Taylor & Francis
Taylor & Francis Group

Expert Review of Endocrinology & Metabolism

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/iere20

Designer GLP1 poly-agonist peptides in the management of diabesity

Laura Statham, Melina Pelling, Petra Hanson, Ioannis Kyrou, Harpal Randeva & Thomas M Barber

To cite this article: Laura Statham, Melina Pelling, Petra Hanson, Ioannis Kyrou, Harpal Randeva & Thomas M Barber (2023) Designer GLP1 poly-agonist peptides in the management of diabesity, Expert Review of Endocrinology & Metabolism, 18:3, 231-240, DOI: 10.1080/17446651.2023.2204976

To link to this article: https://doi.org/10.1080/17446651.2023.2204976

Published online: 24 Apr 2023.

EXPERT REVIEW OF ENDOCRINOLOGY & METABOLISM
2023, VOL. 18, NO. 3, 231–240
https://doi.org/10.1080/17446651.2023.2204976

Taylor & Francis
Taylor & Francis Group

REVIEW

Designer GLP1 poly-agonist peptides in the management of diabesity

Laura Statham[a*], Melina Pelling[a*], Petra Hanson[a,b], Ioannis Kyrou[a,b,c,d,e], Harpal Randeva[a,b,c] and Thomas M Barber[a,b]

[a]Division of Biomedical Sciences, Warwick Medical School, University of Warwick, Coventry, UK; [b]Warwickshire Institute for the Study of Diabetes, Endocrinology and Metabolism, University Hospitals Coventry and Warwickshire, Coventry, UK; [c]Aston Medical School, College of Health and Life Sciences, Aston University, Birmingham, UK; [d]Centre for Sport, Exercise and Life Sciences, Research Institute for Health & Wellbeing, Coventry University, Coventry, UK; [e]Laboratory of Dietetics and Quality of Life, Department of Food Science and Human Nutrition, School of Food and Nutritional Sciences, Agricultural University of Athens, Athens, Greece

ABSTRACT

Introduction: To date, the 21st Century has witnessed key developments in the management of diabesity (a conflation of obesity and Type 2 Diabetes Mellitus [T2D]), including Glucagon Like Peptide 1 (GLP1) receptor agonist therapies, and recently the 'designer' GLP1 Poly-agonist Peptides (GLP1PPs).

Areas covered: A PubMed search of published data on the GLP1PP class of therapies was conducted. The gut-brain axis forms complex multi-directional interlinks that include autonomic nervous signaling, components of the gut microbiota (including metabolic by-products and gram-negative cell wall components [e.g. endotoxinaemia]), and incretin hormones that are secreted from the gut in response to the ingestion of nutrients. The development of dual-incretin agonist therapies includes combinations of the GLP1 peptide with Glucose-dependent Insulinotropic Polypeptide (GIP), Glucagon (Gcg), Cholecystokinin (CCK), Peptide YY (PYY), and Glucagon-Like Peptide 2 (GLP2). Triple incretin agonist therapies are also under development.

Expert opinion: At the dawn of a new era in the therapeutic management of diabesity, the designer GLP1PP class holds great promise, with each novel combination building on a preexisting palimpsest of clinical data and insights. Future innovations of the GLP1PP class will likely enable medically induced weight loss and glycemic control in diabesity to rival or even out-perform those resulting from bariatric surgery.

ARTICLE HISTORY
Received 2 February 2023
Accepted 17 April 2023

KEYWORDS
Incretin; Diabesity; Glucagon Like Peptide 1; obesity; diabetes

1. Introduction

Within the milieu of 21st Century chronic disease, obesity holds a prime position. Obesity now affects >650 million people globally, and represents a leading cause of morbidity, mortality, and health-economic expenditure, with rates having tripled since 1975 [1]. Of all the >50 obesity-related conditions, Type 2 Diabetes Mellitus (T2D) is worthy of special attention, particularly regarding ethnic specificities [2,3]. Globally, T2D now affects 462 million individuals, and itself contributes independently to substantial morbidity (including renal disease, neuropathy, and retinopathy) and premature mortality from cardiovascular disease [4,5]. A common misconception is that obesity alone causes T2D. However, it is also important to outline the genetic component in the pathogenesis of T2D, with an estimated heritability of 40% –70% [6,7]. However, despite its related underlying genetic architecture/predisposition, the clinical/phenotypic expression of T2D is often manifested in the context of weight gain and obesity. Consequently, obesity often co-exists with T2D, with strong epidemiological and pathophysiological links that are mediated primarily through obesity-related insulin resistance. Obesity development itself is also multi-factorial with complex interactions between environmental and genetic factors, including for example the copy number of the amylase gene, *AMY1* [8–10]. The high prevalence of obesity and T2D, their frequent co-existence, and the heightened cumulative metabolic risk conferred independently by each condition, has highlighted the need for novel therapies that improve both body weight and glycemic control concurrently [11–13]. In this context, it is often useful to consider the aims of management of obesity and T2D as a conflation into a single clinical entity, i.e. 'diabesity.'

During much of the 20th Century, our therapeutic armamentarium for pharmacological management of T2D was relatively restricted, with Metformin and Sulphonylureas as the main oral antidiabetic drugs, and the option of additional insulin-based therapies. Conversely, the first two decades of the 21st Century have borne witness to the generation of a multitude of new pharmaco-therapeutic choices for T2D, with important innovations in insulin-based therapies, including new drug classes such as the Sodium Glucose-Like Transporter 2 (SGLT2) therapies and the Glucagon-Like Peptide 1 (GLP1) agonists [11]. Of note, these novel classes of antidiabetic drugs have also been shown to exhibit

CONTACT Thomas M Barber t.barber@warwick.ac.uk Warwickshire Institute for the Study of Diabetes, Endocrinology and Metabolism, University Hospitals Coventry and Warwickshire, Clifford Bridge Road, Coventry CV2 2DX, UK
*Joint first authorship.

Article highlights

- The first two decades of the 21st Century have borne witness to the generation of a multitude of pharmaco-therapeutic choices for T2D.
- The recent rise of 'designer' GLP1 Poly-agonist Peptides (GLP1PPs) has emerged as a novel therapeutic strategy for the effective management of diabesity.
- Incretin hormones act via G-coupled protein receptors (GCPR) to increase intracellular cyclic adenosine monophosphate (cAMP), thereby stimulating glucose-dependent insulin secretion from islet β-cells.
- Beyond GIP and GLP1, there are numerous other gut-derived intestinal hormones that have a variety of physiological effects that include the mediation of hypothalamic control of appetite and metabolism. Amongst these are Glucagon (Gcg), Cholecystokinin (CCK), Peptide YY (PYY), and Glucagon-Like Peptide 2 (GLP2).
- Phase 3 trials demonstrate the superior glycemic and weight-loss efficacy of Tirzepatide compared with placebo, with >20% body weight loss in the majority (57%) of participants in a 72-week trial (on highest dose) with minimal adverse effects.
- Beyond body weight loss and improved glycemic control, the GLP1:Gcg dual agonists have also been assessed for their efficacy in patients with Non-Alcoholic Fatty Liver Disease (NAFLD) and Non-Alcoholic Steatohepatitis (NASH).
- The administration of a novel GLP1:CCK dual agonist in a mouse model resulted in reduced feeding behavior and body weight.
- In a preliminary human-based study, participants tolerated single doses of SAR441255 (a GLP1:GIP:Gcg triple agonist) with mild adverse effects. In diabetic cynomolgus monkeys, SAR441255 associated with a 12.6% reduction in body weight, although the glycemic benefit of SAR441255 was inferior to that of a GLP1:GIP dual agonist therapy (HbA1c reduction of 1.37% vs 1.85%, respectively).

unexpected and serendipitous cardio-renal benefits [14–16]. In recent years, the tsunami of clinical data and novel insight on the impact of these novel therapies has catalyzed a shift in our approach to the treatment of diabesity as a clinical entity worthy of special focus. Thus, in the context of diabesity management, the GLP1 class of therapies has received an inordinate amount of attention, perhaps due to the superior efficacy of certain GLP1 therapies on both glycemia and weight loss, and the potential for cardiovascular benefits [16,17]. Importantly, GLP1 is a natural incretin hormone, and many of the current GLP1 therapies available have a high degree of homology with native human GLP1.

From an endocrine perspective, the gut is a highly complex and interconnected organ system, for which our understanding is still in its infancy [18]. Indeed, GLP1 is just one of a plethora of gut-derived intestinal hormones, which form a physiological system of wondrous complexity. These intestinal hormones are released from the gut in response to nutrients and other post-prandial stimuli and have physiological effects on the digestion and processing of nutrients, pancreatic function, and the central hypothalamic control of appetite and metabolism. Each gut-derived intestinal hormone has its own specific receptor and functioning, and some even promote the growth and development of the gastrointestinal tract itself [19]. On this background, the recent rise of 'designer' GLP1 Poly-agonist Peptides (GLP1PPs) has ensued as a novel therapeutic strategy for the effective management of diabesity. Individual intestinal hormones have pleiotropic and wide-ranging appetitive, metabolic, and growth-promoting effects. Furthermore, there is a plethora of favorable cardiometabolic data for the GLP1 class, and potential for pharmaco-complementarity between GLP1 and the other intestinal hormones. Accordingly, there is a clear rationale for the therapeutic development and innovation of designer GLP1PPs [15]. The potential for combinatorial therapeutics, implicating the hugely complex human gut-derived incretin and intestinal hormones, is almost infinite in scope and is likely to predominate in the coming decades of innovation in diabesity management.

On the eve of the widespread clinical availability of the designer GLP1PP-based therapies and at the birth of this innovative and hugely exciting therapeutic field with all its potential, now is a timely opportunity to provide a concise review. Although beyond the scope of this review, the early pioneering, animal-based studies on the metabolic effects of GLP1 combined with other incretin and intestinal hormones has been reviewed elsewhere [20,21]. Following a brief discussion of the central regulation of appetite and metabolism mediated through gut-derived incretin and intestinal hormones (the 'gut-brain axis'), we provide an overview of the clinical data for designer GLP1PP therapies in development and, in the case of Tirzepatide, recently approved for clinical use. Moreover, we discuss the likely positioning of such novel therapies in the future treatment algorithms of diabesity management and consider the possible future developments in this new and emerging field.

2. The gut-brain axis and intestinal hormones

The 'gut-brain axis' (GBA) is complex and bi-directional, with its signaling mechanisms implicating the autonomous nervous system (primarily parasympathetic signals via the vagus nerve). Furthermore, the gut microbiota likely play an important role in the functioning of the GBA, either indirectly through effects on intestinal hormone release, autonomic functioning, or microbiota-derived metabolic products, or directly through central effects of the microbiota themselves (or microbiota components such as 'endotoxins') [22,23]. Indeed, changes to the gut microbiota, such as those occurring through antibiotic use, can affect gut-derived intestinal hormone release and may even be implicated in the development of depression and anxiety [24]. In addition to neuronal inputs and the effects of the gut microbiota, the central hypothalamic regulation of appetite and metabolism is mediated closely through the actions of some intestinal hormones that are released from the gastrointestinal tract [25].

Gut-derived incretin hormones are members of the glucagon superfamily that are released in response to nutrient stimulation, and drive glucose-dependent insulin release from the islet β-cells in the post-prandial period [5]. Currently, we only know of two incretin hormones: Glucose-dependent Insulinotropic Polypeptide (GIP, the first incretin hormone to be discovered in 1978) and Glucagon-Like Peptide-1 (GLP1, discovered in 1983). Although both are released from the ileum, GIP is synthesized by K cells [26], and GLP1 by L cells. Notably, GLP1 is also released from the colon and neurones within the brainstem [27]. Both GIP and GLP1 share some physiological effects that include insulinotropism and stimulation of the proliferation (and reduced

apoptosis) of islet β-cells. However, each has specific effects that for GIP include increased bone formation and fat accumulation, and for GLP1 include inhibition of the release of glucagon from the islet α-cells, central appetite suppression [28,29], increased cardiac output, and cardio-protection [19]. In addition to effects on glycemic control and appetite suppression, GLP1 also influences gastrointestinal motor function, specifically through delaying gastric emptying. This is important given the effect of gastric emptying as a major determinant of postprandial blood glucose (accounting for around 35% of the variance in peak glucose levels in both T2D and healthy individuals) [30]. It is known that T2D often associates with accelerated gastric emptying, regardless of prevailing glycemic control and co-existing complications [31,32]. Therefore, it is likely that at least some of the metabolic benefits of the GLP1 agonist therapies stem from their effects on delaying gastric emptying, and the impact this has on improved postprandial glycemic control and indirect effects on appetite suppression (with a sensation of feeling fuller for a longer period following a meal).

Incretin hormones are released in response to nutrient ingestion (primarily the macronutrients glucose and fat) [33]. The insulinotropic effect of incretin hormones has been known for nearly six decades through comparisons of serum insulin responses to glucose administered either orally or intravenously (with the former eliciting a more pronounced insulinotropic effect) [34]. Incretin hormones (such as GLP1 receptor agonists) act via G-coupled protein receptors (GCPR) to increase intracellular cyclic adenosine monophosphate (cAMP), with effects that include the stimulation of glucose-dependent insulin secretion from islet β-cells [35,36]. In addition, GLP1 receptor agonists also promote increased beta-cell mass, as evidenced by data from a recent meta-analysis of 360 randomized controlled trials, using Homeostasis Model Assessment of beta-cell function (HOMA-B) and fasting c-peptide levels [37]. Possible mechanisms that mediate the effects of GLP1 receptor agonists on beta cell mass include reduced oxidative inflammation and apoptosis, or improved survival of human islet cells through the stimulation of beta-cell proliferation [38,39].

Natural gut-derived incretin hormones (GIP and GLP1) are small peptides that are rapidly broken down and excreted via the renal system [27]. This rapid breakdown of natural incretin hormones has stymied the therapeutic development of incretin agonist drugs. The first GLP1 agonist, Exenatide, was approved in 2006 for the management of T2D. Since then, numerous other GLP1 agonist therapies have been developed and approved for use in T2D and, latterly, for obesity management [40].

3. Current designer GLP1PP dual agonist therapies

Beyond GIP and GLP1, there are numerous other gut-derived intestinal hormones that have a variety of physiological effects that include the mediation of the central hypothalamic control of appetite and metabolism. Amongst these are Glucagon (Gcg), Cholecystokinin (CCK), Peptide YY (PYY), and Glucagon-Like Peptide 2 (GLP2). In recent years, GLP1 has been synthetically bound to these other intestinal hormones in a 1:1 ratio (sometimes termed a 'twincretin'), with the therapeutic intention to pharmacologically target the physiological pathways of each intestinal hormone (GLP1 and its therapeutic partner) synergistically. Due to the inherent limitations of dose escalation of GLP-1 mono-agonists, an overarching aim of the design of many GLP1PP molecules has been to enhance the overall metabolic and appetitive efficacy of GLP1 monotherapy. Through binding to their respective receptors, the unimolecular peptides combined with GLP1 in the various designer GLP1PPs act effectively as an add-on monotherapy. Although the rationale for designer GLP1PP therapy development has centered on their metabolic benefits (including for diabesity management), the clinical utility of the GLP1PP agents extends well beyond metabolic control. In this section, we provide an overview of the clinical and pre-clinical data for the main designer GLP1PPs currently in development.

3.1. GLP1:GIP

The co-administration of GLP1 with GIP results in a more pronounced insulinotropic effect than that with either hormone administered alone [41]. These preliminary data provided the rationale and clinical justification for the development of the first designer GLP1PP drug, Tirzepatide, as a GLP1:GIP dual agonist. Tirzepatide was recently approved by the FDA for the management of T2D. Phase 3 trials of 2,539 participants demonstrated the superior glycemic and weight-loss efficacy of Tirzepatide compared with placebo, with its highest dose providing >20% body weight loss in the majority (57%) of participants in a 72-week trial, with minimal adverse effects [42]. The glycemic efficacy of Tirzepatide likely stems from the enhanced insulinotropic effects of the dual agonists, GLP1 and GIP. This combination likely results in strengthened agonism at each receptor through an imbalanced and biased dual mechanism of action, with enhanced insulin secretion during the post-prandial phase [43]. Effectively, the presence of the GLP1 moiety within the GLP1:GIP dual agonist may enhance the effects of the GIP moiety at its receptor and vice versa. Such enhancement in GLP1 and GIP effects through dual agonism is relevant for T2D (in which resistance to the effects of GLP1 and GIP at their respective receptors pertains) and may explain the superior glycemic efficacy of Tirzepatide [44]. Furthermore, improvements in glycemic control that stem from the effects of the GLP1:GIP dual agonist may further improve the sensitivity to GLP1 and GIP at their respective receptors [45]. However, it should be made clear that these hypotheses regarding possible mechanisms of action of GLP1:GIP dual agonists remain speculative, contentious and incompletely understood. Furthermore, the mechanisms that underlie the metabolic efficacy of Tirzepatide remain unknown. In one study, it was shown that selective stimulation of GIP secretion in the context of augmented plasma-intact GIP and intact GLP1 (through the use of a Dipeptidyl Peptidase-4 [DPP4] Inhibitor drug) failed to yield significant glucose lowering effects in T2D [46]. This argues against a simple additive effect of GLP1 and GIP actions on glycemic control.

Exploration of the underlying mechanisms of action of the GLP1:GIP dual agonists should be a focus for future research and will likely inform future potential innovative therapeutic avenues.

3.2. GLP1:Gcg

Our notion of the physiological role of Gcg has centered around its glucogenic effects (including gluconeogenesis and glycogenolysis), that essentially counteract the physiological effects of insulin through its release from the islet α-cells during times of fasting to maintain euglycemia [47]. However, although Gcg has been known for over six decades to play a role in the regulation of energy expenditure, the underlying mechanisms have remained elusive and the complete spectrum of Gcg effects/physiology remains enigmatic [48,49]. For example, in addition to its release from the islet α-cells, Gcg is also released from the gut as a by-product of pre-pro-glucagon [48,50]. The established effect of Gcg on the enhancement of metabolic rate, combined with the central hypothalamic appetite-suppressant effects of GLP1, provides a rational for combining GLP1 with Gcg as a designer GLP1PP.

There are two GLP1:Gcg dual agonist molecules that are currently under clinical investigation: Mazdutide (Innovent Biologics) and Cotadutide (AstraZeneca). Mazdutide is currently undergoing a phase II clinical trial following recently published Phase Ib trial data that showed a 11.7% reduction in body weight in overweight and obese patients over a 12-week period for the 9 mg dose [51]. Regarding Cotadutide, a phase II trial based on 834 adults with T2D demonstrated weight loss and glycemic outcomes at 54-weeks comparable to those with Liraglutide [52]. A further study on the metabolic effects of Cotadutide in participants of Asian origin (a population with an increased susceptibility to T2D) over a 48-day period showed significant reductions in blood glucose (including within the postprandial phase) and body weight [53]. Unfortunately, the GLP1:Gcg dual agonist molecules appear to associate with greater gastrointestinal intolerability compared with that for GLP1-based monotherapies.

Beyond body weight loss and improved glycemic control, the GLP1:Gcg dual agonists have also been assessed for their efficacy in patients with Non-Alcoholic Fatty Liver Disease (NAFLD) and Non-Alcoholic Steatohepatitis (NASH). A phase 2b study on the metabolic and hepatic effects of Cotadutide revealed a significant reduction in both serum transaminase levels (at the 300 μg dose) and triglyceride concentration compared with those measures in the Liraglutide and placebo groups [53]. Furthermore, Cotadutide therapy was associated with a significant improvement in the fatty liver index (−8.18 at the 300 μg dose compared with −6.22 and −1.62 in the Liraglutide and placebo groups, respectively). The authors speculated that the improvement in fatty liver index and serum transaminase level in the Cotadutide group may reflect the physiological effects of Gcg through improved hepatic lipoprotein processing. Furthermore, the effect of GLP1 on lipoprotein processing within the intestine may complement the hepatic lipoprotein effects of Gcg [54], thereby improving fatty liver index and serum transaminase levels.

3.3. GLP1:CCK

CCK, synthesized and secreted by I cells of the duodenum, has physiological roles within both the gastrointestinal system (to mediate gastric emptying) and the hypothalamic appetite center (to suppress appetite and promote satiety) [55]. Notably, CCK agonists alone have not shown a significant impact on food intake or body weight in animal models. However, the co-administration of CCK with a GLP1 agonist in diet-induced obese rats resulted in a greater loss of body weight than that which occurred with a GLP1 agonist monotherapy [56]. Furthermore, the administration of a novel GLP1:CCK dual agonist in a mouse model resulted in reduced feeding behavior and body weight [57]. There is currently a lack of human-based studies regarding GLP1:CCK dual agonists, although the rodent-based studies outlined here provide proof of concept, and a rationale for exploring the metabolic utility of such therapies in human-based trials on diabesity.

3.4. GLP1:PYY

PYY is released from the colon and L cells within the distal ileum. PYY crosses the blood–brain barrier and binds to Neuroreceptor Y2 receptors within the hypothalamic appetite center, where it exerts a potent anorectic effect [58]. Obesity is associated with lower levels of PYY within the serum, thereby promoting the hypothalamic Neuroreceptor Y2 receptors as a potential target for novel drug therapies to tackle obesity. Moreover, the combination of GLP1 with PYY in a single molecule was inspired by the weight-loss success of Roux-en-Y gastric bypass surgery for obesity, likely mediated at least in part through changes in serum levels of GLP1 and PYY [59]. The development of novel GLP1:PYY dual agonists may therefore represent an opportunity to medically replicate the weight-losing effects of Roux-en-Y gastric bypass surgery.

Despite the theoretical weight-losing benefits of novel GLP1:PYY dual agonists, to date these therapies have only been explored in rodent-based models. One example is 'GEP44' which in rat and shrew models resulted in significant weight loss and improved blood glucose control [60]. Interestingly however, the effects of GEP44 may not be confined to appetite suppression, as evidenced by data from a separate rodent-based study in which GEP44 was associated with reduced opioid-seeking behavior (without suppression of food intake) [61]. Furthermore, PYY may also have a role in mediating behavior related to drug abuse through mechanisms that are incompletely understood. An *in vivo* study on the appetitive effects of a GLP1:PYY dual agonist ('analogue 19') in lean mice revealed a significant reduction in food intake compared with food intake in response to GLP1 or PYY administered separately as monotherapies [62]. As with the GLP1:Gcg dual agonist studies outlined above, GLP1:PYY dual agonists have also been explored in rodent-based models of NASH, including a study on 'Peptide 6q' in a 'Diet-Induced Obesity (DIO)-NASH' mouse model. Compared with Liraglutide, Peptide

6q resulted in significant reductions in serum levels of AST and ALT (key markers of liver function) and liver fat content. These data reveal that in addition to improvements in body weight and glycemic control, Peptide 6q also manifests anti-steatotic properties, at least in rodent models [63]. These rodent-based data provide proof of concept for the potential clinical utility of GLP:PYY dual agonist therapies to justify further exploration in human-based studies.

3.5. GLP1:GLP2

Teduglutide (a GLP2 analogue) is currently licensed in the UK for use in short bowel syndrome. This makes GLP1:GLP2 dual peptides unique compared to their counterparts as their individual components are already licensed for use individually [64].

GLP2 is co-secreted with GLP1 from the L cells of the distal ileum in response to nutrients. However, although released from the gut in response to food, technically GLP2 is not an incretin hormone as it does not elicit an incretin effect. Rather, GLP2 enhances intestinal growth and function, improves bone growth, and has a role in neuroprotection [65]. Dapiglutide is a GLP1:GLP2 dual agonist (administered subcutaneously), associated with a dose-dependent loss of body weight (mean weight loss of 4.5% with the highest dose) in a reported study on healthy participants ($n = 40$) over a four-week period [66]. Dapiglutide was well tolerated with a similar side-effect profile (including nausea and vomiting) to that of GLP1 agonists. In addition to its weight-loss effects, several studies demonstrate the GI benefits of Dapiglutide, with protective effects within the small intestine, including increased intestinal surface area via the promotion of growth of the intestinal crypts [67,68]. Furthermore, Dapiglutide may also have a role in improving the gut barrier function and promoting intestinal motility and functional adaptation to intestinal resection [67–69]. Accordingly, Dapiglutide is clinically indicated for the treatment of Short Bowel Syndrome (SBS) following intestinal resection and associated with malabsorption and/or intestinal failure.

Continuous infusion of a GLP1:GLP2 dual agonist therapy in patients with SBS resulted in favorable clinical outcomes compared with the administration of either peptide alone. Only infusions containing both GLP1 and GLP2 resulted in overall improved hydration status, increased total body weight (due to increased absolute wet weight) and reduced post prandial glucose [70]. Recently, a rodent-based study demonstrated beneficial effects of Dapiglutide on the promotion of the intestinal barrier function, including improved tight junctions within the jejunum and reduced volume depletion via epithelial sodium channel (ENaC) activation within the colon [67]. A further rodent-based study of SBS revealed favorable effects of Dapiglutide on intestinal growth, body weight, food intake, volume status and stool water content. Reflective of these benefits, there was an attainment of 92% vs 85% of their initial weight at day 14 in the Dapiglutide-treated and control mice, respectively [68].

Finally, beyond the weight-losing and intestinal growth-promoting effects of Dapiglutide, GLP1:GLP2 dual agonists may also provide hepatic benefits, with a recently reported rodent-based model of NASH showing GLP1:GLP2 dual agonist-induced improvements in liver disease parameters, including hepatic fibrosis, insulin sensitivity and liver fat index [66].

3.6. GLP1:FGF21

Fibroblast Growth Factor 21 (FGF21) is a peptide molecule that is secreted mainly from the liver. The inherent instability and short half-life of the FGF21 peptide makes it difficult to research. The main physiological function of FGF21 is the control of blood glucose and lipid profile. In mice, a GLP1:FGF21 dual agonist has demonstrated beneficial effects on both body weight and hepatic inflammatory markers [71]. However, these are preliminary data and the GLP1:FGF21 dual agonist has yet to be assessed in human-based studies.

4. Current designer GLP1PP triple agonist therapies

There is no logical reason to restrict combinations of intestinal peptides to dual agonists. Based on the outlined pharmacological and physiological effects of the individual gut-derived intestinal hormones that are well-known, and their potential for complementarity when combined in a single molecule, it is entirely logical to explore combinations of intestinal hormones in higher orders than mere duplets. Indeed, the design and clinical assessment of triple incretin agonists is already underway.

GLP1:GIP:Gcg ('SAR441255') represents one of the first triple incretin agonist therapies to be developed. In a preliminary human-based study ($n = 48$), participants tolerated single doses of SAR441255 and adverse effects (including nausea) were mild. In diabetic cynomolgus monkeys, SAR441255 associated with a 12.6% reduction in body weight, although the glycemic benefit of SAR441255 was inferior to that of a GLP1:GIP dual agonist therapy (HbA1c reduction of 1.37% vs 1.85%, respectively). Through *in vivo* analysis of receptor occupation within this animal model, there was high GLP1 and Gcg receptor binding within target organs, including liver, pancreas, and kidneys [72]. However, the binding capacity of GIP within GLP1:GIP:Gcg triple agonist therapies remains unknown. In addition to weight loss and improved glycemia, the GLP1:GIP:Gcg triple agonist therapies may also have neurological benefits. These include improved visual recognition and spatial memory in a mouse model of mild Traumatic Brain Injury (TBI), and improved working and reference memory (via testing in a radial maze) in a mouse model of Alzheimer's disease [73,74]. GLP1:CCK:Gcg is a further GLP1PP triple agonist therapy in development. In a diabetic-induced mouse model, there was improvement in glucose control with this triple agonist therapy compared with Liraglutide (a GLP1 mono-agonist) and Cotadutide (a GLP1:Gcg dual agonist). Furthermore, in the short-term there was considerable growth of islet cells and regain of pancreatic tissue in response to the administration of GLP1:CCK:Gcg [75].

5. Future directions

It is important to consider how the outlined field of designer GLP1PP therapies is likely to evolve, and how this will impact

on future treatment algorithms for diabesity. To date, innovations within the GLP1PP field have focused primarily on dual agonist therapies, combining GLP1 with another intestinal hormone. This is understandable given our clinical experience of the GLP1 class in the management of T2D and obesity, and the superior efficacy of GLP1 therapies for weight loss, glycemic control and in some cases cardiovascular effects. However, as our clinical experience of the other intestinal hormones expands, it seems likely that future generations of designer incretin molecules will also focus more on non-GLP1 molecular combinations. Given the serendipitous nature of this new and emerging field, it seems likely that multiple novel combinations of incretin and intestinal hormones will continue to be developed for exploration of their comparative efficacy and tolerability. Furthermore, given the plethora of gut-derived intestinal hormones (including some that are yet to be identified), and the apparent amenability of the incretin and intestinal peptides to be combined *in vitro* in a 'designer' fashion for therapeutic benefits, it seems inevitable that future developments will also include incretin and intestinal combinations that are quadruple, quintuple and beyond.

The history of pharmacotherapies for obesity is chequered, with numerous examples of therapies that have been withdrawn due to safety concerns. A key advantage of many GLP1 therapies and the GLP1PP class pertains to their modeling on human peptides, often with a high degree of homology. From a safety perspective, it is often preferable to focus on natural human peptides as therapies rather than molecules that are alien to the human body (including less potential for antibody formation and immune attack, for example). Whilst gastrointestinal intolerability, including nausea, remain troublesome side-effects of the GLP1 class for some patients, future GLP1PP developments may tackle this (e.g. through possible 'dilutional' effects of combining GLP1 with other peptides). From a glycemic and weight loss efficacy perspective, the GLP1PP therapies (including, for example, Tirzepatide) appear superior to the GLP1 monotherapy class. The current positioning of GLP1 therapies for T2D management, although traditionally post-oral glycemic therapies and pre-insulin-based therapies, has transitioned in recent times toward earlier usage based on their cardiovascular benefits. Indeed, there are many factors that influence the positioning of therapies in treatment algorithms, including duration of clinical experience, efficacy and safety concerns, mode of administration, and of course, cost.

Currently, the GLP1PP therapies are injectable, although future developments may facilitate alternate administrations, including via the oral route. Although cost is difficult to predict, it seems reasonable to assume that the GLP1PP therapies will be at least as expensive as the GLP1 class, and likely more so. Given the impact of cardiovascular outcome data on the positioning of existing therapies for T2D, as evidenced by that outlined above for the GLP1 class (and the Sodium Glucose-Like Transporter 2 [SGLT2] inhibitor class), it is reasonable to predict that data originating from future cardiovascular and cardio-renal outcome studies for the GLP1PP therapies (in the context of management of both T2D and obesity) will have a strong influence on their future positioning. In a scenario in which GLP1PP therapies prove superior to existing GLP1 monotherapies for cardiovascular, glycemic, and weight-loss outcomes, such GLP1PP therapies may then replace and supersede GLP1 monotherapies within future T2D treatment algorithms. Given that innovative designer GLP1PP therapies are likely to dominate the field of diabesity for many years and decades to come, we should be prepared for dynamism within future treatment algorithms for diabesity, demanding a more flexible and adaptable approach to the design and implementation of such future treatment algorithms to optimize management.

Finally, we should consider the superior weight-losing properties of the GLP1PP class of therapies, with early evidence from the clinical trials for Tirzepatide. Bariatric surgery (including gastric bypass) enables sustained loss of body weight and improved glycemic control, at least in part, through reprogramming of gut-derived incretin hormones, including for example the early release of GLP1 from distal ileal L-cells in response to a faster transit of nutrients through the stomach following a meal, and therefore earlier satiety effects and improved glycemic stability and control [10]. Whilst the precise mechanism(s) of weight loss and glycemic improvement following bariatric surgery remains incompletely understood (and may be procedure-specific), our current understanding is that ultimately, weight loss following bariatric surgery is mediated primarily through 'medical' (rather than structural) effects ('medical' is used here as an umbrella term to encompass physiological effects and is likely to implicate an important role for the gut-derived incretins and intestinal hormones). It follows, therefore, that the beneficial appetitive and metabolic effects that stem from bariatric surgery should be, at least in part, replicable through the administration of incretins and intestinal hormones with precise dosages, timings, ordering, and durations. The rise of the designer GLP1PP class provides an excellent and timely opportunity to explore in greater detail than ever, the 'holy grail' of weight loss: the 'sweet spot' combination and timing of incretin peptide administration that provides optimal weight loss (and maintenance) akin, and even potentially superior to traditional bariatric surgical procedures.

6. Conclusions

Diabesity contributes to much morbidity and mortality globally [76,77]. Our current management strategies are limited by difficulties associated with the longer-term adoption of lifestyle (including dietary) modification, and the restricted resource and relative invasiveness of bariatric surgery [78]. Currently, our best option for durable and effective glycemic control and weight loss in diabesity rests with bariatric surgery, with a reduction in HbA1c of 1.8–3.5% (compared with 0.4–1.5% for pharmacotherapies) in a recent review of the literature [79]. Although not fully understood, the glycemic and weight-loss benefits of bariatric surgery likely stem from changes in the release of incretin hormones from increased rapidity of nutrient transit through the gut, although other mechanisms that implicate possible changes in the gut microbiota may also pertain [80].

The birth of the GLP1PP designer therapies requires us to sea-change our traditional perspectives on diabesity

management. The current clinical data on the first available GLP1PP therapy, Tirzepatide, with its 20.9% mean weight loss at the higher dose, thrusts the GLP1PP class toward the hallowed realms of bariatric surgery [42]. As a non-invasive and non-procedure limited therapeutic option, Tirzepatide has the potential to be considered as a viable clinical alternative for at least some patients who would otherwise proceed to bariatric surgery.

Despite their apparent superior glycemic and weight-loss efficacy, our enthusiasm for the GLP1PP class of therapies should be tempered by a current lack of longer-term data, particularly regarding their safety. Furthermore, important unanswered questions remain. These include possible biochemical and/or therapeutic limitations of multiple conjugated peptide hormones, and whether we should assume that efficacy correlates with the number of conjugated peptides. The generation of the quadruple agonists ZLY18 and RLA8, that each consists of Free Fatty Acid 1 (FFA1), Peroxisome Proliferator-activated Receptor α (PPARα), PPARγ and PPARδ, and which appears to manifest metabolic efficacy in NAFLD, provides proof of concept for the development and potential clinical utility of quadruple agonist therapies [81]. Furthermore, there remains the intriguing possibility of combining gut-derived incretin hormones, such as GLP1, with other non-incretin peptide hormones, such as Amylin (implicated in energy regulation and released with insulin by the islet beta-cells, and often deficient in T2D) [82]. Pramlintide, an amylin analogue, is an adjunct therapy for both Type 1 Diabetes Mellitus (T1D) and T2D to improve glycemic control [83]. The administration of both GLP1 and amylin concurrently in monkeys was shown to act in an additive manner to suppress appetite and reduce food intake, demonstrating their potential as a combined co-agonist [84].

Other future avenues include novel combinations of gut-related incretin and intestinal hormones, such as a triple GLP1PP agonist with the combination of GLP1, oxyntomodulin, and PYY. In human-based studies of both pre-diabetes and T2D, the co-administration of these individual peptides results in effective weight loss and improved glucose control [85]. Furthermore, there is increased secretion of GLP1, oxyntomodulin, and PYY following Roux-en-Y Gastric Bypass (RYGB), a response that may mediate some of the glycemic and weight-loss effects of this procedure [59]. Enhanced secretion of GLP1 following RYGB likely stems from faster transit of nutrients into the distal ileum. In support of this hypothesis, a human-based study explored the metabolic effects of glucose infusions administered through a transnasal catheter and positioned into the proximal and distal small intestine. It was shown that both the incretin effect and gastrointestinal-mediated glucose disposal were more pronounced for distal compared with proximal small intestinal glucose infusions [86]. Finally, GLP1 may manifest other therapeutic benefits beyond those of improved metabolic control. These include possible hitherto unexplored neurological benefits (as suggested from some rodent-based studies), with potential applications in the future management of stroke, peripheral neuropathy, amyotrophic lateral sclerosis, and Huntington's disease [87–89]. Further research should focus on the potential extra-metabolic (including neurological and gastrointestinal) effects of GLP1 and other intestinal hormones, both as monotherapies and in combination.

To conclude, the gut endocrine system is complex. We are in our infancy regarding understanding the complete physiology of gut-derived incretin and intestinal hormones and their potential therapeutic utility. There are almost limitless opportunities to combine gut-related incretin and intestinal hormones in GLP1PP multi-agonist therapies. An important area for further research would be to assess the potential cardiovascular and renal benefits of GLP1PP therapies, to facilitate our mechanistic understanding of this class, and to explore potential benefits beyond glycemic control and weight loss. Although much uncertainty exists regarding the longer-term efficacy, safety, tolerability, and cardiometabolic benefits of the designer GLP1PP class, we can be certain that the next few years and decades will bear witness to a new dawn in the management of diabesity, and one in which the novel designer GLP1PP class of therapies predominates.

7. Expert opinion

Our chaotic and stressful modern-day environment interacts in myriad complex ways with our genetic architecture, mediated through epigenetic effects that modify the expression profiles of genes. It is from this environmental and genetic entanglement that weight gain ensues, resulting in the clinical manifestations of obesity. Obesity, with its associated insulin resistance, acts as a forerunner for a multiplicity of obesity-related conditions, of which T2D looms prominently. The frequent co-existence of obesity and T2D, and the shared epidemiology and pathophysiology (including environmental and genetic factors) underlying each condition, merits therapeutic targeting of 'diabesity' as a conflation of T2D and obesity.

Our therapeutic armamentarium for diabesity has been transformed in recent years with the emergence of designer molecules that combine natural, human-based incretin hormones (including GLP1) in polypeptide combinations. The recent FDA approval of Tirzepatide, as the first dual GLP1:GIP incretin agonist therapy available for clinical usage, represents an important landmark in this new era of designer GLP1PP therapies. Many other GLP1PPs are currently in development, and most combine GLP1 with an additional intestinal peptide (including Gcg, CCK, and PYY) as dual agonists. Recent developments also include triple agonist therapies, and we even have proof of concept from a rodent-based model for the development of a quadruple agonist therapy. Despite the current lack of data on cardiovascular and renal-based outcomes for the GLP1PP therapies, the clinical efficacy of Tirzepatide regarding both glycemic and weight-loss effects appear favorable compared with GLP1 monotherapies. It is important to recognize that no head-to-head studies of Tirzepatide versus GLP1 monotherapies have yet been executed, and it is difficult to make direct comparisons between therapies from separate trials each with their own design, endpoints, population, and selection criteria. However, despite these caveats, we should be buoyed by the propitious clinical data for Tirzepatide, which bodes well for the future development of the GLP1PP class of therapies.

The numerous potential combinations of incretin and intestinal hormones, together with the inherent complexity of the gut endocrine system (with pleiotropic and sometimes unexpected effects), indicate that the new era of designer GLP1PPs will likely dominate the therapeutic landscape of diabesity in the coming years. In preparation for the inevitable influx of new therapies for diabesity, it is important that we adopt a more responsive, adaptable, and flexible approach to our future therapy guidelines, to optimize the management of our patients with diabesity according to the latest clinical evidence, and to ensure dynamism as a core feature of future treatment algorithms for diabesity.

Funding

This paper was not funded.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

References

1. WHO: Obesity and overweight [internet]. World Health Organisation; 2021. [cited 2022 Dec 30]; Available from: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight
2. Golubic R, Barber TM, Caleyachetty R. Obesity definition for personalised treatment of type 2 diabetes. Lancet. 2022;399(10342):2189.
3. Caleyachetty R, Barber TM, Mohammed NI, et al. Ethnicity-specific BMI cutoffs for obesity based on type 2 diabetes risk in England: a population-based cohort study. Lancet Diabetes Endocrinol. 2021;9(7):419–426. DOI:10.1016/S2213-8587(21)00088-7
4. Khan MAB, Hashim MJ, King JK, et al. Epidemiology of type 2 diabetes - global burden of disease and forecasted trends. J Epidemiol Glob Health. 2020;10(1):107–111.
5. LaBarre J. Sur les possibilités d'un traitement du diabète par l'incrétine. Bull Acad R Med Belg. 1932;12:620–634.
6. Avery AR, Duncan GE. Heritability of type 2 diabetes in the Washington State Twin Registry. Twin Res Hum Genet. 2019;22(2):95–98.
7. Willemsen G, Ward KJ, Bell CG, et al. The concordance and heritability of type 2 diabetes in 34,166 twin pairs from international twin registers: the discordant twin (DISCOTWIN) Consortium. Twin Res Hum Genet. 2015;18(6):762–771. DOI:10.1017/thg.2015.83
8. Hanson P, Weickert MO, Barber TM. Obesity: novel and unusual predisposing factors. Ther Adv Endocrinol Metab. 2020;11:2042018820922018.
9. Elder PJD, Ramsden DB, Burnett D, et al. Human amylase gene copy number variation as a determinant of metabolic state. Expert Rev Endocrinol Metab. 2018;13(4):193–205.
10. Barber TM, Bhatti AA, Elder PJD, et al. AMY1 gene copy number correlates with glucose absorption and visceral fat volume, but not with insulin resistance. J Clin Endocrinol Metab. 2020;105(10):e3586–3596. DOI:10.1210/clinem/dgaa473
11. Brown E, Wilding JPH, Barber TM, et al. Weight loss variability with SGLT2 inhibitors and GLP-1 receptor agonists in type 2 diabetes mellitus and obesity: mechanistic possibilities. Obes Rev. 2019;20(6):816–828.
12. Hanson P, Randeva H, Cuthbertson DJ, et al. The DAPA-DIET study: metabolic response to Dapagliflozin combined with dietary carbohydrate restriction in patients with Type 2 Diabetes Mellitus and Obesity-A longitudinal cohort study. Endocrinol Diabetes Metab. 2022;5(6):e381. DOI:10.1002/edm2.381
13. Davies MJ, Russell-Jones D, Barber TM, et al. Glycaemic benefit of iGlarlixi in insulin-naive type 2 diabetes patients with high HbA1c or those with inadequate glycaemic control on two oral antihyperglycaemic drugs in the LixiLan-O randomized trial. Diab Obes Metab. 2019;21(8):1967–1972. DOI:10.1111/dom.13791
14. Caruso I, Giorgino F. SGLT-2 inhibitors as cardio-renal protective agents. Metabolism. 2022;127:154937.
15. Giugliano D, Scappaticcio L, Longo M, et al. GLP-1 receptor agonists and cardiorenal outcomes in type 2 diabetes: an updated meta-analysis of eight CVOTs. Cardiovasc Diabetol. 2021;20(1):189. DOI:10.1186/s12933-021-01366-8
16. Brown E, Wilding JPH, Alam U, et al. The expanding role of SGLT2 inhibitors beyond glucose-lowering to cardiorenal protection. Ann Med. 2021;53(1):2072–2089.
17. Ma H, Lin YH, Dai LZ, et al. Efficacy and safety of GLP-1 receptor agonists versus SGLT-2 inhibitors in overweight/obese patients with or without diabetes mellitus: a systematic review and network meta-analysis. BMJ Open. 2023;13(3):e061807.
18. Gribble FM. The gut endocrine system as a coordinator of postprandial nutrient homoeostasis. Proc Nutr Soc. 2012;71(4):456–462.
19. Seino Y, Fukushima M, Yabe D. GIP and GLP-1, the two incretin hormones: similarities and differences. J Diabetes Investig. 2010;1(1–2):8–23.
20. Conlon JM, O'Harte FPM, Flatt PR. Dual-agonist incretin peptides from fish with potential for obesity-related Type 2 diabetes therapy - a review. Peptides. 2022;147:170706.
21. Capozzi ME, DiMarchi RD, Tschöp MH, et al. Targeting the incretin/glucagon system with triagonists to treat diabetes. Endocr Rev. 2018;39(5):719–738.
22. Carabotti M, Scirocco A, Maselli MA, et al. The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems. Ann Gastroenterol. 2015;28(2):203–209.
23. Barber TM, Valsamakis G, Mastorakos G, et al. Dietary influences on the microbiota–gut–brain axis. Int J Mol Sci. 2021;22(7):3502. DOI:10.3390/ijms22073502
24. Foster JA, McVey Neufeld KA. Gut-brain axis: how the microbiome influences anxiety and depression. Trends Neurosci. 2013;36(5):305–312.
25. Nauck MA, Meier JJ. Incretin hormones: their role in health and disease. Diab Obes Metab. 2018;20(Suppl 1):5–21.
26. Buchan AM, Polak JM, Capella C, et al. Electron immunocytochemical evidence for the K cell localization of gastric inhibitory polypeptide (GIP) in man. Histochemistry. 1978;56(1):37–44.
27. Baggio LL, Drucker DJ. Biology of incretins: gLP-1 and GIP. Gastroenterology. 2007;132(6):2131–2157.
28. Delgado-Aros S, Kim DY, Burton DD, et al. Effect of GLP-1 on gastric volume, emptying, maximum volume ingested, and postprandial symptoms in humans. Am J Physiol Gastrointest Liver Physiol. 2002;282(3):G424–31.
29. Drucker DJ. Mechanisms of action and therapeutic application of glucagon-like peptide-1. Cell Metab. 2018;27(4):740–756.
30. Jalleh RJ, Jones KL, Rayner CK, et al. Normal and disordered gastric emptying in diabetes: recent insights into (patho)physiology, management and impact on glycaemic control. Diabetologia. 2022;65(12):1981–1993.
31. Watson LE, Xie C, Wang X, et al. Gastric emptying in patients with well-controlled type 2 diabetes compared with young and older control subjects without diabetes. J Clin Endocrinol Metab. 2019;104(8):3311–3319.
32. Xie C, Huang W, Wang X, et al. Gastric emptying in health and type 2 diabetes: an evaluation using a 75 g oral glucose drink. Diabet Res Clin Pract. 2021;171:108610.

33. Barber TM, Begbie H, Levy J. The incretin pathway as a new therapeutic target for obesity. Maturitas. 2010;67(3):197–202.
34. Perley MJ, Kipnis DM. Plasma insulin responses to oral and intravenous glucose: studies in normal and diabetic sujbjects. J Clin Invest. 1967;46(12):1954–1962.
35. Stožer A, Paradiž Leitgeb E, Pohorec V, et al. The role of CAMP in beta cell stimulus-secretion and intercellular coupling. Cells. 2021;10(7):1658.
36. Graaf C, Donnelly D, Wootten D, et al. Glucagon-Like Peptide-1 and Its Class B G protein-coupled receptors: a long march to therapeutic successes. Pharmacol Rev. 2016;68(4):954–1013.
37. Wu S, Gao L, Cipriani A, et al. The effects of incretin-based therapies on β-cell function and insulin resistance in type 2 diabetes: a systematic review and network meta-analysis combining 360 trials. Diab Obes Metab. 2019;21(4):975–983.
38. Lee YS, Jun HS. Anti-diabetic actions of glucagon-like peptide-1 on pancreatic beta-cells. Metabolism. 2014;63(1):9–19.
39. Cunha DA, Ladrière L, Ortis F, et al. Glucagon-like peptide-1 agonists protect pancreatic beta-cells from lipotoxic endoplasmic reticulum stress through upregulation of BiP and JunB. Diabetes. 2009;58(12):2851–2862.
40. Trujillo JM, Nuffer W, Smith BA. GLP-1 receptor agonists: an updated review of head-to-head clinical studies. Ther Adv Endocrinol Metab. 2021;12:2042018821997320.
41. Elahi D, McAloon-Dyke M, Fukagawa NK, et al. The insulinotropic actions of glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (7-37) in normal and diabetic subjects. Regul Pept. 1994;51(1):63–74.
42. Jastreboff AM, Aronne LJ, Ahmad NN, et al. Tirzepatide once weekly for the treatment of obesity. N Engl J Med. 2022;387(3):205–216.
43. El Eid L, Reynolds CA, Tomas A, et al. Biased agonism and polymorphic variation at the GLP-1 receptor: implications for the development of personalised therapeutics. Pharmacol Res. 2022;184:106411.
44. Willard FS, Douros JD, Gabe MB, et al. Tirzepatide is an imbalanced and biased dual GIP and GLP-1 receptor agonist. JCI Insight. 2020;5(17):e140532.
45. An Z, Prigeon RL, D'Alessio DA. Improved glycemic control enhances the incretin effect in patients with type 2 diabetes. J Clin Endocrinol Metab. 2013;98(12):4702–4708.
46. Wu T, Ma J, Bound MJ, et al. Effects of sitagliptin on glycemia, incretin hormones, and antropyloroduodenal motility in response to intraduodenal glucose infusion in healthy lean and obese humans and patients with type 2 diabetes treated with or without metformin. Diabetes. 2014;63(8):2776–2787.
47. Gerich JE. Physiology of glucagon. Int Rev Physiol. 1981;24:243–275.
48. Kleinert M, Sachs S, Habegger KM, et al. Glucagon regulation of energy expenditure. Int J Mol Sci. 2019;20(21):5407.
49. Janah L, Kjeldsen S, Galsgaard KD, et al. Glucagon receptor signaling and glucagon resistance. Int J Mol Sci. 2019;20(13):3314.
50. Drucker DJ. Mini review: the glucagon-like peptides. Endocrinology. 2001;142(2):521–527.
51. Ji L, Gao L, Jiang H, et al. Safety and efficacy of a GLP-1 and glucagon receptor dual agonist mazdutide (IBI362) 9 mg and 10 mg in Chinese adults with overweight or obesity: a randomised, placebo-controlled, multiple-ascending-dose phase 1b trial. EClinicalMedicine. 2022;54:101691.
52. Nahra R, Wang T, Gadde KM, et al. Effects of cotadutide on metabolic and hepatic parameters in adults with overweight or obesity and type 2 diabetes: a 54-week randomized phase 2b study. Diabetes Care. 2021;44(6):1433–1442.
53. Asano M, Sekikawa A, Kim H, et al. Pharmacokinetics, safety, tolerability and efficacy of cotadutide, a glucagon-like peptide-1 and glucagon receptor dual agonist, in phase 1 and 2 trials in overweight or obese participants of Asian descent with or without type 2 diabetes. Diab Obes Metab. 2021;23(8):1859–1867.
54. Xiao C, Pavlic M, Szeto L, et al. Effects of acute hyperglucagonemia on hepatic and intestinal lipoprotein production and clearance in healthy humans. Diabetes. 2011;60(2):383–390.
55. Moran TH, Kinzig KP. Gastrointestinal satiety signals II. Cholecystokinin. Am J Physiol Gastrointest Liver Physiol. 2004;286(2):G183–8.
56. Trevaskis JL, Sun C, Athanacio J, et al. Synergistic metabolic benefits of an exenatide analogue and cholecystokinin in diet-induced obese and leptin-deficient rodents. Diab Obes Metab. 2015;17(1):61–73.
57. Hornigold DC, Roth E, Howard V, et al. A GLP-1: cCK fusion peptide harnesses the synergistic effects on metabolism of CCK-1 and GLP-1 receptor agonism in mice. Appetite. 2018;127:334–340.
58. Batterham RL, Cowley MA, Small CJ, et al. Gut hormone PYY(3-36) physiologically inhibits food intake. Nature. 2002;418(6898):650–654.
59. le Roux CW, Aylwin SJ, Batterham RL, et al. Gut hormone profiles following bariatric surgery favor an anorectic state, facilitate weight loss, and improve metabolic parameters. Ann Surg. 2006;243(1):108–114.
60. Milliken BT, Elfers C, Chepurny OG, et al. Design and evaluation of peptide dual-agonists of GLP-1 and NPY2 receptors for glucoregulation and weight loss with mitigated nausea and emesis. J Med Chem. 2021;64(2):1127–1138.
61. Zhang Y, Rahematpura S, Ragnini KH, et al. A novel dual agonist of glucagon-like peptide-1 receptors and neuropeptide Y2 receptors attenuates fentanyl taking and seeking in male rats. Neuropharmacology. 2021;192:108599.
62. Østergaard S, Paulsson JF, Kjaergaard Gerstenberg M, et al. The Design of a GLP-1/PYY dual acting agonist. Angew Chem Int Ed Engl. 2021;60(15):8268–8275.
63. Yang Q, Tang W, Sun L, et al. Design of Xenopus GLP-1-Based Long-Acting Dual GLP-1/Y(2) Receptor Agonists. J Med Chem. 2022;65(20):14201–14220.
64. Rosete BE, Wendel D, Horslen SP. Teduglutide for pediatric short bowel syndrome patients. Expert Rev Gastroenterol Hepatol. 2021;15(7):727–733.
65. Drucker DJ. Glucagon-like peptide 2. J Clin Endocrinol Metab. 2001;86(4):1759–1764.
66. Olsen MB, Hövelmann U, Griffin J, et al. 335-OR: dapiglutide, a Once-Weekly GLP-1R/GLP-2R dual agonist, was safe and well tolerated and showed dose-dependent body weight loss over four weeks in healthy subjects. Diabetes. 2022;71(Supplement_1):335–OR.
67. Reiner J, Thiery J, Held J, et al. The dual GLP-1 and GLP-2 receptor agonist dapiglutide promotes barrier function in murine short bowel. Ann N Y Acad Sci. 2022;1514(1):132–141.
68. Reiner J, Berlin P, Held J, et al. Dapiglutide, a novel dual GLP-1 and GLP-2 receptor agonist, attenuates intestinal insufficiency in a murine model of short bowel. JPEN J Parenter Enteral Nutr. 2022;46(5):1107–1118.
69. Jeppesen PB, Hartmann B, Thulesen J, et al. Elevated plasma glucagon-like peptide 1 and 2 concentrations in ileum resected short bowel patients with a preserved colon. Gut. 2000;47(3):370–376.
70. Madsen KB, Askov-Hansen C, Naimi RM, et al. Acute effects of continuous infusions of glucagon-like peptide (GLP)-1, GLP-2 and the combination (GLP-1+GLP-2) on intestinal absorption in short bowel syndrome (SBS) patients. A placebo-controlled study. Regul Pept. 2013;184:30–39.
71. Pan Q, Lin S, Li Y, et al. A novel GLP-1 and FGF21 dual agonist has therapeutic potential for diabetes and non-alcoholic steatohepatitis. EBioMedicine. 2021;63:103202.
72. Bossart M, Wagner M, Elvert R, et al. Effects on weight loss and glycemic control with SAR441255, a potent unimolecular peptide GLP-1/GIP/GCG receptor triagonist. Cell Metab. 2022;34(1):59–74.e10.
73. Li Y, Glotfelty EJ, Namdar I, et al. Neurotrophic and neuroprotective effects of a monomeric GLP-1/GIP/Gcg receptor triagonist in cellular and rodent models of mild traumatic brain injury. Exp Neurol. 2020;324:113113.
74. Li T, Jiao JJ, Hölscher C, et al. A novel GLP-1/GIP/Gcg triagonist reduces cognitive deficits and pathology in the 3xTg mouse model of Alzheimer's disease. Hippocampus. 2018;28(5):358–372.

75. Zhao S, Yan Z, Du Y, et al. A GLP-1/glucagon (GCG)/CCK(2) receptors tri-agonist provides new therapy for obesity and diabetes. Br J Pharmacol. 2022;179(17):4360–4377.
76. WHO: Accelerating action to stop obesity [internet]. World Health Organisation; 2022. [cited 2022 Dec 30]; Available from: https://www.who.int/news/item/04-03-2022-world-obesity-day-2022-accelerating-action-to-stop-obesity#:~:text=Effective%20steps%20include%20restricting%20the,access%20to%20affordable%2C%20healthy%20food.
77. Safaei M, Sundararajan EA, Driss M, et al. A systematic literature review on obesity: understanding the causes & consequences of obesity and reviewing various machine learning approaches used to predict obesity. Comput Biol Med. 2021;136:104754.
78. Sánchez-Garrido MA, Brandt SJ, Clemmensen C, et al. GLP-1/Glucagon receptor co-agonism for treatment of obesity. Diabetologia. 2017;60(10):1851–1861.
79. Arterburn DE, Telem DA, Kushner RF, et al. Benefits and risks of bariatric surgery in adults: a review. JAMA. 2020;324(9):879–887.
80. Oduro-Donkor D, Turner MC, Farnaud S, et al. Modification of fecal microbiota as a mediator of effective weight loss and metabolic benefits following bariatric surgery. Expert Rev Endocrinol Metab. 2020;15(5):363–373.
81. Zhou Z, Ren Q, Jiao S, et al. Discovery of new and highly effective quadruple FFA1 and PPARα/γ/δ agonists as potential anti-fatty liver agents. Eur J Med Chem. 2022;229:114061.
82. Schmitz O, Brock B, Rungby J. Amylin agonists: a novel approach in the treatment of diabetes. Diabetes. 2004;53(suppl_3):S233–8.
83. Jorsal T, Rungby J, Knop FK, et al. GLP-1 and amylin in the treatment of obesity. Curr Diab Rep. 2015;16(1):1.
84. Bello NT, Kemm MH, Ofeldt EM, et al. Dose combinations of exendin-4 and salmon calcitonin produce additive and synergistic reductions in food intake in nonhuman primates. Am J Physiol Regul Integr Comp Physiol. 2010;299(3):R945–52.
85. Behary P, Tharakan G, Alexiadou K, et al. Combined GLP-1, oxyntomodulin, and peptide YY improves body weight and glycemia in obesity and prediabetes/type 2 diabetes: a randomized, single-blinded, placebo-controlled study. Diabetes Care. 2019;42(8):1446–1453.
86. Zhang X, Young RL, Bound M, et al. Comparative Effects Of Proximal And Distal Small Intestinal Glucose Exposure On Glycemia, Incretin Hormone Secretion, And The Incretin Effect In Health And Type 2 Diabetes. Diabetes Care. 2019;42(4):520–528.
87. Bader M, Li Y, Tweedie D, et al. Neuroprotective effects and treatment potential of incretin mimetics in a murine model of mild traumatic brain injury. Front Cell Dev Biol. 2019;7:356.
88. Yang X, Qiang Q, Li N, et al. Neuroprotective mechanisms of glucagon-like peptide-1-based therapies in ischemic stroke: an update based on preclinical research. Front Neurol. 2022;13:844697.
89. Martin B, Golden E, Carlson OD, et al. Exendin-4 improves glycemic control, ameliorates brain and pancreatic pathologies, and extends survival in a mouse model of Huntington's disease. Diabetes. 2009;58(2):318–328.