Targeting the Enteroendocrine System for Treatment of Obesity

Emily L. Miedzybrodzka, Fiona M. Gribble, and Frank Reimann

Contents

E. L. Miedzybrodzka · F. M. Gribble (✉) · F. Reimann
Wellcome Trust – MRC Institute of Metabolic Science, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK
e-mail: fmg23@cam.ac.uk

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Abstract

Mimetics of the anorexigenic gut hormone glucagon-like peptide 1 (GLP-1) were originally developed as insulinotropic anti-diabetic drugs but also evoke significant weight loss, leading to their recent approval as obesity therapeutics. Co-activation of receptors for GLP-1 and other gut hormones which reduce food intake – peptide YY ($PYY_{3–36}$), cholecystokinin (CCK) and glucose-dependent insulinotropic peptide (GIP) – is now being explored clinically to enhance efficacy. An alternative approach involves pharmacologically stimulating endogenous secretion of these hormones from enteroendocrine cells (EECs) to recapitulate the metabolic consequences of bariatric surgery, where highly elevated postprandial levels of GLP-1 and $PYY_{3–36}$ are thought to contribute to improved glycaemia and weight loss.

Keywords

CCK · Diabetes · Enteroendocrine · GIP · GLP-1 · Gut hormone · Obesity · PYY

1 Introduction

Obesity is a growing global health concern, and the major modifiable risk factor for type 2 diabetes mellitus (T2DM) and cardiovascular disease. Even relatively modest weight loss (5–10%) can substantially improve insulin sensitivity, pancreatic β-cell function, inflammation, and cardiovascular risk scores (Magkos et al. 2016). Beyond lifestyle modification and poorly-tolerated drugs, the most effective weight loss strategy for common obesity has been bariatric surgery.

Several pharmacological agents targeting the gut hormone axis have recently been developed as novel obesity therapeutics, after successful use in the treatment of T2DM. Once-weekly injections of the long-acting glucagon-like peptide 1 (GLP-1) mimetic semaglutide were recently shown to promote substantial weight loss in obese subjects in a series of phase III trials, with reductions of over 15% observed in half of participants (Wilding et al. 2021). This heralds a new era for obesity therapeutics and encourages development of other medications which activate the same anorexigenic pathways, while minimising side effects. This chapter examines existing and potential approaches to target the enteroendocrine system in obesity, including drugs which directly activate receptors for GLP-1 and other gut hormones, bariatric surgery, and modulation of endogenous enteroendocrine cell (EEC) secretion.

2 Gut Hormone Mimetics: GLP1R Agonism and Beyond

2.1 GLP-1 Receptor Agonists

GLP-1 itself cannot be given therapeutically due to its extremely short half-life (1–2 min), so several injectable GLP1R agonist peptides which are partly resistant to dipeptidyl peptidase 4 (DPP4) degradation have been developed (Drucker and Nauck 2006). Since the approval of the first such GLP1R agonist exenatide in 2005, significant advances have been made to increase half-life, allowing a shift from twice-daily to once-weekly injections and oral formulations (Marso et al. 2016; Zinman et al. 2019). Prominent side effects of incretin mimetics include nausea and GI symptoms such as diarrhoea, although these are somewhat reduced in second-generation treatments and are normally manageable following dose titration (Drucker and Nauck 2006; Zinman et al. 2019).

Following phase III trials showing outstanding weight loss efficacy of 10–20% in overweight subjects, the long-acting GLP1R agonist semaglutide has recently received FDA approval for treatment of obesity (Ryan 2021). This weight loss was far greater than the 5–10% achieved with another GLP1R agonist liraglutide, which was FDA-approved for obesity in 2014 (Mehta et al. 2017). This success is likely to encourage development of next-generation anti-obesity drugs targeting the GLP-1 system, which have the dual benefit of weight loss and improved glycaemic control. GLP1R agonists also reduce the risk of cardiovascular events such as stroke and myocardial infarction (Kristensen et al. 2019), although the underlying mechanisms and the extent of GLP1R expression in the heart and blood vessels remain unclear (McLean et al. 2021).

2.2 DPP4 Inhibitors

Another class of antihyperglycaemic drugs targeting the incretin system are the orally-bioavailable DPP4 inhibitors which increase the circulating half-life of both GLP-1 and the related hormone glucose-dependent insulinotropic peptide (GIP). While DPP4 inhibitors such as sitagliptin increase glucose-stimulated insulin secretion, they do not induce significant weight loss, unlike GLP1R agonists (Drucker and Nauck 2006). DPP4 has a broad range of other substrates, including peptide YY (PYY) and neuropeptide Y, which may have implications for the overall metabolic effects of DPP4 inhibition (Mulvihill and Drucker 2014). DPP4 cleavage converts $PYY_{1–36}$ to $PYY_{3–36}$, which mediates the majority of PYY's anorexigenic effects via NPY2R (Ballantyne 2006). Indeed, the appetite-suppressive effects of $PYY_{1–36}$ are lost in rats genetically deficient in DPP4 (Unniappan et al. 2006) and activation of NPY1R is linked to increased feeding (Kanatani et al. 2000). It has therefore been proposed that reduced $PYY_{3–36}$ and increased $PYY_{1–36}$ levels following DPP4 inhibition account for the lack of weight loss (Aaboe et al. 2010). An alternative possibility, however, would be that intestinal-derived active GLP-1 levels reached under normal physiological conditions are insufficient to promote weight loss. This

is supported by findings that the DPP4 inhibitor linagliptin did not enhance anorexia in diet-induced obese (DIO) mice even in the presence of an NPY2R agonist, despite elevated active GLP-1 levels (Hansen et al. 2021), and that GLP1R inhibition did not affect food intake reduction seen following selective chemogenetic activation of distal colonic L-cells, whereas NPY2R inhibition did (Lewis et al. 2020).

2.3 GLP1R/GCGR Co-agonism

In the development of novel incretin mimetics, there is increasing interest in the use of dual or triple agonists targeting other receptors in addition to the GLP1R. The rationale is that these may combine beneficial effects on body weight, glycaemic control and insulin sensitivity while minimising side effects (Brandt et al. 2018). The co-activation of gut hormone receptors also more closely mimics the physiological response to a meal, where multiple enteroendocrine peptides are co-secreted.

Despite the glucose-elevating effects of glucagon (GCG), chronic administration increases energy expenditure, likely via central mechanisms and hepatic upregulation of fibroblast growth factor 21 (FGF21) (Habegger et al. 2013). Glucagon action in the liver also reduces hepatic lipid content and alters hepatocyte metabolism to reduce the extent of non-alcoholic steatohepatitis (NASH), a common obesity co-morbidity (Boland et al. 2020). Balanced synthetic co-agonists of the GLP1R/GCGR, which mimic the activity of oxyntomodulin, are capable of improving glycaemic control in mice and humans (Ambery et al. 2018; Henderson et al. 2016). The GLP1R/GCGR co-agonist SAR425899 induced similar weight loss to liraglutide in a phase IIb trial, while improving HbA1c and increasing β-cell responsiveness to a mixed meal tolerance test (Schiavon et al. 2021); however, this drug was discontinued in 2018 due to incidence of adverse events and disappointing efficacy (Sanofi 2018). A separate phase IIb trial in overweight T2DM patients showed the GLP1R/GCGR co-agonist cotadutide (MEDI0382) evokes slightly greater weight loss (~5%) than a higher dose of liraglutide (Nahra et al. 2021). Unlike liraglutide, cotadutide reduces hepatic fibrosis and lipid content in preclinical NASH models (Boland et al. 2020) and improves markers of hepatic function in T2DM patients (Nahra et al. 2021). The compound BI456906 has also recently entered phase II trials with a direct comparison to semaglutide (Boehringer Ingelheim 2019). Weight loss efficacy of existing GLP1R/GCGR co-agonists does not appear greater than that achieved by best-in-class GLP1R agonists, but these co-agonists may prove particularly useful in the treatment of individuals with obesity and concomitant liver disease.

2.4 GLP1R/GIPR Co-agonism

GIP was long-ignored as a therapeutic target for obesity because of studies linking loss of GIPR signalling to protection from adiposity, and a demonstrated clinical

inefficacy in patients with uncontrolled T2DM (Chia et al. 2009; Nauck et al. 1993). Although native GIP and GIPR agonists have at best moderate effects on food intake or body weight (Coskun et al. 2018; Mroz et al. 2019), dual incretin agonists which activate both the GLP1R and GIPR have recently been demonstrated to have greater efficacy in restoring normoglycaemia and reducing body weight than GLP1R agonists alone. The first unimolecular GLP1R/GIPR agonist was the pegylated DPP4-resistant compound NNC0090–2746 (Finan et al. 2013), which evoked similar improvements in HbA_{1c} and body weight to liraglutide in T2DM patients, while also reducing total cholesterol levels (Frias et al. 2017). More striking results have recently been achieved with the dual agonist tirzepatide, a once-weekly injectable peptide biased towards GIPR activation (Coskun et al. 2018). Tirzepatide reduces hyperglycaemia and body weight to a greater extent than the GLP1R agonist comparator dulaglutide, with over a third of T2DM patients achieving over 10% reduction in body weight when treated with the highest dose of tirzepatide (Frias et al. 2018). On-going phase III trials are assessing the cardiovascular outcomes of tirzepatide in T2DM (SURPASS), and the weight loss effects in non-diabetic individuals with obesity (SURMOUNT).

Given this clinical efficacy of dual GLP1R/GIPR agonists, recent work has focused on understanding the underlying mechanisms. In terms of glucose tolerance, improved glycaemic control – which could be initially mediated by GLP1R agonism – is known to re-sensitise pancreatic β-cells to the effects of GIP in T2DM patients (Hojberg et al. 2009). As GIPR antagonists have also been demonstrated to induce weight loss in some (Killion et al. 2018), but not all (Mroz et al. 2019; West et al. 2021), preclinical models, chronic activation of the GIPR has been proposed to cause receptor desensitisation which antagonises endogenous GIP activity (Killion et al. 2020); however, there is currently no substantial evidence to support this hypothesis. Chemogenetic activation of hypothalamic GIPR-expressing cells, which only show a small degree of overlap with neuronal GLP1R expression, acutely reduces food intake in mice (Adriaenssens et al. 2019). A recent publication demonstrated c-fos-staining, marking neuronal activation, in hypothalamic neurons in response to a peripherally administered GIPR agonist; this agonist reduced food intake and weight gain in DIO mice, an effect that was abolished when central GIPR expression was conditionally knocked out through a *Nestin*-Cre approach (Zhang et al. 2021). The importance of synergistic activation of GIPR- and GLP1R-expressing neurons and downstream anorexigenic pathways, and the potential of GIP for the treatment of obesity in humans, remains an area of active study.

2.5 GLP1R/GCGR/GIPR Triple Agonism

Monomeric drugs which act as triple agonists at the GIP, GLP-1 and GCG receptors have also been developed, in an attempt to combine the beneficial effects of GLP1R/GCGR and GLP1R/GIPR co-agonists. These tri-agonists induce greater body weight loss (up to 30% in DIO mice) alongside improved glucose tolerance and a reversal of steatohepatitis (Finan et al. 2015). Given its effects on liver fat and fibrosis, the

tri-agonist HM15211 has now entered phase II trials for the treatment of NASH (Hanmi 2020). Many additional compounds have also been developed and are progressing through preclinical and phase I pipelines for treatment of T2DM (Lilly 2021).

2.6 GLP1R/NPY2R Co-agonism

Several studies have demonstrated additive or synergistic effects of GLP-1 receptor agonists with $PYY_{3–36}$ (De Silva et al. 2011; Neary et al. 2005; Talsania et al. 2005). In humans, acute (150 min) intravenous infusions of native $PYY_{3–36}$ in conjunction with GLP-1 reduced energy intake (Schmidt et al. 2014). Similarly, subcutaneous infusion of GLP-1, oxyntomodulin and $PYY_{3–36}$ over 28 days in overweight individuals improved glycaemic control and caused greater weight loss than semaglutide, but it is impossible to delineate the contribution of each peptide in this study (Behary et al. 2019). High doses of native $PYY_{3–36}$ induce significant nausea, so doses of PYY analogues would have to be carefully titrated, as is currently done for GLP1R agonists (Gantz et al. 2007). Long-acting analogues of $PYY_{3–36}$ have been developed and reported to reduce food intake and body weight in primate (Rangwala et al. 2019) and rodent (Lear et al. 2020) models of obesity, alone and in conjunction with GLP1R agonists. Unlike GIP and glucagon, no unimolecular GLP1/$PYY_{3–36}$ co-agonists have been reported but co-administration of the long-acting PYY analogue PYY 1875 with semaglutide is currently being assessed in phase I human studies for obesity (Novo Nordisk 2019).

2.7 CCK1R Agonism

CCK also has potent anorexigenic effects and several CCK1R agonists were developed in the 2000s as satiety agents (Cawston and Miller 2010). While many of these drugs reduced food intake and body weight in preclinical models, they were deemed no more effective than diet alteration in human studies and were therefore discontinued (Jordan et al. 2008). Co-administration of CCK1R and GLP1R agonists (Trevaskis et al. 2015), or unimolecular co-agonists (Hornigold et al. 2018; Irwin et al. 2015), induces impressive (up to 28%) weight loss in rodent models. A new long-acting CCK1R agonist which reduces food intake and body weight in the obese mini-pig model has recently been developed (Christoffersen et al. 2020). This has not yet progressed to clinical trials but represents a promising compound for use in conjunction with GLP1R agonists if the preclinical efficacy is sustained in longer-term human studies.

2.8 Co-administration of GLP-1 and Amylin Receptor Agonists

Amylin is an anorexigenic hormone co-secreted with insulin from pancreatic β-cells, also expressed in the hypothalamus and, likely at lower levels, in EECs (Boyle et al. 2018; Habib et al. 2012; Li et al. 2015). The area postrema of the brainstem is thought to be critical for the satiety effects of amylin, although other brain regions including the hypothalamic arcuate/ventromedial nuclei and ventral tegmental area may influence control of hedonic feeding (Boyle et al. 2018). Several amylin receptors exist, which are formed when the calcitonin receptor complexes with one or more receptor activity modifying proteins (RAMPs) (Hay et al. 2018). The amylin analogue pramlintide evokes small (typically <5%) reductions in body weight in obese subjects (Aronne et al. 2007). It also induces modest improvements in glycaemic control via inhibition of gastric emptying and suppression of glucagon secretion, and has therefore been approved for treatment of both type 1 and type 2 diabetes (Ryan et al. 2005). A newer once-weekly amylin analogue cagrilintide has demonstrated efficacy in early clinical trials for obesity, alone (phase II) (Fletcher et al. 2021) or in combination with semaglutide (phase Ib) (Enebo et al. 2021). Initial results show a promising additive effect of GLP-1 and amylin receptor agonism, but this has yet to be confirmed in large-scale trials.

2.9 Summary of Gut Hormone Mimetic Treatments

Incretin mimetics have been used clinically for over a decade and are effective in improving glucose tolerance for patients with T2DM with a tolerable safety profile. The potent anorexigenic effects of the once-weekly GLP-1R agonist semaglutide and dual GLP1R/GIPR co-agonist tirzepatide in recent phase III trials represent ground-breaking opportunities for the pharmacological treatment of obesity. These drugs can induce clinically meaningful weight loss of 10–20% in overweight and obese patients, with or without diabetes, and are likely also to confer other beneficial effects such as reduction of cardiovascular mortality. Current pharmaceutical development is focused on combining GLP1R agonism with activity at other hormone receptors to further improve these results, ameliorate other complications of obesity such as NASH and minimise adverse effects.

3 Bariatric Surgery

Currently, bariatric surgical rearrangements of the gastrointestinal tract remain the most successful means of inducing weight loss in patients with severe obesity. Several mechanisms have been proposed to underlie these metabolic changes (reviewed in chapter “Bariatric Surgery”) but a key driver is accelerated nutrient delivery to the distal small intestine and subsequent dramatic increase in secretion of gut hormones such as GLP-1, PYY and oxyntomodulin (Holst et al. 2018; Larraufie et al. 2019). Postprandial excursions of GLP-1, PYY and CCK are strongly elevated

immediately post-operatively (Laferrere et al. 2007; Peterli et al. 2012), with exaggerated responses maintained for as long as 20 years after surgery (Naslund et al. 1997). Clinical studies using the GLP1R antagonist exendin-9 demonstrate a clear role for GLP-1 in mediating the beneficial effects of bariatric surgery on postprandial insulin secretion and glucose tolerance (Jorgensen et al. 2013; Larraufie et al. 2019; Salehi et al. 2014), but the importance of post-surgical PYY elevation has been studied in less detail. Following Roux-en-Y gastric bypass (RYGB), double *Glp1r/Npy2r* knockout mice achieve similar weight loss to wild-type animals (Boland et al. 2019); however, in human RYGB patients the combination of the GLP1R-antagonist exendin-9 and DPP-4 inhibition increases food intake, whilst each treatment alone is ineffective (Svane et al. 2016).

It has been hypothesised that increased circulating GLP-1 and PYY may be the result of altered exposure of the gastrointestinal epithelium to nutrients after surgery leading to changes in stimulus responsiveness or EEC differentiation. Although immunohistochemistry studies in rats (Mumphrey et al. 2013) and humans (Rhee et al. 2015) have reported small changes in L-cell number or density following RYGB, these are insufficient to explain the substantial increase in circulating levels of GLP-1 and PYY. Furthermore, in lean human and mouse models of bariatric surgery there were no major differences in EEC peptide content or transcriptome before and after gastrectomy in humans or mice (Larraufie et al. 2019), suggesting that altered nutrient flow is the critical factor underlying enhanced gut hormone secretion.

4 Stimulating Endogenous EEC Secretion

Pharmacologically stimulating endogenous secretion of anorexigenic and insulinotropic hormones or selectively expanding L-cell number could potentially mimic the positive effects of bariatric surgery. In addition to nutrient stimulation, it is possible to directly target the sensory machinery employed by electrically active enteroendocrine cells (Fig. 1). Although existing trials have focused on treating T2DM, the profound weight loss induced by RYGB and GLP-1 receptor agonism is proof of principle that the gut hormone axis is also a promising target for anti-obesity drugs.

4.1 Nutrient Encapsulation

Initial attempts to stimulate endogenous gut hormone secretion focused on oral delivery of nutritional stimuli. Oral ingestion of the amino acid glutamine modestly increases circulating GLP-1 concentrations (Greenfield et al. 2009) and improves postprandial glycaemic control in T2DM (Samocha-Bonet et al. 2011). Use of a slow-release enteric coating to reduce dosage by selectively delivering glutamine to the L-cell-rich distal gut evoked a small increase in circulating GLP-1 and insulin in

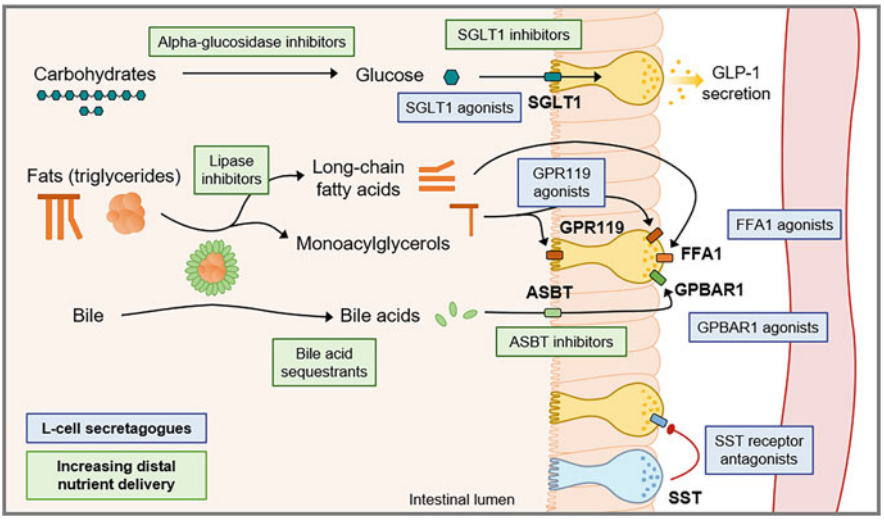

Fig. 1 Mechanisms of stimulating endogenous enteroendocrine cell secretion

fasted individuals, but no metabolic improvements were seen following an oral glucose tolerance test (Meek et al. 2016).

Similar enteric capsules have been used for ileocolonic delivery of free fatty acids and bile acids, in attempt to mimic the rerouting of nutrients observed with bariatric surgery. In fasted T2DM subjects, addition of encapsulated lauric acid to a meal lowers postprandial glucose and evokes a small increase in GLP-1 (Ma et al. 2013). Hydrolysed pine nut oil capsules slightly increase GLP-1 and GIP responses to oral glucose in healthy and overweight volunteers, compared to placebo capsules (Sorensen et al. 2021). Neither study demonstrated notable alterations in circulating insulin levels, likely reflecting inadequate stimulation of incretin release. Acute infusion of the bile salt taurocholate into the rectum potently increases GLP-1, PYY and insulin concentrations, while reducing ad libitum food intake and plasma glucose (Adrian et al. 2012). However, the high doses required for beneficial metabolic effects caused adverse reactions, including rectal irritation and abdominal pain. In a 28-day trial of participants with obesity or T2DM, ileocolonic delivery of conjugated bile acid capsules evoked small but significant improvements in glucose homeostasis, likely mediated by modest increases in GLP-1 (Calderon et al. 2020).

In developing treatments for obesity, it is important to avoid therapeutics with an inherently high caloric load, which would likely negate any beneficial anorexigenic effects. Given the limited success of using nutritional stimuli to evoke secretion of GLP-1, compared to the major elevations following bariatric surgery, efforts have largely shifted towards the use of pharmacological agonists to selectively target receptors on EECs.

4.2 Pharmacological Targeting of Enteroendocrine GPCRs

G-protein coupled receptors (GPCRs) make a significant contribution to regulation of gut hormone secretion in response to products of fat or protein digestion, neurotransmitters and other paracrine or endocrine signals. Activation of EEC receptors coupled to Gq or Gs, leading to Ca^{2+} and cyclic adenosine monophosphate (cAMP) elevation respectively, is widely recognised to stimulate hormone release. Bile acids strongly evoke gut hormone secretion via the Gs-coupled G-protein bile acid receptor GPBAR1 (Brighton et al. 2015), and monoacylglycerols also act via cAMP signalling downstream of GPR119 (Moss et al. 2016). Several Gq-coupled receptors are important for the postprandial stimulation of gut hormone secretion: the long-chain fatty acid receptors FFA1/GPR40 (Edfalk et al. 2008) and FFA4/GPR120 (Hirasawa et al. 2005), the short chain fatty acid receptor FFA2/GPR43 (Tolhurst et al. 2012), and the aromatic amino acid-responsive calcium sensing receptor CaSR (Pais et al. 2016) and GPR142 (Lin et al. 2016).

Given the inherently druggable nature of GPCRs alongside their cell surface accessibility and relatively localised expression in specific cell populations, these receptors represent a key target in the development of novel therapeutics to enhance endogenous enteroendocrine secretion. Several synthetic compounds which target EEC receptors have been developed to stimulate gut hormone release in attempts to mimic the weight loss effects of bariatric surgery.

4.3 FFA1 (GPR40) Agonists

Agonists of the free fatty acid receptor FFA1/GPR40 were initially developed for their direct effect on pancreatic β-cells (Itoh and Hinuma 2005). The partial agonist TAK-875 showed promising results in T2DM patients, increasing insulin secretion and improving glycaemic control without inducing hypoglycaemia (Burant et al. 2012); however, signs of hepatotoxicity during large-scale phase III trials halted development of TAK-875 (Kaku et al. 2016). There is currently no evidence to suggest these adverse effects were FFA1-mediated (Otieno et al. 2018) and, as liver expression of this receptor is negligible (Briscoe et al. 2003), it is hoped that newer drugs will avoid similar hepatic injury.

An example of a full FFA1 agonist is AM-1638, which evokes GIP and GLP-1 secretion, and causes GLP1R-dependent reductions in plasma glucose in mice (Luo et al. 2012). The structurally-related AM-6226 improves glucose tolerance in a primate model, more effectively than the DPP4 inhibitor sitagliptin (Brown et al. 2018). Other FFA1 agonists in preclinical development which stimulate GLP-1 secretion include SCO-267 (Ueno et al. 2019) and ZYDG2 (Jain et al. 2018). Given its dual role in insulin and incretin secretion, FFA1 presents a promising target for the treatment of T2DM. Whether newer agonists are able to stimulate sufficient release of GLP-1 and other anorexigenic hormones to evoke meaningful effects on body weight remains to be determined.

4.4 GPR119 Agonists

GPR119, the Gs-coupled monoacylglycerol receptor, is also expressed in both enteroendocrine and pancreatic α and β-cells (Chu et al. 2007; Moss et al. 2016). Preclinical studies with the agonist AR231453 demonstrate GPR119-dependent stimulation of GLP-1, GIP and PYY release, and improvements in glucose tolerance which were reduced in *Glp1r* knockout mice (Chu et al. 2008; Flock et al. 2011). Intriguingly, GPR119 agonism also slows gastric emptying independently of GLP1R, GIPR, GLP-2R and NPY2R (Flock et al. 2011). Nasogastric delivery of the endogenous GPR119 agonist 2-oleoylglycerol in humans induces a small increase in GLP-1 and GIP levels, but this was insufficient to alter insulin or glucose profiles (Hansen et al. 2011).

Despite promising early animal data, the effects of GPR119 agonists on glycaemic control in diabetic populations have been inconclusive. The agonist JNJ-38431055 stimulated GLP-1 and GIP release without altering insulin (Katz et al. 2012). Another agonist GSK1292263 increased circulating PYY approximately five-fold in T2DM subjects but did not affect GLP-1, GIP or glucose levels (Nunez et al. 2014). While this increase in anorexigenic PYY is comparable to postprandial levels after bariatric surgery, there were no differences in self-reported hunger scores. In a phase II trial of Japanese T2DM patients, the agonist DS-8500a improved Hba1c levels, to a lesser extent than sitagliptin, alongside beneficial improvements in lipid and cholesterol (Yamada et al. 2018). The same drug did not alter glycaemic control in a North American cohort when co-dosed with metformin (Sankyo 2018). There are no on-going listed clinical trials of GPR119 agonists for T2DM or obesity, but the agonist MBX-2982 recently entered phase II trials to evaluate whether it can enhance glucagon secretion during insulin-induced hypoglycaemia in type 1 diabetes (CymaBay 2020).

4.5 GPBAR1 (TGR5) Agonists

Activation of the Gs-coupled G-protein bile acid receptor GPBAR1 (previously known as TGR5/GPR131) evokes release of GLP-1, PYY, GIP, GLP-2 and insulin (Bala et al. 2014; Kuhre et al. 2018; Parker et al. 2012b; Thomas et al. 2009). Furthermore, there is preclinical evidence that GPBAR1 agonism may enhance resting brown adipose thermogenesis and decrease inflammation, providing additional benefits in the treatment of obesity (van Nierop et al. 2017).

Bile acids and selective GPBAR1 agonists stimulate GLP-1 secretion and improve glucose homeostasis in wild-type, but not *Gpbar1* knockout, mice (Thomas et al. 2009). Colorectal infusion of bile acids also increases PYY/GLP-1 secretion in humans and suppresses appetite in both T2DM and healthy-weight volunteers (Adrian et al. 2012); however, in contrast to animal studies, oral or intrajejunal dosing of bile acids in humans induces very little GLP-1 release with no effect on insulin levels (Hansen et al. 2016; Meyer-Gerspach et al. 2013). In the only published clinical study using a selective GPBAR1 agonist, T2DM subjects were

treated with SB-756050 for 6 days (Hodge et al. 2013). This trial produced disappointing effects on glucose tolerance, although there was some indication of increased GLP-1 secretion at certain doses in response to acute GPBAR1 stimulation.

GPBAR1 is widely expressed, and care must therefore be taken to balance the potential therapeutic benefits of receptor activation (improved glucose homeostasis, reduced inflammation) with the risk of diverse off-target effects. These adverse reactions have primarily been studied in animal or cell models but include gallstone formation, cardiovascular alterations, constipation, pruritus and promotion of cell proliferation [reviewed in van Nierop et al. (2017)]. It was initially hoped that it may be possible to target the enteroendocrine cell GPBAR1 directly from the gut lumen with a non-absorbable agonist, to minimise effects in other organ systems; however, it has since been demonstrated that activation of GPBAR1 occurs at the basolateral surface of L-cells, following absorption across the epithelial layer by the apical sodium-dependent bile acid transporter (ASBT) (Brighton et al. 2015).

4.6 Bile Acid Sequestrants and ASBT Inhibitors

Given the challenge of selectively targeting GPBAR1 in EECs pharmacologically, other approaches which alter the intestinal availability of endogenous bile acids may prove effective in the treatment of obesity. The majority (~95%) of bile acids are actively reabsorbed by the ASBT in the distal small intestine and returned to the liver via the portal vein for re-secretion, although a small proportion enter the systemic circulation (Dawson et al. 2009). Bile acids which reach the colon can be modified by the microbiota to form passively-absorbed unconjugated bile acids (Mekhjian et al. 1979), or lost in faeces.

Bile acid sequestrants are non-absorbable resins designed to increase faecal loss of bile acids and therefore increase de novo synthesis to reduce total plasma cholesterol. As well as improving dyslipidaemia, the sequestrant colesevelam also significantly lowers glycaemia in T2DM patients (Bays 2011), an effect which was GPBAR1-dependent in mice (Potthoff et al. 2013). Sequestrants increase delivery of bile acids to the distal intestine and slightly increase postprandial GLP-1 and GIP levels in T2DM patients (Beysen et al. 2012; Brufau et al. 2010); although this is not to the extent seen following bariatric surgery, likely reflecting the need for bile acid absorption for incretin secretion. A recent study of post-RYGB subjects also demonstrated that addition of colesevelam to a meal does not alter circulating GLP-1 levels, arguing against an important role for endogenous bile acids in mediating postprandial GLP-1 release in this cohort (Jonsson et al. 2021).

ASBT inhibitors which block small intestinal bile acid absorption have also been trialled. Although ileal GPBAR1-mediated hormone secretion depends on bile acid absorption via ASBT (Brighton et al. 2015), passive absorption of secondary bile acids in the colon – where there is a large pool of GLP-1 and PYY positive EECs – is likely to still enable GPBAR1 activation (Billing et al. 2019). In diabetic rats, oral administration of ASBT inhibitors promoted GLP-1 and insulin release (Chen et al.

2012). Patients with chronic constipation treated with high doses of the ASBT inhibitor elobixibat for 14 days showed slightly elevated postprandial GLP-1 levels (Rudling et al. 2015). The inhibitor GSK2330672 reduced fasting plasma glucose levels in T2DM subjects, although GLP-1 levels were not measured (Nunez et al. 2016). Notwithstanding gastrointestinal side effects, primarily diarrhoea, ASBT inhibitors are still under development for the treatment of hypercholesterolaemia, NASH and functional constipation. The impact of these drugs on energy intake and body weight should be monitored as they progress through clinical trials, although preclinical studies showed little alteration (Rao et al. 2016).

4.7 Slowing Macronutrient Digestion

Macronutrient breakdown is required for both absorption and stimulation of EEC secretion. Therapies which slow nutrient digestion may therefore reduce the total calories absorbed, while increasing nutrient availability in the GLP-1 and PYY-rich regions of the ileum and colon. Orlistat, a lipase inhibitor approved for the treatment of obesity, reduces breakdown of lipids to fatty acids and monoacylglycerols and delivers a large fat load distally. In healthy volunteers, orlistat taken before a meal reduces circulating GLP-1, PYY and CCK while also reducing satiety (Ellrichmann et al. 2008). The requirement for lipid digestion and subsequent absorption of fatty acids to access basolaterally-located FFA1 (Christensen et al. 2015) appears to limit the ability of orlistat to enhance gut hormone release. Alpha-glucosidase inhibitors, such as acarbose and miglitol, are approved therapies for T2DM which slow the digestion of starch and sucrose to reduce postprandial glucose elevations. These drugs appear to evoke small increases in GLP-1 after a meal or sucrose ingestion, while reducing GIP secretion from the proximal gut (Narita et al. 2012; Seifarth et al. 1998). Postprandial effects on plasma GLP-1 have not been observed in every study (Hucking et al. 2005) and, like orlistat, the efficacy of alpha-glucosidase inhibitors is likely limited by the need for carbohydrate digestion to stimulate EECs in the distal gut.

4.8 SGLT1 Inhibitors

Glucose, from ingested carbohydrates or free sugars, is absorbed across the intestinal epithelium by the apical sodium-dependent glucose cotransporter SGLT1. In electrically active EECs, this coupled uptake of glucose and positively charged sodium ions results in membrane depolarisation and subsequent hormone release (Parker et al. 2012a). Paradoxically, blocking SGLT1 leads to a pronounced increase in circulating GLP-1 at later time points, as well as reducing postprandial glucose excursions (Powell et al. 2017). Following preclinical success, the non-absorbable SGLT1 inhibitor LX-2761 has entered phase I trials as an oral anti-diabetic agent (Lexicon 2018). In parallel to ASBT inhibition, it is hypothesised that blocking proximal uptake increases the delivery of glucose to the distal intestine. As SGLT1

can no longer mediate GLP-1 release in response to glucose, alternative glucose-sensing mechanisms or increased availability of glucose-derived metabolites may be important for EEC activation in this setting.

4.9 Somatostatin Receptor Antagonists

An alternative strategy involves using somatostatin receptor (SSTR) antagonists to release tonic inhibition of enteroendocrine secretion (Jepsen et al. 2019). Specifically, a selective antagonist of SSTR5 – which is highly enriched in ileal L-cells (Moss et al. 2012) – has been shown to improve glycaemic control in mice, in a GLP-1-dependent manner (Jepsen et al. 2021; Sprecher et al. 2010). In rodents, SSTR5 antagonists only improve glucose tolerance when administered orally, further implicating an incretin-like effect rather than direct stimulation of pancreatic insulin secretion (Jepsen et al. 2021). SSTR5 expression does appear to be higher in human than rodent β-cells, and so antagonism may have a dual benefit of stimulating gut hormone and insulin release in man (Farb et al. 2017). Several SSTR antagonists have recently been developed for oral administration (Hirose et al. 2017), but clinical studies for these drugs in obesity or T2DM have not yet been reported.

4.10 Future Directions in Manipulating Endogenous EEC Secretion

The success of L-cell secretagogues in preclinical and clinical studies has been limited to relatively small increases in circulating gut hormone levels. Injectable GLP-1 analogues and bariatric surgery both induce ~ten-fold elevations in concentrations of circulating GLP-1 or equivalents, leading to potent anorexigenic effects (Calara et al. 2005; Yousseif et al. 2014). It appears clear that increasing endogenous gut hormone secretion to these levels will require synergistic activation of multiple pathways. For example, single oral administration of an SSTR5 antagonist, GPBAR1 agonist or FFA1 agonist in mice induces modest (<five-fold) stimulation of GLP-1 secretion (Briere et al. 2018). By contrast, co-treatment with a GPBAR1 or FFA1 agonist (to directly evoke GLP-1 release), a SSTR5 antagonist (to release L-cell inhibition) and a DPP4 inhibitor (to prevent breakdown) elevated circulating GLP-1 to supraphysiological levels, far greater than those achieved post-surgery or during treatment with exogenous incretin mimetics. Similarly, the use of a lipid nanocarrier system for oral exenatide delivery has recently been shown to induce enhanced GLP-1 secretion, synergistically improving glucose tolerance compared to subcutaneous exenatide (Xu et al. 2020). An alternative approach could combine basolateral activation of GPBAR1 or FFA1 from the circulation with a non-caloric drug targeting receptors on the apical processes of open-type EECs, such as the electrogenic glucose transporter SGLT1.

In recent years, bulk and single cell RNA sequencing of human EECs has been carried out using immunolabelled dissociated tissue, or genetically modified reporter organoids (Beumer et al. 2020; Goldspink et al. 2020; Roberts et al. 2019). L-cells

express several receptors not previously implicated in postprandial nutrient sensing or neurohormonal regulation, which may represent novel targets for the selective manipulation of endogenous gut hormone secretion.

5 Enhancing EEC Number

Intestinal epithelial cells – exposed to the extreme chemical and physical conditions of the intestinal lumen – have a rapid turnover time, typically only 3–5 days (Darwich et al. 2014). If it were possible to selectively enhance EEC differentiation, this could represent a promising strategy to increase endogenous gut hormone release. Several studies have characterised which transcription factors (TFs) are expressed by specific enteroendocrine cell subtypes and the time course of this expression (Beumer et al. 2020; Gehart et al. 2019). The hormonal repertoire of individual EECs is much broader than suggested by the classical single letter (e.g., 'L'-cell) classification system and expression of specific hormones is dependent on a combination of factors, including the cell's location within the gastrointestinal tract, position along the crypt-villus axis and possibly extrinsic influences such as nutritional status. A number of compounds – such as short chain fatty acids and bile acids – have been proposed to physiologically modulate EEC differentiation in organoid and mouse models (Lund et al. 2020; Petersen et al. 2014). Although attempts have been made to develop drugs which boost EEC number (Beumer et al. 2018; Petersen et al. 2015, 2018; Tsakmaki et al. 2020), significant further work is required to selectively target TFs active in specific EEC populations before this approach could be considered for therapeutically increasing gut hormone secretion.

6 Conclusion

As evidenced by recent trials of the GLP-1 receptor agonist semaglutide and the GLP-1/GIP receptor dual agonist tirzepatide, the anorexigenic and insulinotropic gut hormone axes can be effectively manipulated to induce significant weight loss in human subjects. Directly targeting the gut for the treatment of obesity also remains an attractive therapeutic strategy. Pharmacological agonists activating multiple gut hormone receptors, which have demonstrated early clinical success, could be replaced by effective stimulation of plurihormonal EECs. Increasing hormone release from the gut would also enable the activation of local receptors, such as those on vagal afferent neurons, which appear to underlie at least some of the actions of EEC products. By synergistically manipulating several pathways controlling endogenous enteroendocrine secretion, it is theoretically possible to mimic the effectiveness of bariatric surgery in a pill.

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