HHS Public Access

Author manuscript

Cell Metab. Author manuscript; available in PMC 2024 September 05.

Published in final edited form as:

Cell Metab. 2023 September 05; 35(9): 1519–1529. doi:10.1016/j.cmet.2023.07.010.

GIPR/GLP-1R dual agonist therapies for diabetes and weight loss– Chemistry, Physiology and Clinical application

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Abstract

The incretin system is an essential metabolic axis that regulates postprandial metabolism. The two incretin peptides that enable this effect are the glucose-dependent insulinotropic polypeptide (GIP) and the glucagon-like peptide 1 (GLP-1), which have cognate receptors (GIPR and GLP-1R) on islet β-cells as well as in other tissues. Pharmacologic engagement of the GLP-1R is a proven strategy for treating hyperglycemia in diabetes and for reducing body weight. Tirzepatide is the first monomeric peptide with dual activity at both incretin receptors now available for clinical use, and in clinical trials has shown unprecedented effects to reduce blood glucose and body weight. Here we discuss the foundational science that led to the development of monomeric multi-incretin

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Author Contributions

All authors wrote, edited, and approved of the final version of this manuscript.

Declaration of Interests

JEC and DAD receive funding to carry out basic research from Eli Lilly, Novo Nordisk, and Merck MSD. JEC has served in an advisory role for Boehringer Ingelheim and Structure Therapeutics. DAD has served in an advisory role for Structure Therapeutics and Eli Lilly.

In this review, Campbell et al. discuss the development of multireceptor therapeutics that target incretin receptors to improve glycemic control and induce weight loss. This is a twenty-year perspective of how dual incretin agonists have evolved, culminating in the clinical use of tirzepatide, along with a discussion of potential mechanisms by which GIPR agonism can enhance the clinical efficacy of GLP-1R agonists.

receptor agonists, culminating in the development of tirzepatide. We also look to the future of this field and comment on how the concept of multi-receptor agonists will continue to progress for the treatment of metabolic disease.

Introduction

For decades now, there has been an urgent need for medicines capable of controlling body fat, managing excess weight and eliminating obesity. The lack of effective, scalable interventions to treat the general increase in human body weight that marks the past 50 years has made obesity one of the major public health concerns worldwide. The discovery of leptin[1] revealed the existence of molecular systems controlling mammalian food intake, energy homeostasis and body weight. Yet, despite enormous growth in scientific understanding following this discovery, to date the only therapeutic approach offering weight loss of 20% or more is bariatric surgery. However, in the last twenty years drug development targeting the glucagon-like peptide 1 receptor (GLP-1R) has opened a new window of opportunity for reliable, significant medical weight loss at tolerable doses[2] (Figure 1). More recently, the discovery of monomolecular peptides that simultaneously function at the GLP-1R and other family B G-protein coupled receptors (GPCR) as dual and triple receptor co-agonists has demonstrated clinical weight loss at levels not previously approached by medical therapy. As one example, tirzepatide, is a GIPR/GLP-1R co-agonist, and the first drug in this emerging class to achieve registration for treatment of adult-onset diabetes. It also demonstrated more than 20% placebo-corrected, weight loss in participants with obesity, without diabetes[3]. These results may herald the beginning of pharmaceutical management of excess weight with potential to reduce morbidity and mortality, analogous to treatment of hyperglycemia, dyslipidemia and hypertension.

Endocrine pathways exert broad control over metabolic homeostasis, exemplified by the pleiotropic actions of insulin. The discovery of insulin in 1921[4] has been fundamental in demonstrating the therapeutic benefit of hormones, but also in unlocking insights into normal physiology and pathophysiology across multiple metabolic networks. Similarly, glucagon was ‘accidentally’ discovered as a contaminant during optimization of insulin purification[5], and then largely ignored for decades until the realization of its potential use to reverse insulin-induced hypoglycemia. This renewed interest in the physiology of glucagon and its receptor led to work that was the foundation of three Nobel prizes[6–8]. The actions of insulin and glucagon have been conceptualized as a dual hormonal balance that is central to the control of glucose metabolism, and provides a model for coordinate signaling in tissues like the liver. Even prior to the discovery of insulin, it had been proposed that hormonal factors produced in the intestine might have glucoregulatory actions[9]. Following the discovery of insulin, the Belgian physiologist La Barre demonstrated that duodenal extracts stimulate insulin secretion and termed these gut-derived hormones incretins[10,11]. Glucose-dependent insulinotropic polypeptide (GIP) was identified and validated as an incretin in the 1970s in research led by the Canadian physiologists Brown and Dupre[12,13]. Subsequent pursuit of additional incretins eventually led to the discovery of glucagon-like peptide 1 (GLP-1) in 1987[14–16]. The relative contribution of GIP versus GLP-1 to mediate postprandial insulin secretion has been extensively studied and appears to differ along the

continuum from metabolic health to type 2 diabetes (T2D). However, both preclinical[17–20] and clinical [21,22] studies largely agree that GIP and GLP-1 are the two primary physiological incretins that mediate nutrient signaling from the intestine to the pancreatic islets, to properly regulate insulin secretion in control of postprandial glucose metabolism.

The incretin effect accounts for as much as 70% of postprandial insulin secretion and defects in the incretin axis significantly contributes to the impaired insulin secretion in T2D[23]. Consequently, medicinal agents have been designed to activate and enhance incretin receptor activity to reduce hyperglycemia and forestall T2D[24,25]. Three formative observations in incretin research have shaped this area of drug development, and elevated GLP-1 over GIP as the principal agent. First, infusions of GLP-1 were demonstrated to normalize blood glucose in participants with type 2 diabetes[26,27]. Second, several studies suggested that patients with T2D were insensitive to the insulinotropic actions of GIP, while GLP-1 was a potent insulin secretagogue in these participants[28]. Third, transgenic mice with deletion of the GIP receptor (GIPR) were protected from weight gain on a high fat diet, leading to the inference that GIP signaling promotes obesity[29]. Thus, the last 20 years have seen enormous thought and energy invested in the development of peptidic GLP-1R agonists (GLP-1RA). This work has included pharmacokinetic optimization, with steps to prevent peptide inactivation and to extend the pharmacodynamics to minimize the number of injections required for therapeutic effect. Once daily drugs caused larger reductions in hemoglobin A1c than twice daily agents, and weekly administration had an even bigger impact. One crucial observation made in the early clinical trials with GLP-1RA was that treated patients consistently lost weight relative to controls receiving placebo. This finding coincided with physiologic studies demonstrating that GLP-1R activation reduced food intake[30–32]. With the creation of more potent GLP-1RA, the weight-reducing effects were enhanced to a point where they were considered for treatment of people with obesity without diabetes[2]. A defining moment in the progression of GLP-1RA from primarily glucose lowering agents, to drugs used specifically for weight loss were the results from trials with the GLP-1RA semaglutide, that caused weight reduction of ~15% in participants with obesity without diabetes[33]. It is worth noting that moderate reductions in blood pressure are observed after treatment with GLP-1RAs[34]. Moreover, the results of cardiovascular outcome trials in persons with T2D given GLP-1RA demonstrating reduced stroke, myocardial infarction, and cardiovascular death[35] along with the emerging evidence demonstrating positive effects of GLP-1RAs[36,37] on kidney outcomes adds further impetus that these drugs have pleiotropic benefits. However, while the clinical results with semaglutide support indications for treatment of obesity per sé (Wegovy^{R}) as well as T2D (Ozempic^{R}), weight reduction with these agents remains considerably less than the best surgical results, and is often only a fraction of what most patients require for correction of the co-morbidities of increased body weight. Thus, even with progress in pharmacological weight loss, there remains a significant unmet need for obesity treatment.

Discovery of multi-receptor agonists for the GIPR and GLP-1R

The multifactorial nature of physiological control of metabolism and body weight, coupled with the demonstration that gastric bypass procedures increase secretion of GLP-1 and several other gut-derived hormones, suggested that engineering medicines

combining GLP-1R activity with other hormonal stimuli might offer superior clinical outcomes. The first breakthrough confirming this hypothesis pertained to the seemingly antithetical combination of glucagon receptor (GCGR) activity with GLP-1R agonism, as a monomolecular, similarly sized co-agonist[38]. This dual agonist produced enhanced metabolic and body weight benefits compared to a GLP-1R monoagonist in preclinical models. Moreover, several versions of glucagon/GLP1 co-agonists are now progressing through clinical trials in participants with diabetes and obesity (Table 1), testing the translational potential of this first multi-receptor agonist (MRA) approach.

A subsequent iteration on MRAs was the possibility that GIPR activation could bring different but equally valuable metabolic synergy in combination with GLP-1R agonism. Once again, the design strategy was contrary to the mainstream view in that GIPR agonism was thought to add little to glycemic lowering in people with diabetes, and could prove deleterious for weight gain. In fact, GIPR antagonism as a mechanism to improve metabolic outcomes has been proffered by some experts[39]. A series of studies between 2006 and 2013 led to the creation of active GIPR/GLP-1R co-agonists[40]. The goal here was to use combinatorial chemistry to create single molecules with multi-receptor potency comparable to the native incretins that might produce large effect sizes in preclinical studies such that effects were likely to be translatable to humans. It was established early on that GLP-1 and GIP are sufficiently homologous to enable a single peptide sequence with high potency agonism at both receptors. A series of rationally designed modifications included the interchange of specific GIP-derived amino acids, the addition of the C-terminally extended residues from the reptilian GLP-1R agonist, exendin-4, and select non-canonical amino acids at position 2 and 20. The result was a single peptide with subnanomolar, balanced activity at both incretin receptors and minimal activity at the glucagon receptor[40]. Additions of either fatty acyl or polyethylene glycol (PEG) side-chains did not interfere with the relative potencies at each receptor, and provided sustained duration of action in vivo by delaying renal clearance. In obese mice, the GIPR/GLP-1R co-agonist produced greater decreases in body weight and food intake, as well as improved glycemic and lipid outcomes, when compared to equal doses of either exendin-4 or liraglutide. The fatty acylated co-agonist also produced a greater rate of insulin secretion compared to liraglutide during a hyperglycemic clamp in cynomolgus monkeys[40].

The original GIPR/GLP-1R agonist was modified with a C-18 acyl group to extend pharmacokinetics, and began Phase 1 clinical trials at Marcadia Biotech with Roche support (RG7697)[41,42], leading to subsequent Phase 2 studies that were funded by Novo Nordisk (NNC0090–2746)[43]. The original drug candidate had pharmacokinetics that were suitable for daily dosing, and also dose limiting GLP-1R mediated GI adverse effects in healthy[41] participants and those with T2D[42]. Phase 2 trials utilized a fixed 1.8 mg, once-daily dosing in participants with T2D for 12-weeks and included a titrated liraglutide (1.8mg) open-label reference arm[43]. The co-agonist reduced HbA1c by 1.36% and reduced body weight by 3.3%, while in participants receiving the active comparator liraglutide the respective differences were 0.96% and 1.7%. While the effects of the dual incretin receptor agonist were promising, the changes in glycemic control and body weight were not statistically different from liraglutide at the single dose tested. A longer study with an optimized dose in a dose-titrated manner in similar fashion to the unblinded control was planned as a

more definitive test of clinical benefits. However, studies conducted concurrently showed unexpected superiority of once-weekly forms of GLP-1 drug candidates to daily forms, and raised questions as to whether the addition of GIP was necessary for a useful incretin agonist. Thus, the dual agonist was shelved, and the two-incretin concept pursued by adding a weekly dose of a novel, high potency GIPR agonist (NNC080–0389) to semaglutide (2.4 mg) in participants with T2D (ClinicalTrials.gov: NCT05144984), while also exploring the action of different molecular forms of longer-action, multimodal GIP-based agonists in preclinical studies.

Tirzepatide was the second dual incretin receptor agonist advanced to clinical study. While NNC0090–2746 was generated by chemical modification of a glucagon/GLP-1 co-agonist, tirzepatide was developed by selective alterations in the native GIP sequence to provide agonism at the GLP-1R [44]. It possesses high affinity for both the GIPR (Ki = 0.135 nM) and the GLP-1R (Ki = 4.23 nM) in human cell lines. These binding affinities compare similarly to native GIP for its receptor but are approximately 5-fold lower when compared to native GLP-1 for its receptor [44]. It is important to note that these values are based on the human GIPR (hGIPR), while tirzepatide is much less potent (30–100-fold reduced) at the mouse GIPR (mGIPR)[45]. The human GIP sequence, which differs from the mouse sequence, is a less potent and a partial agonist at the mGIPR[46]. This may be the basis of the relatively low affinity of tirzepatide at the mGIPR since it is derived from the human GIP sequence. Still, high-doses of tirzepatide stimulates insulin secretion and lowers glycemia in mice with selective deletion of either the *Gipr* or *Glp1r*, supporting in vivo activity at both receptors[44,45]. Receptor pharmacology studies suggest that tirzepatide engages the hGIPR in a manner similar to GIP but displays biased signaling at the GLP-1R to favor cAMP generation over beta-arrestin recruitment (Figure 2)[47–49]. Thus, in comparison to NNC0090–2746, which has balanced activity at both incretin receptors, tirzepatide potency is distorted towards hGIPR. Whether this imbalance is optimal and enhances the efficacy of tirzepatide remains to be determined. Support for this idea may come from an ongoing clinical trial where increased relative amounts of GIPR agonism (NNC0090–0389; 1:1 to 1:9) are provided with semaglutide. On the other hand, the pharmacology of NNC0090–0389 and semaglutide at their respective receptors differ from tirzpetide at the incretin receptors, providing an alternative reason if the results of various ratios are inconclusive. Remarkably, the structural differences between tirzepatide and NNC0090–2746 are modest (Figure 3). Both peptides start with a 28 amino acid sequence that is extended by the addition of an 11 or 12 amino acid C-terminal tail based on exendin-4. Twenty of the 28 amino acids are common to both peptides, with the greatest difference residing in the middle sequence where tirzepatide possesses homology with hGIP, while NNC0090–2764 is similar to GLP-1. Interestingly, the mid-section of tirzepatide also possesses a lysine residue to facilitate the 20-carbon fatty diacid, while NNC0090–2764 has a fatty-acyl group with a monoacid at the C-terminus. The location and composition of the fatty acid modification appears to be a crucial determinant in how tirzepatide engages both the GIPR and GLP-1R[50]. In addition to providing a pharmacokinetic profile that enables once-weekly dosing, the acylation moiety of tirzepatide also contributes to the interaction with both the GIPR and GLP-1R, as well as possibly the cell membrane[50]. The acylation does not appear to influence the potency of action at the GIPR, enabling tirzepatide to act as a full agonist at the human GIPR. However,

this addition drives biased agonism at the GLP-1R, reducing beta-arrestin recruitment and subsequently leading to less internalization[47,50]. These studies reveal that the pharmacology profile of tirzepatide is not only determined by the peptide sequence, but also the location and composition of the acyl side chain.

A phase 2 clinical study with tirzepatide included four different once-weekly doses (1, 5, 10 and 15 mg) and used the GLP-1R monoagonist dulaglutide (1.5 mg), as an active comparator in people with T2D followed for 26 weeks[43]. The results of this first extended study were impressive, with the 15 mg dose of tirzepatide producing a 2.4% reduction in HbA1c (compared to 1.1% for dulaglutide) and 11.3 kg weight loss (compared to 4.8 kg for dulaglutide). Phase 3 clinical trials compared tirzepatide at 5, 10 and 15 mg doses to semaglutide (1 mg) in a 40-week trial of patients with T2D[51]. All doses of tirzepatide produced greater reductions in HbA1c, fasting glycemia, lipid levels, and weight loss compared to semaglutide. Remarkably, the 15 mg dose of tirzepatide decreased HbA1c by 2.46% and body weight by 12.4 kg at the end of the study. Tirzepatide was approved by the Food and Drug Administration in May 2022 for the treatment of T2D, and later in October received Fast Track designation for treatment of obesity. The remarkable impact on weight loss initiated the investigation of tirzepatide for the treatment of obesity independent of diabetes. Phase 3 clinical trials tested 5, 10 and 15 mg doses of tirzepatide for 72 weeks (Table 2)[3]. Placebo subtracted weight loss at the end of the study was 13.6% (5 mg), 19% (10mg), and 20.1% (15mg), and over 50% of the participants treated with 10 or 15 mg doses achieved greater than 20% weight loss. Pooled analysis of the tirzepatide-treated groups demonstrated clinically meaningful improvements in blood pressure, lipid profiles, and fasting insulin values. Whether the improvement in these outcomes is secondary to weight loss, or attributable to direct actions of GIPR/GLP1R agonism in key tissues (Figure 4) is currently the focus of ongoing mechanistic studies. This clinical trial did not include patients with T2D, and the emerging data suggests that the weight-loss effects of tirzepatide are reduced in patients with diabetes, a difference also observed in trials with 2.4 mg of semaglutide[2]. These results from longer trials with tirzepatide have elevated the performance standard for drug therapy directed at T2D and obesity. Most importantly, clinical assessment of cardiovascular safety of tirzepatide in patients with T2D at low, medium, and high cardiovascular risk are ongoing (Table 2), and it is not yet clear whether effects will be comparable to selective GLP-1R agonists[52,53].

NNC0090–2764 and tirzepatide are potent agonists at both the GIPR and GLP-1R, and yet have reported different degrees of efficacy in glycemic control and weight loss. There are several potential explanations for this which may be useful in guiding development of next generation drug candidates with biological action at similar and different receptors. The longest duration study of NNC0090–2764 was only 12-weeks, while the most impressive results with tirzepatide were obtained at 26-weeks and longer. Twelve-week studies were initially designed to obtain a quality assessment of the impact on HbA1C but have proven to be of insufficient duration to confidently assess weight loss relative to placebo, and especially differential efficacy to other weight lowering drugs. Improvements in HbA1c and weight loss for the different doses of tirzepatide did not separate until past the 12-week period[3,51], which is partially a function of the scheduled dose titration vital to achieving optimal clinical outcomes. Such a titration was not employed with NNC0090–

2746 in the 12-week study, as commonly employed with once-daily liraglutide (the unblinded comparator). Another difference of considerable importance is the once-weekly form of action, where semaglutide at 10% the weekly dose of once daily liraglutide demonstrates twice the weight lowering efficacy. The difference in pharmacokinetics could account for unique receptor engagement that impacts the biological outcomes or more likely increased access to privileged sites that control appetite. In this latter regard, it is important to note that in obese rodents, daily administration of NNC0090–2746 and tirzepatide have effects that are much more similar than the clinical results would predict. In rodents, both peptides have abbreviated pharmacokinetics compared to humans as albumin clearance is nearly ten-times faster. In addition, the differences between the two co-agonists may be attributable to unique receptor pharmacology with tirzepatide engaging the GLP-1R in a manner different from GLP-1, including reduced beta-arrestin recruitment and internalization[47,48,50]. Furthermore, the relative balance of GIPR versus GLP-1R agonism is different between NNC0090–2764 and tirzepatide, with the latter favoring GIPR agonism. In mice, NNC0090–2764 demonstrates superior body weight reduction relative to pharmacokinetically-matched GLP-1R monoagonism and this difference was lost with ablation of CNS-GIPR expression[54]. These collective results support GIPR agonism as a key component for the enhanced efficacy of dual-agonists. However, how much relative GIPR to GLP-1R agonism is optimal, and whether biased agonism is rending a unique virtue to the clinical efficacy of tirzepatide are challenging, but tractable, questions requiring additional study.

Contribution of GIPR agonism

The GIPR is expressed in numerous locations throughout the body that potentially impact the metabolic processes that govern glycemic control and body weight (Figure 4)[55]. There is evidence for expression of the GIPR by alpha-, beta-, and delta-cells in pancreatic islets[56–58], white and brown adipose tissue[59,60], and various regions of the CNS[54,61,62]. Understanding how pharmacological GIPR activation in these cell types regulates physiological and clinical outcomes independently and in concert with GLP-1R activation is necessary to delineate the mechanism of actions for MRA that incorporate GIPR activity.

Islets: The GIPR is expressed to a similar degree in all three major endocrine cell types of the pancreatic islets. In beta-cells, GIP stimulates insulin secretion in a glucose-dependent manner[56], and in alpha-cells, GIP stimulates glucagon in an amino-acid and glucose-dependent manner[57]. Activity of GIP in both alpha- and beta-cells is needed for insulin secretion and glycemic control following a meal[57]. GIP stimulates somatostatin secretion, however, the factors that govern this, and the implications for metabolism have not been worked out. GIP and GLP-1 are known to have additive effects on insulin secretion when infused at physiological levels into healthy humans[63], but it is unclear if GIP can provide additive effects to pharmacological levels of GLP-1R agonism. Moreover, the additive effects between GIP and GLP-1 are lost when given to participants with T2D[64], potentially due to the observation that the insulin response to physiological levels of infused GIP are decreased in participants with T2D[28]. Interestingly, maintaining a period of euglycemia restores some of the insulinotropic activity of GIP in patients with T2D[65]. Thus,

combining GIPR and GLP-1R agonism may enhance insulin secretion in patients with T2D by first rescuing dysfunctional beta-cells with GLP-1R agonism followed by additive effects on insulin secretion provided by both receptors. Moreover, GIP has been shown to stimulate insulin secretion through both direct actions on beta-cells and indirect actions mediated by alpha- to beta-cell communication[57] and GIP is considered the predominant physiological incretin with respect to insulin secretion[21]. However, direct evidence that the GIPR activity of tirzepatide contributes to the improved glycemic control in patients with T2D has not been established, although antagonizing the GIPR reduced tirzepatide-stimulated insulin secretion in isolated human islets to a greater degree than antagonizing the GLP-1R[45]. With respect to the alpha-cell, GLP-1R agonists reduce glucagon secretion, GIPR agonists enhance glucagon secretion and the combined actions of GIP and GLP-1 infusion on glucagon secretion is offset to produce a neutral outcome[64]. To this end, tirzepatide robustly stimulated glucagon secretion in isolated human islets, further emphasizing a meaningful contribution of tirzepatide activity at the GIPR (Figure 2)[45].

Central nervous system (CNS): Chronic peripheral[54,66] and central[54] GIPR agonism decreases body weight by reduction in food intake, suggesting a CNS-mediated mechanism. In line with this notion, GIPR is expressed in the hypothalamus and hindbrain[54,61,62,67,68], and a single 3rd ventricle bolus injection of GIP is sufficient to decrease body weight and food intake in diet-induced obese mice[54]. When injected into the brain or the periphery, GIP activates neurons in the hypothalamus[54], and targeted (DREADD-mediated) activation of hypothalamic GIPR neurons decreases food intake in mice[61]. Confirming the metabolic relevance of central GIPR signaling, neuronal loss of GIPR renders mice resistant to GIP-induced body weight loss and GIPR/GLP-1R co-agonism is more potent than selective GLP-1R agonism for weight loss[54]. Interestingly, intracerebroventricular administration of an antibody directed against the GIPR decreases body weight, along with an increase in hypothalamic leptin signaling[62]. Future studies will have to address how that finding can be reconciled with the abundance of clinical studies showing superior metabolic benefits of molecules activating the human GIP receptor, including dissection of weight loss components into fluid as well as bone-, fat-, and muscle mass. Other groups have demonstrated that chronic systemic GIPR antagonism produces a moderate[69,70] to null[66] effect on body weight in obese mice, suggesting this is not an efficacious mechanism to pursue alone. However, GIPR antagonism seems to synergize with GLP-1R agonism to produce robust effects on body weight[66,69], although the mechanism of action has not been described, raising the question as to how both pharmacological agonism and antagonism of the GIPR can produce similar decreases in weight loss. Interestingly, neither peripheral antagonism of the GIPR or knockout of the GIPR gene produce strong reductions in food intake, suggesting that the reduction in body weight stems from a separate, and yet to be fully resolved mechanism. On the other hand, GIPR agonism does reduce food intake in a manner that requires GIPR expression in the CNS[54]. Proposed mechanisms for this include activation of hypothalamic neurons that suppress food intake[61] and activation of hindbrain neurons that engage an anti-emetic effect[67,71]. The latter could have important implications for the mechanism of tirzepatide, as GIPR neurons in the hindbrain could temper the nausea induced by activation of neighboring GLP-1R neurons[67], enabling greater systemic GLP-1R activity with manageable gastrointestinal effects. However, there is a clear need for

a better understanding of the effects of GIPR in the CNS, including the translation of these preclinical results.

Insulin sensitivity: In addition to increasing insulin secretion, there is emerging evidence that GIPR agonism could also increase peripheral insulin sensitivity. Chronic treatment with tirzepatide enhanced insulin sensitivity in obese mice through a mechanism that was independent of weight loss and the GLP-1R[72]. Moreover, these insulin-sensitizing effects of tirzepatide could be replicated with chronic GIPR agonism alone. Interestingly, the enhanced insulin-mediated glucose disposal was attributed to a greater degree of glucose uptake into adipose tissue but not skeletal muscle; nor were there changes in hepatic glucose production. Adipose tissue expresses the GIPR, whereas muscle and liver do not, arguing for a direct action of GIPR agonism in adipose tissue to improved insulin sensitivity. GIPR agonism in adipose tissue has been argued to enhance the lipid-buffering capacity of white adipose tissue, promoting advantageous storage of excess fat and limiting ectopic storage in less efficient storage sites like muscle or liver[73]. Healthy storage of adipose tissue delays the progressive insulin resistance associated with obesity[74], providing a plausible hypothesis that if GIPR agonism in adipose tissue can promote lipid storage in the correct location, this could result in positive effects on insulin sensitivity. This hypothesis is supported by previous reports that argue for beneficial effects of GIP activity in adipose tissue[75,76], while others also argue that GIPR has negative effects in adipose tissue[77,78]. Further complicating these interpretations are recent reports that the GIPR is expressed predominantly in the non-adipocyte fractions of both mouse and human adipose tissue[60], illustrating the need to clarify how GIPR agonists regulate adipose tissue function and how this might impact insulin sensitivity.

GIPR agonism versus antagonism

The utility of GIPR antagonism paired with GLP-1R agonism is also being explored[79], with preclinical compounds utilizing this strategy producing similar effects on weight loss to what has been reported for GIPR/GLP-1R agonism[69]. Rationale for this approach is founded on the phenotype of loss-of-function models for the GIPR that produce a protective effect against diet-induced obesity including germline deletion of *Gipr*[29] and deletion of *Gip*[80]. Moreover, loss of function mutations in the human *GIPR* are associated with reductions in BMI[81]. Interestingly, germline deletion of *Glp1r* also produced protection against diet-induced obesity[17,82] which can be mimicked with pharmacological antagonism of the GLP-1R[70], providing a similar paradox of gain- and loss-of-function studies for the GLP-1 system on body weight. The mechanism by which antagonism of the incretin system can reduce body weight remains unclear, but seems like an area where understanding would be valuable. In addition, it is essential to understand the full implications of chronic GIPR antagonism on parameters beyond body weight, in areas where GIPR has been shown to have positive effects including islet function, glucose tolerance, bone health, and immune function. As the clinical investigation of GIPR antagonism continues, it will be essential to monitor these outcomes.

What's next for multi-receptor agonists

The recent success and clinical implementation of tirzepatide has accelerated interest in the pursuit of MRA. Every current candidate continues to utilize GLP-1R agonism as a cornerstone component (Table 1). There is considerable interest in pairing GLP-1R agonism with glucagon receptor agonism to enhance both energy expenditure to maximize weight loss and potentially leverage the lipid oxidative properties of glucagon in hepatocytes to target nonalcoholic fatty liver disease. Early clinical phase 1 data has provided mixed results on body weight, with some compounds failing to outperform GLP-1R agonists[83], while others have shown greater efficacy[84]. Some GLP-1R/GCGR agonists have produced greater than 10% decreases in weight loss in a 12-week period, which matches the rate of tirzepatide and illustrates the potential of this strategy. Separate from body weight, the outcomes on markers of hepatic steatosis, fibrosis and inflammation will test the utilization of these compounds for nonalcoholic steatohepatitis (NASH); tirzepatide is also being tested for use in NASH (Table 2). In contrast single molecule MRA, the combination of semaglutide and a long-acting GIPR agonists is an alternative application of dual incretin agonist signaling under investigation. There is also motivation for combining activity at both incretin receptors with glucagon receptor activity through the development of triagonists. Recent phase 1 trial results of the GIP/GLP-1/glucagon triple co-agonist LY3437943 showed promising reductions in body weight and blood glucose as well as a safety profile consistent with those of other incretin-based therapeutic agents in early phases of development[85,86]. Phase 2 trials showed 24.2% weight loss with the highest dose (12 mg) of LY3437943 in 48 weeks, with 26% of the participants in this group losing greater than 30% BW[87]. There is also tremendous activity in the development of small molecule agonists targeting the incretin system, to produce drugs that are orally available and more economical to produce. The most advanced compounds are small molecule GLP-1R agonists which have progressed through to clinical trials[88,89]. There is considerable interest in the development of small molecule GIPR and GCGR agonists, most likely to be paired with GLP-1R agonists. Whether this area could expand to have single small molecules that target multiple receptors remains to be seen. Finally, the combination of GLP-1R agonism with a long-acting amylin analogue has demonstrated promising effects on body weight. The highest dose (2.4 mg of each agonist) decreased body weight in participants with overweight by 17% in 20 weeks[90]. Whether these results demonstrate the ceiling for pharmacologically targeting body weight has yet to be met.

Conclusion

Historically, pharmacological targeting of obesity has been largely unproductive, with interventions that produced safe weight loss reducing body weight by 5% or less. Almost three decades ago, the discovery of leptin triggered a new era of molecular obesity research. Since then, a multitude of signals have been uncovered that are involved in the regulation of human body weight, energy homeostasis and fat mass. However, until recently targeting any single pathway has not conferred benefits comparable to those of bariatric surgery. The discovery of human gut hormone dual and triple agonists has opened new possibilities for medical weight loss. Combining GIP and GLP-1R agonism was first discovered and reported a decade ago[40] and has now fully evolved as the GIP/GLP-1R

co-agonist tirzepatide that can achieve more than 20% weight loss in obesity as well as offering superior benefits in diabetes. Understanding the mechanisms that drive the efficacy of this combination will no doubt be aggressively pursued in the coming years, along with the continued emergence of additional combinatorial approaches, further expanding pharmacological options for a more personalized metabolic medicine of the future.

Acknowledgements

This work was co-funded by the NIH (DK123075, DK125353, DK046492) and the European Research Council ERC-CoG Trusted no.101044445. TDM further received funding from German Research Foundation (DFG TRR296, TRR152, SFB1123 and GRK 2816/1) and the German Center for Diabetes Research (DZD e.V.). MHT received funding from the European Research Council ERC AdG *HypoFlam* no. 695054.

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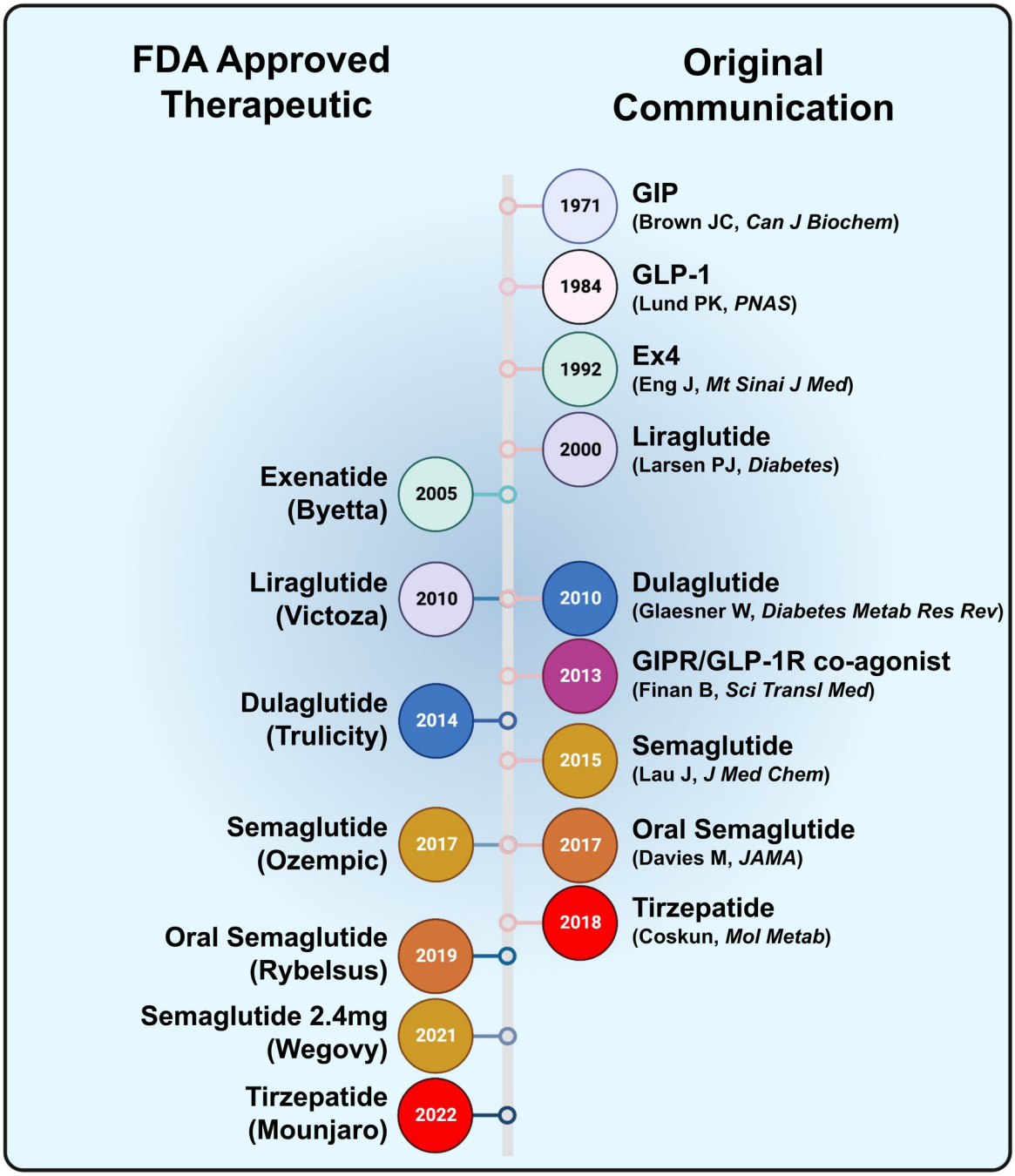

Figure 1. Timeline of the discovery of seminal incretin-based therapies.

The left side indicates the year each therapy was approved by the United States Food and Drug Administration (FDA). The right side indicates the year the first communication was published.

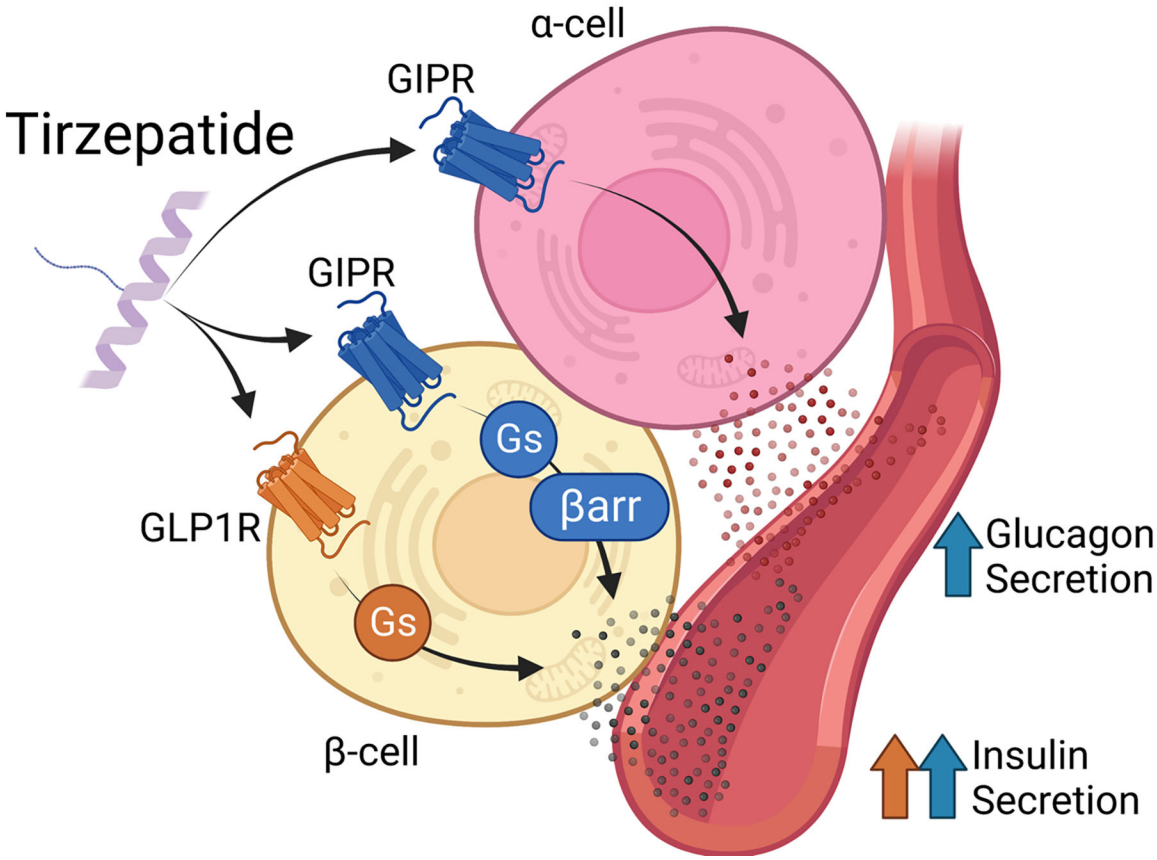

Figure 2. Tirzepatide action in islet endocrine cells.

Tirzepatide stimulates insulin secretion through both the GLP-1R and GIPR in beta-cells. It engages the GIPR receptor similar to native GIP, acting as a full agonist to signal through both Gs/cAMP and β-arrestin (βarr) pathways. On the other hand, tirzpetide engages the GLP-1R in a biased manner, favoring Gs/cAMP signaling over β-arrestin. Tirzpeatide also stimulates glucagon secretion from alpha-cells through the GIPR through undefined mechanisms.

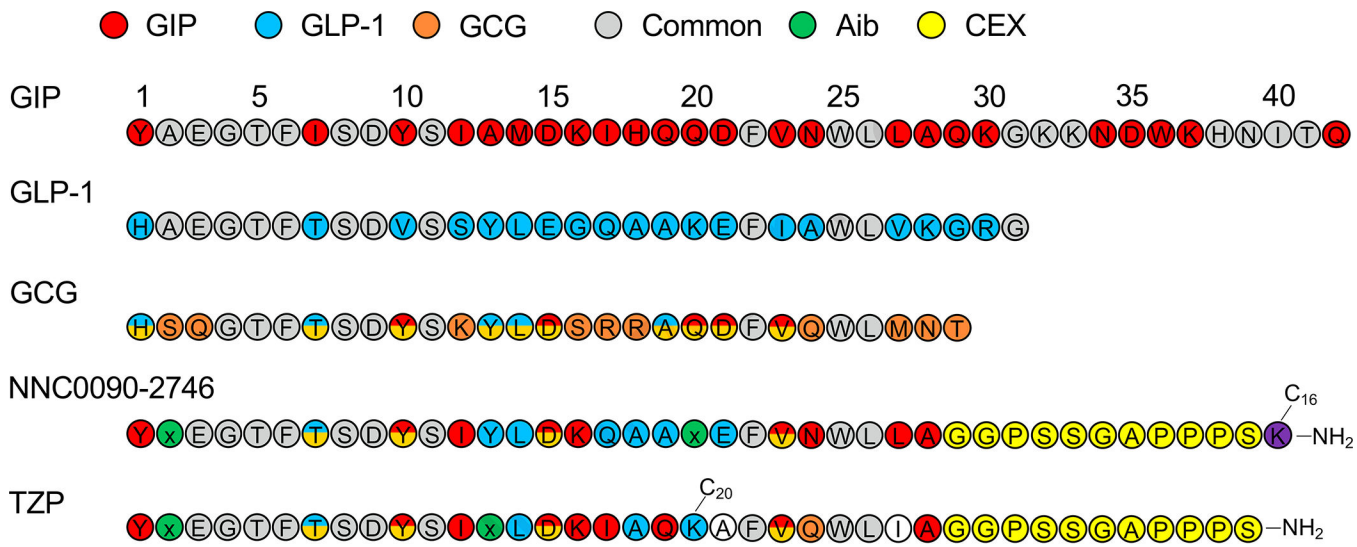

Figure 3. Amino acid sequence of human GIP, GLP-1, glucagon (GCG), NNC0090–2746, and tirzepatide (TZP).

Amino acids are colored according to their specificity for GIP (red), GLP-1 (blue), or glucagon (orange). Amino acids common to all three peptides are shown in gray, while amino acids shared between two peptides are shown with split colors. Aib (green) is a non-proteinogenic amino, while the c-terminal extension of exendin-4 (CEX) is shown in yellow.

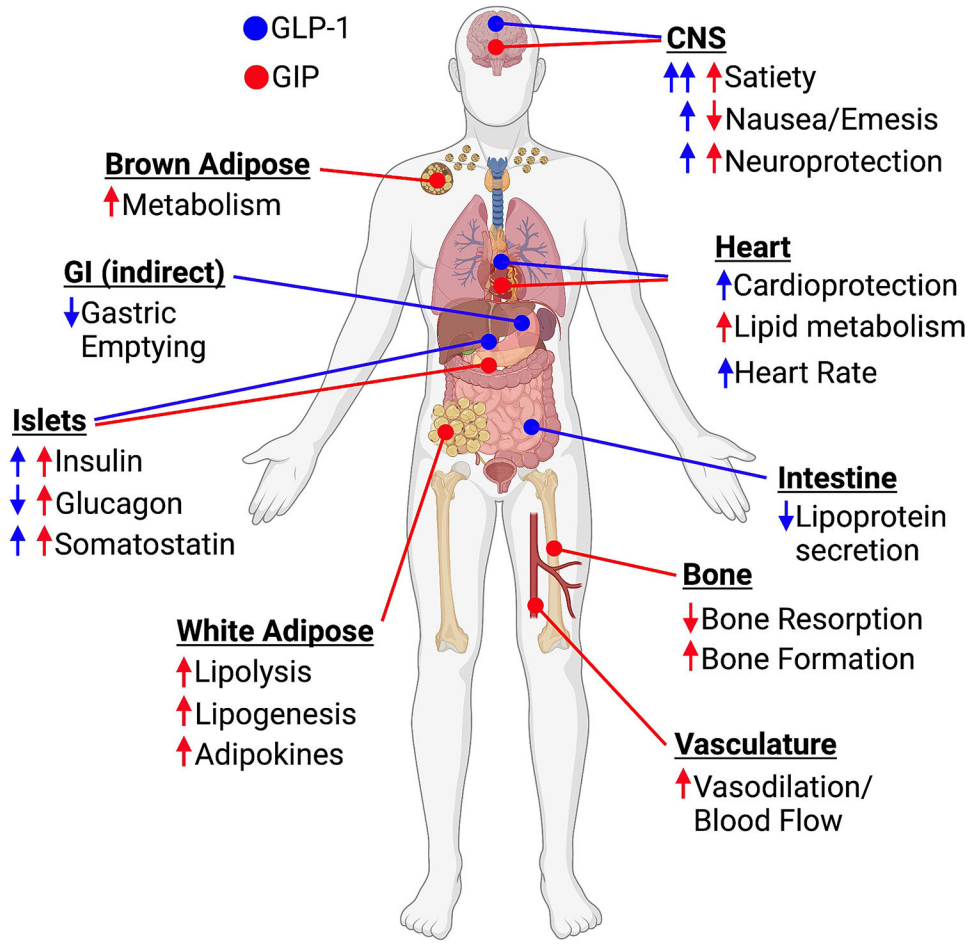

Figure 4. Key metabolic sites of action for GLP-1 (blue) and GIP (red).

Table 1 –

Ongoing clinical trials for multi-receptor agonists

Compound	Stage	Published Results
GLP1R/GCGR		
LY3305677	Phase 1b	84
Cotadutide	Phase 2b	83
BI-456906	Phase 1	
Efinopegduite	Phase 2	91
ATL-801	Phase 1	
GLP1R/GIPR		
Semaglutide + GIPR agonist	Phase 1	
GLP1R/GIPR/GCGR		
SAR441255	Phase 1	
LY3437943	Phase 2	92
HM15211	Phase 2	
GLPIR/Amylin		
Semaglutide + Cagrilintide	Phase 1b	90

Table 2 –

Summary of clinical trials for tirzepatide

	Participants	Intervention	Primary Outcome	Results
SURPASS				
1	T2D	Tirzepatide 5, 10 and 15 mg	Change in A1C	[93]
2	T2D	Tirzepatide vs 1.0 mg semaglutide	Change in A1C	[51]
3	T2D	Tirzepatide vs insulin degludec	Change in A1C	[94]
4	T2D	Tirzepatide vs insulin glargine	Change in A1C	[52]
5	T2D	Tirzepatide with insulin glargine	Change in A1C	[95]
6	T2D	Tirzepatide vs insulin lispro	Change in A1C	Anticipated end of 2023
CVOT	T2D with CV risk	Tirzepatide vs dulaglutide	MACE-3 (Myocardial infarction, Stroke, CV death)	Anticipated 2024[53]
EARLY	T2D < 4 years	Tirzepatide vs. antihyperglycemic care	Change in A1C	Anticipated 2025
SWITCH	T2D	Dulaglutide treatment continued or switched to tirzepatide	Change in A1C	Anticipated 2024
SWITCH-2	T2D	GLP-1R agonist treatment continued or switched to tirzepatide	Change in A1C	Anticipated end of 2023
SURMOUNT				
1	Overweight/Obese	Tirzepatide 5, 10, and 15 mg	Change in body weight	3
2	Overweight/Obese T2D	Tirzepatide 5, 10, and 15 mg	Change in body weight	Anticipated 2023
3	Overweight/Obese	Tirzepatide in combination with lifestyle intervention	Change in body weight	Anticipated 2023
4	Overweight/Obese	Tirzepatide continuation versus switch to placebo	Change in body weight	Anticipated 2023
5	Overweight/Obese	Tirzepatide vs 2.4 mg semaglutide	Change in body weight	Anticipated 2025
MMO	Overweight/Obese	Tirzepatide vs placebo	Time to first occurrence of allcause death, nonfatal MI, nonfatal stroke, or heart failure	Anticipated 2027
SUMMIT	Heart failure with preserved ejection fraction	Tirzepatide 5, 10 and 15 mg	All-cause mortality, hearth failure events, 6-minute walk test	Anticipated 2024
SYNERGY-NASH	Overweight/Obese with NASH	Tirzepatide 5, 10 and 15 mg	NASH scoring	Anticipated 2024