J, Ye F, Bosshard A, Bernard C, Cuber JC & Chayvialle JA (1994). Stimulation of glucagon-like peptide-1 secretion by muscarinic agonist in a murine intestinal endocrine cell line. *Endocrinology* **134**, 2011–2017.

Balks HJ, Holst JJ, von zur Mühlen A & Brabant G (1997). Rapid oscillations in plasma glucagon-like peptide-1 (GLP-1) in humans: cholinergic control of GLP-1 secretion via muscarinic receptors. *J Clin Endocrinol Metab* **82**, 786–790.

Brubaker PL (1988). Control of glucagon-like immunoreactive peptide secretion from fetal rat intestinal cultures. *Endocrinology* **123**, 220–226.

Brubaker PL & Drucker DJ (2004). Glucagon-like peptides regulate cell proliferation and apoptosis in the pancreas, gut, and central nervous system. *Endocrinology* **145**, 2653–2659.

Brubaker PL, Schloos J & Drucker DJ (1998). Regulation of glucagon-like peptide-1 synthesis and secretion in the GLUTag enteroendocrine cell line. *Endocrinology* **139**, 4108–4114.

Brubaker PL & Vranic M (1987). Fetal rat intestinal cells in monolayer culture: a new in vitro system to study the glucagon-like immunoreactive peptides. *Endocrinology* **120**, 1976–1985.

Cani PD, Holst JJ, Drucker DJ, Delzenne NM, Thorens B, Burcelin R & Knauf C (2007). GLUT2 and the incretin receptors are involved in glucose-induced incretin secretion. *Mol Cell Endocrinol* **276**, 18–23.

Chu ZL, Carroll C, Alfonso J, Gutierrez V, He H, Lucman A, Pedraza M, Mondala H, Gao H, Bagnol D, Chen R, Jones RM, Behan DP & Leonard J (2008). A role for intestinal endocrine cell-expressed G protein-coupled receptor 119 in glycemic control by enhancing glucagon-like peptide-1 and glucose-dependent insulinotropic peptide release. *Endocrinology* **149**, 2038–2047.

Cordier-Bussat M, Bernard C, Levenez F, Klages N, Laser-Ritz B, Philippe J, Chayvialle JA & Cuber JC (1998). Peptones stimulate both the secretion of the incretin hormone glucagon-like peptide 1 and the transcription of the proglucagon gene. *Diabetes* **47**, 1038–1045.

Damholt AB, Buchan AM & Kofod H (1998). Glucagon-like-peptide-1 secretion from canine L-cells is increased by glucose-dependent-insulinotropic peptide but unaffected by glucose. *Endocrinology* **139**, 2085–2091.

Díez-Sampedro A, Lostao MP, Wright EM & Hirayama BA (2000). Glycoside binding and translocation in Na^+-dependent glucose cotransporters: comparison of SGLT1 and SGLT3. *J Membr Biol* **176**, 111–117.

Drucker DJ, Jin T, Asa SL, Young TA & Brubaker PL (1994). Activation of proglucagon gene transcription by protein kinase-A in a novel mouse enteroendocrine cell line. *Mol Endocrinol* **8**, 1646–1655.

Drucker DJ & Nauck MA (2006). The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. *Lancet* **368**, 1696–1705.

Dumoulin V, Moro F, Barcelo A, Dakka T & Cuber JC (1998). Peptide YY, glucagon-like peptide-1, and neurotensin responses to luminal factors in the isolated vascularly perfused rat ileum. *Endocrinology* **139**, 3780–3786.

Edfalk S, Steneberg P & Edlund H (2008). Gpr40 is expressed in enteroendocrine cells and mediates free fatty acid stimulation of incretin secretion. *Diabetes* **57**, 2280–2287.

Edwards CM (2004). GLP-1: target for a new class of antidiabetic agents? *J R Soc Med* **97**, 270–274.

Eissele R, Göke R, Willemer S, Harthus HP, Vermeer H, Arnold R & Göke B (1992). Glucagon-like peptide-1 cells in the gastrointestinal tract and pancreas of rat, pig and man. *Eur J Clin Invest* **22**, 283–291.

Elliott RM, Morgan LM, Tredger JA, Deacon S, Wright J & Marks V (1993). Glucagon-like peptide-1 (7–36) amide and glucose-dependent insulinotropic polypeptide secretion in response to nutrient ingestion in man: acute post-prandial and 24-h secretion patterns. *J Endocrinol* **138**, 159–166.

Gribble FM, Williams L, Simpson AK & Reimann F (2003). A novel glucose-sensing mechanism contributing to glucagon-like peptide-1 secretion from the GLUTag cell line. *Diabetes* **52**, 1147–1154.

Habib AM, Reimann F, Parker HE & Gribble FM (2007). Expression of glucose-sensing machinery in intestinal GLP-1 secreting cells. *Diabetologia* **50** (suppl. 1), S287.

Hall WL, Millward DJ, Long SJ & Morgan LM (2003). Casein and whey exert different effects on plasma amino acid profiles, gastrointestinal hormone secretion and appetite. *Br J Nutr* **89**, 239–248.

© 2009 The Authors. Journal compilation © 2009 The Physiological Society

Hansen L, Hartmann B, Mineo H & Holst JJ (2004). Glucagon-like peptide-1 secretion is influenced by perfusate glucose concentration and by a feedback mechanism involving somatostatin in isolated perfused porcine ileum. *Regul Pept* **118**, 11–18.

Herrmann C, Göke R, Richter G, Fehmann HC, Arnold R & Göke B (1995). Glucagon-like peptide-1 and glucose-dependent insulin-releasing polypeptide plasma levels in response to nutrients. *Digestion* **56**, 117–126.

Herrmann-Rinke C, Vöge A, Hess M & Göke B (1995). Regulation of glucagon-like peptide-1 secretion from rat ileum by neurotransmitters and peptides. *J Endocrinol* **147**, 25–31.

Hirasawa A, Tsumaya K, Awaji T, Katsuma S, Adachi T, Yamada M, Sugimoto Y, Miyazaki S & Tsujimoto G (2005). Free fatty acids regulate gut incretin glucagon-like peptide-1 secretion through GPR120. *Nat Med* **11**, 90–94.

Holst JJ (2007). The physiology of glucagon-like peptide 1. *Physiol Rev* **87**, 1409–1439.

Iakoubov R, Izzo A, Yeung A, Whiteside CI & Brubaker PL (2007). Protein kinase Cz is required for oleic acid-induced secretion of glucagon-like peptide-1 by intestinal endocrine L cells. *Endocrinology* **148**, 1089–1098.

Jang HJ, Kokrashvili Z, Theodorakis MJ, Carlson OD, Kim BJ, Zhou J, Kim HH, Xu X, Chan SL, Juhaszova M, Bernier M, Mosinger B, Margolskee RF & Egan JM (2007). Gut-expressed gustducin and taste receptors regulate secretion of glucagon-like peptide-1. *Proc Natl Acad Sci U S A* **104**, 15069–15074.

Katsuma S, Hirasawa A & Tsujimoto G (2005). Bile acids promote glucagon-like peptide-1 secretion through TGR5 in a murine enteroendocrine cell line STC-1. *Biochem Biophys Res Commun* **329**, 386–390.

Layer P, Holst JJ, Grandt D & Goebell H (1995). Ileal release of glucagon-like peptide-1 (GLP-1). Association with inhibition of gastric acid secretion in humans. *Dig Dis Sci* **40**, 1074–1082.

Margolskee RF, Dyer J, Kokrashvili Z, Salmon KS, Ilegems E, Daly K, Maillet EL, Ninomiya Y, Mosinger B & Shirazi-Beechey SP (2007). T1R3 and gustducin in gut sense sugars to regulate expression of Na^+-glucose cotransporter 1. *Proc Natl Acad Sci U S A* **104**, 15075–15080.

Matschinsky FM (2002). Regulation of pancreatic β-cell glucokinase: from basics to therapeutics. *Diabetes* **51** (suppl. 3), S394–S404.

Matsumura K, Miki T, Jhomori T, Gonoi T & Seino S (2005). Possible role of PEPT1 in gastrointestinal hormone secretion. *Biochem Biophys Res Commun* **336**, 1028–1032.

Nielsen LB, Ploug KB, Swift P, Ørskov C, Jansen-Olesen I, Chiarelli F, Holst JJ, Hougaard P, Pörksen S, Holl R, de Beaufort C, Gammeltoft S, Rorsman P, Mortensen HB, Hansen L & Hvidøre Study Group (2007). Co-localisation of the Kir6.2/SUR1 channel complex with glucagon-like peptide-1 and glucose-dependent insulinotrophic polypeptide expression in human ileal cells and implications for glycaemic control in new onset type 1 diabetes. *Eur J Endocrinol* **156**, 663–671.

Overton HA, Babbs AJ, Doel SM, Fyfe MC, Gardner LS, Griffin G, Jackson HC, Procter MJ, Rasamison CM, Tang-Christensen M, Widdowson PS, Williams GM & Reynet C (2006). Deorphanization of a G protein-coupled receptor for oleoylethanolamide and its use in the discovery of small-molecule hypophagic agents. *Cell Metab* **3**, 167–175.

Parker HE, Habib AM, Rogers GJ, Gribble FM & Reimann F (in press). Glucose-dependent secretion of glucose-dependent insulinotropic polypeptide – molecular mechanisms in murine K-cells. *Diabetologia* doi: 10.1007/s00125-008-1202-x.

Reimann F & Gribble FM (2002). Glucose sensing in GLP-1 secreting cells. *Diabetes* **51**, 2757–2763.

Reimann F, Habib AM, Tolhurst G, Parker HE, Rogers GJ & Gribble FM (in press). Glucose-sensing in L-cells: a primary cell study. *Cell Metab* doi: 10.1016/j.cmet.2008.11.002.

Reimann F, Ward PS & Gribble FM (2006). Signalling mechanisms underlying the release of glucagon-like peptide-1. *Diabetes* **55** (suppl. 2), S78–S85.

Reimann F, Williams L, da Silva Xavier G, Rutter GA & Gribble FM (2004). Glutamine potently stimulates glucagon-like peptide-1 secretion from GLUTag cells. *Diabetologia* **47**, 1592–1601.

Reimer RA, Darimont C, Gremlich S, Nicolas-Metral V, Ruegg UT & Mace K (2001). A human cellular model for studying the regulation of glucagon-like peptide-1 secretion. *Endocrinology* **142**, 4522–4528.

Ritzel U, Fromme A, Ottleben M, Leonhardt U & Ramadori G (1997). Release of glucagon-like peptide-1 (GLP-1) by carbohydrates in the perfused rat ileum. *Acta Diabetol* **34**, 18–21.

Rorsman P (1997). The pancreatic β-cell as a fuel sensor: an electrophysiologist's viewpoint. *Diabetologia* **40**, 487–495.

Rozengurt E & Sternini C (2007). Taste receptor signaling in the mammalian gut. *Curr Opin Pharmacol* **7**, 557–562.

Simpson AK, Ward PS, Wong KY, Collord GJ, Habib AM, Reimann F & Gribble FM (2007). Cyclic AMP triggers glucagon-like peptide-1 secretion from the GLUTag enteroendocrine cell line. *Diabetologia* **50**, 2181–2189.

Theodorakis MJ, Carlson O, Michopoulos S, Doyle ME, Juhaszova M, Petraki K & Egan JM (2006). Human duodenal enteroendocrine cells: source of both incretin peptides, GLP-1 and GIP. *Am J Physiol Endocrinol Metab* **290**, E550–E559.

Acknowledgements

This work is supported by funding from the Wellcome Trust and the Lister Institute for Preventive Medicine.

© 2009 The Authors. Journal compilation © 2009 The Physiological Society