

Incretin-Based Interventions for Diabetes and Obesity: An Evaluation of GIP/GLP-1 Dual Agonism Versus Selective GLP-1 Receptor Agonism

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Diabetes mellitus and obesity remain preeminent global health crises, with diabetes prevalence exceeding 589 million and obesity projected to affect half of the global adult population by 2030. The advent of incretin-based pharmacotherapy has revolutionized the management of these metabolic conditions. This review synthesizes two converging domains: the superior clinical profile of dual glucose-dependent insulinotropic polypeptide (GIP)/glucagon-like peptide-1 (GLP-1) receptor agonism compared to selective GLP-1 agonism, and the cellular determinants of GIP-mediated metabolic improvements. Drawing on pivotal data from the SURMOUNT-5 head-to-head trial, the SURPASS clinical program, and the Ravussin metabolic sub-study, we observe that dual agonism provides a significant clinical advantage; tirzepatide achieved 20.2% mean weight loss compared with 13.7% for semaglutide at 72 weeks. Mechanistically, GIP receptor activation facilitates weight loss through enhanced fat oxidation, optimized adipose tissue lipid buffering, and adiponectin-mediated insulin sensitization, alongside complementary central nervous system (CNS)-mediated appetite suppression. Despite challenges, including the “GIP paradox” (agonism vs. antagonism), reliance on rodent models, and a lack of long-term longitudinal data, the evidence establishes dual incretin agonism as a therapeutic leap. Future perspectives highlight triple receptor agonists and pharmacogenomic stratification as the next frontiers in precision metabolic medicine.

Keywords: tirzepatide; semaglutide; type 2 diabetes mellitus; adipose tissue; GIP paradox; dual GIP/GLP-1 receptor agonists; clinical trials

Introduction

Diabetes mellitus and obesity are among the most pressing global health challenges of our time. As of 2024, the International Diabetes Federation estimates that roughly 589 million adults worldwide live with diabetes, a number expected to climb to 853 million by 2050 [1]. Running alongside this trend is a dramatic rise in obesity, which now affects over one billion people and is on track to impact half the adult population by 2030 [2]. When type 2 diabetes (T2D) and obesity occur together, also referred to as “diabesity”, the consequences are especially serious, with substantially elevated risks of cardiovascular disease, chronic kidney disease, and early death [3]. Even after decades of lifestyle-based interventions, bariatric surgery, and conventional drug therapies, the demand for more effective, better-tolerated treatments has only grown.

At the center of recent progress is the incretin system. Incretins are peptide hormones released by the gut in response to food intake, and their main job is to boost glucose-dependent insulin secretion from pancreatic β -cells. The two key incretins, glucose-dependent in-

sulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1), are together responsible for an estimated 50–70% of the insulin released after a meal in healthy individuals. This phenomenon is known as the incretin effect [4]. Over the past two decades, drugs targeting the GLP-1 receptor (GLP-1R) have proven remarkably successful: GLP-1 receptor agonists (GLP-1 RAs) like semaglutide show strong efficacy in both lowering blood glucose and reducing body weight across large clinical trials [5]. More recently, tirzepatide, a dual GIP/GLP-1R agonist, has raised an intriguing possibility that activating both incretin pathways at once could yield metabolic benefits that GLP-1R agonism alone cannot match [6].

This review examines whether dual agonism truly advances beyond selective GLP-1R agonism, considering both clinical trials and proposed mechanisms. Head-to-head trial data show that tirzepatide outperforms semaglutide on weight loss endpoints, but the underlying reasons, especially how much of the advantage comes from glucose-dependent insulinotropic polypeptide receptor (GIPR) activation specifically, remain incompletely understood [6,7]. There is growing evidence that GIPR agonism plays a dis-

tinct role in boosting fat oxidation, modulating adipose tissue metabolism, and improving insulin sensitivity through both peripheral and central pathways [7,8]. That said, much of the mechanistic evidence still comes from rodent models, and how well these findings translate to humans remains an open question.

Incretin-based interventions for diabetes and obesity are organized around two connected themes. First, it compares the clinical efficacy of tirzepatide and semaglutide as representative dual and single incretin receptor agonists. Then, it examines the physiological role of GIPR agonism in fat oxidation and weight loss at the molecular and cellular level. Throughout, attention is given to the challenges of moving from preclinical findings to the clinical setting, and the review concludes by considering the broader clinical implications, outstanding research gaps, and future directions in this fast-moving field [9,10].

Background of the Incretin Concept

The incretin concept has roots stretching back over a century. In 1902, Bayliss and Starling identified secretin, the first hormone ever described, and showed that chemical signals produced in the gut could regulate distant organs like the pancreas [11]. This opened the door to the idea that the gastrointestinal tract might also release factors that stimulate insulin secretion. By 1906, Moore and colleagues were already trying to treat diabetes with duodenal extracts, believing that some gut-derived substance could support pancreatic function. The term “incretin” itself was coined by La Barre in 1932 to describe a hypothetical intestinal hormone that promoted insulin release. This is as opposed to “excretin” which refers to substances driving exocrine pancreatic secretion [11]. It would take several more decades, however, before the analytical tools existed to isolate and characterize the actual peptides involved.

The definitive proof came in the 1960s. Studies by McIntyre and colleagues and Perley and Kipnis showed that oral glucose produced a much larger insulin response than the same amount of glucose given intravenously [11,12]. This gap confirmed the incretin effect as a real physiological phenomenon and initiated the search for the responsible hormones. In the early 1970s, Brown and colleagues purified gastric inhibitory polypeptide from porcine intestinal extracts and demonstrated that it stimulated insulin secretion in a glucose-dependent fashion, establishing GIP as the first known incretin [12,13]. GIP was later renamed glucose-dependent insulinotropic polypeptide to better capture its actual function, since the original name had been based on its ability to inhibit gastric acid secretion [11].

Even after GIP was identified, immunoneutralization and surgical resection studies showed that it could not fully account for the incretin effect. This pointed to at least one more incretin hormone [13]. The breakthrough arrived in the mid-1980s, when cloning of the proglucagon gene by

Bell and colleagues revealed two new glucagon-like peptides, GLP-1 and GLP-2 [11]. Follow-up work in the laboratories of Habener and Holst showed that the truncated form, GLP-1(7–36 amide), had insulinotropic activity even more potent than full-length GLP-1 [11,12]. Importantly, GLP-1 also turned out to suppress glucagon release from the α -cells, slow gastric emptying, and promote satiety via central nervous system pathways, making it an especially attractive drug target. Together, GIP and GLP-1 were confirmed as the two principal incretin hormones, and studies with selective receptor antagonists showed that they collectively account for the full incretin effect in healthy people [5].

Incretins are unique not just because they stimulate insulin secretion, but because they only do so when blood glucose levels are elevated. GIP and GLP-1 are derived from different populations of enteroendocrine cells in the intestinal lining. GIP is made mainly by K-cells, concentrated in the duodenum and proximal jejunum and activated primarily by luminal fat and carbohydrate. GLP-1 is secreted by L-cells, found mostly in the distal ileum and colon, triggered by nutrients reaching the lower gastrointestinal (GI) tract [12,13]. At the cellular level, both hormones bind their respective G-protein-coupled receptors (GIPR and GLP-1R) on pancreatic β -cells, engaging the Gas subunit. This activates adenylyl cyclase, raising intracellular cyclic adenosine monophosphate (cAMP), which in turn switches on protein kinase A (PKA) and exchange protein activated by cyclic-AMP 2 (Epac2). Incretins do not independently trigger insulin secretion; they only potentiate the glucose-stimulated insulin secretion (GSIS) that glucose itself initiates. Glucose enters the β -cell via glucose transporter 2 (GLUT2) transporters and is metabolized to increase the intracellular adenosine triphosphate/adenosine diphosphate (ATP/ADP) ratio, which is the primary signal that closes ATP-sensitive potassium channels (KATP channels), depolarizes the membrane, and triggers insulin exocytosis. Incretin signaling through cAMP/PKA and cAMP/Epac2 amplifies this glucose-initiated process at multiple points: PKA sensitizes KATP channels to the ATP/ADP ratio (lowering the threshold for closure), enhances L-type calcium channel conductance, and facilitates granule mobilization and fusion through phosphorylation of soluble N-ethylmaleimide-sensitive factor-attachment protein receptor (SNARE) complex components [13,14]. Epac2 mobilizes calcium from intracellular endoplasmic reticulum (ER) stores and promotes granule docking through Rab3-interacting molecule 2 (Rim2) and Mammalian Unc-13 homolog 1 (Munc13-1) interactions. Because every step depends on glucose having already initiated the cascade, the risk of hypoglycemia is inherently low. This is a major clinical advantage over sulfonylureas, which close KATP channels independently of glucose and can therefore cause hypoglycemia.

A two-minute half-life provides a poor foundation for drug development. Both GIP and GLP-1 are rapidly broken down by dipeptidyl peptidase-4 (DPP-4), which inactivates them within minutes of release, roughly 2 minutes for GLP-1 and 5-7 minutes for GIP. This poses a huge pharmacological challenge. Two strategies subsequently emerged to address this limitation: DPP-4 inhibitors, which extend the life of the body's own incretins, and engineered GLP-1R agonists designed to resist degradation [11]. The latter approach proved powerful, with synthetic GLP-1 RAs including exenatide, liraglutide, and semaglutide each improving on glycemic control and weight loss over the previous generation [12]. Drug development focused almost entirely on GLP-1 rather than GIP because studies in patients with T2D showed that GIP's insulin-stimulating potency was severely blunted, whereas GLP-1 remained effective at supraphysiological doses [5]. This apparent "resistance" to GIP in T2D led the field to dismiss GIP as a therapeutic target, a view later challenged by the clinical success of tirzepatide, as discussed below.

Dual Versus Single Incretin Receptor Agonism

To understand the differences between semaglutide and tirzepatide, it is first necessary to examine their molecular structures, as these shape how each drug interacts with its target receptors and downstream signaling. Semaglutide and tirzepatide share the same once-weekly subcutaneous administration route but differ in their receptor targets, molecular structure, and pharmacological profile. The following sections describe each agent before a direct comparison.

Molecular Structure and Mechanism of Semaglutide

Semaglutide is a selective GLP-1R agonist, a 31-amino acid synthetic analogue of human GLP-1(7-37) that has been engineered with several structural tweaks to overcome native GLP-1's rapid degradation [5]. At position 8, the primary DPP-4 cleavage site, alanine is swapped for α -aminoisobutyric acid (Aib), which blocks enzymatic breakdown. At position 34, lysine is replaced with arginine to ensure site-specific acylation. The remaining lysine at position 26 is linked to an octadecanedioic (C18) fatty diacid chain through a linker containing a mini-polyethylene glycol spacer and a γ -glutamic acid; this allows non-covalent binding to serum albumin, stretching the circulating half-life to roughly 165 hours and making once-weekly dosing possible. The result is a drug that a patient injects once a week and largely forgets about, a marked improvement over multiple daily injections that defined diabetes management for decades. When semaglutide binds GLP-1R on β -cells, it triggers the *G* α s/adenylyl cyclase/cAMP/PKA pathway, boosting glucose-dependent insulin secretion and suppressing glucagon release from α -cells [13]. Beyond the pancreas, it slows gastric emptying and acts on GLP-1Rs in

the hypothalamic arcuate nucleus and brainstem to suppress appetite and caloric intake [5,12]. This combination of peripheral metabolic effects and central appetite suppression established semaglutide as the most effective single-agent GLP-1 RA available and the clinical benchmark against which tirzepatide is evaluated. Specific trial outcomes are discussed in the section "Head-to-Head Clinical Evidence: The SURMOUNT-5 Trial".

Molecular Structure and Mechanism of Tirzepatide

Tirzepatide is a dual GIP/GLP-1R agonist, a single synthetic molecule designed to engage both incretin receptors simultaneously [13,15]. It is a linear 39-amino acid molecule based on the native human GIP sequence, incorporating structural elements from both GIP and GLP-1. In total, it contains regions homologous to GIP, residues shared with GLP-1 and exendin-4, and a limited number of unique positions that distinguish it from corresponding parent peptides [15]. A key structural feature is the N-terminal tyrosine (Tyr1), which is present in native GIP but replaced by histidine in GLP-1. Cryo-electron microscopy shows that Tyr1 inserts deeply into the GIP receptor binding pocket, and substitution with histidine reduces GIPR binding affinity by ~20-fold, playing a central role in tirzepatide's preferential activity at the GIP receptor [16].

Tirzepatide is structurally engineered to be more stable and resistant to degradation, which also prolongs its time in circulation. At position 2, native alanine is replaced with α -aminoisobutyric acid (Aib), conferring resistance to DPP-4 cleavage, while a second Aib substitution at position 13 further stabilises the peptide structure [15,16]. The C-terminal is amidated to guard against carboxypeptidase degradation. Its pharmacokinetic profile is primarily directed by acylation at lysine-20 with a C20 fatty diacid (eicosanedioic acid), attached via a hydrophilic linker composed of a γ -glutamic acid spacer and two 8-amino-3,6-dioxaoctanoic acid (AEEA) units. This lipid chain allows tight non-covalent binding to serum albumin, giving a half-life of about 116.7 hours and once-weekly dosing [15]. Prominently, the C20 fatty diacid is two carbons longer than semaglutide's C18 chain, and molecular dynamics simulations propose it folds differently depending on whether tirzepatide is bound to GIPR or GLP-1R, potentially supporting its specific receptor behaviour [16].

These structural choices shape tirzepatide's receptor binding and signaling profile. *In vitro*, tirzepatide binds GIPR and generates cAMP at roughly the same potency as native GIP. At GLP-1R, however, its binding affinity is about fivefold weaker than GLP-1, and its potency at stimulating cAMP is reduced further, roughly 20-fold weaker [15,16]. Favoring GIPR over GLP-1R is believed to contribute to the hypothesis that stronger GIPR activation paired with moderate GLP-1R activation produces better metabolic outcomes. On top of this, tirzepatide shows biased agonism at GLP-1R: it drives cAMP signaling (the

Gs pathway) while causing less β -arrestin recruitment than native GLP-1 [16]. That distinction matters: β -arrestin recruitment mediates receptor internalization, desensitization, and some of the gastrointestinal side effects associated with GLP-1R activation. Tirzepatide's reduced β -arrestin engagement may help explain its better tolerability [16]. Tirzepatide was approved by the Food and Drug Administration (FDA) for T2D in May 2022 (Mounjaro) and for chronic weight management in November 2023 (Zepbound) [13,15].

Head-to-Head Clinical Evidence: The SURMOUNT-5 Trial

The SURMOUNT-5 trial, published by Aronne and colleagues [6] in the *New England Journal of Medicine* in July 2025, was the first direct head-to-head comparison of tirzepatide and semaglutide for obesity treatment. This phase 3b, multicenter, open-label trial was conducted across 32 clinical sites in the United States and Puerto Rico, enrolling 751 adults aged 18 or older with a body mass index (BMI) of 30 or above, or 27 or above with at least one weight-related comorbidity such as hypertension, dyslipidemia, obstructive sleep apnea, or cardiovascular disease. People with T2D were excluded so that weight loss effects could be assessed without glycemic confounders. Participants were randomly assigned 1:1 to receive tirzepatide or semaglutide by weekly subcutaneous injection, each escalated to the maximum tolerated dose: 10 or 15 mg for tirzepatide, and 1.7 or 2.4 mg for semaglutide.

The primary endpoint was percent change in body weight from baseline to week 72, analyzed using a mixed-model-for-repeated-measures approach. Key secondary endpoints included change in waist circumference and the proportion of participants reaching weight loss thresholds of 10%, 15%, 20%, and 25% [6]. The trial was open-label due to differences in dose-escalation schedules and injection devices between the two medications, meaning that both participants and investigators were aware of treatment allocation. This design should be considered a limitation, especially for subjective outcomes.

The results favored tirzepatide. At 72 weeks, tirzepatide produced a mean weight loss of -20.2% (95% confidence interval (CI), -21.4 to -19.1) compared with -13.7% (95% CI, -14.9 to -12.6) for semaglutide, a between-group difference of 6.5 percentage points ($p < 0.001$). Waist circumference dropped by 18.4 cm with tirzepatide versus 13.0 cm with semaglutide ($p < 0.001$). Tirzepatide-treated participants were roughly 1.3, 1.6, 1.8, and 2.0 times more likely to achieve at least 10%, 15%, 20%, and 25% weight loss, respectively, and 32% of those on tirzepatide reached the 25% threshold. Gastrointestinal adverse events led to discontinuation in approximately twice as many participants receiving semaglutide (5.6%) as those receiving tirzepatide (2.7%). This fits with the idea that GIPR co-activation may temper GLP-1R-mediated nausea [6]. Key

molecular and clinical characteristics of both agents are summarized in Table 1 (Ref. [6,7,8,15,16,17,18]) below.

SURMOUNT-5 also highlighted something worth paying attention to: women achieve approximately 6 percentage points greater weight loss than men across both treatment groups. No formal statistical test was reported for this difference, so it should be treated as an observation rather than a confirmed finding, although it is not trivial. The Semaglutide Treatment Effect in People with obesity (STEP) trials, which enrolled only 19–26% men compared to 35% in SURMOUNT-5, consistently showed higher overall weight loss [6].

A meta-analysis of 14 RCTs found that women lose approximately 1.69% more weight than men on GLP-1 RAs broadly, and that gap widens as overall weight loss increases, where the losses are among the largest ever reported for a pharmacological intervention [19]. Women have higher plasma concentrations of GLP-1 RAs due to lower average body weight and reduced drug clearance, meaning they are effectively exposed to more drug per dose [19,20]. Estrogen may also play a role, with some evidence suggesting it acts synergistically with GLP-1 signaling in appetite-regulating neural circuits. Although this remains a hypothesis rather than an established mechanism [20]. Women are still underrepresented in preclinical GLP-1 research, and sex-disaggregated pharmacokinetic and efficacy data are rarely reported as primary outcomes. As these drugs come into use among tens of millions of patients, this gap is becoming increasingly difficult to justify.

Supporting Evidence From the SURPASS Program and Original Mechanistic Studies

Beyond weight loss, mechanistic analyses from the SURPASS program provide further insight into its metabolic effects. A post hoc analysis of SURPASS-1 examined tirzepatide monotherapy in 478 participants with early T2D over 40 weeks, looking at β -cell function and insulin sensitivity using the homeostatic model assessment (HOMA2). Tirzepatide increased homeostatic model assessment of β -cell function (HOMA2-B) (a marker of β -cell function based on C-peptide) by up to 92% at week 40 in a dose-dependent manner, while fasting proinsulin levels fell by 49–55% compared to just 0.6% with placebo. The drop in the proinsulin-to-C-peptide ratio hints that tirzepatide was not just increasing insulin output but also improving the quality of β -cell processing. Reductions in homeostatic model assessment of insulin resistance (HOMA2-IR), fasting insulin, and increases in adiponectin and insulin-like growth factor-binding protein-binding protein 2 also pointed to genuine improvements in insulin sensitivity [17].

A companion post hoc analysis of SURPASS-2 extended these observations by directly comparing tirzepatide with semaglutide (1 mg) in 1879 participants with T2D receiving background metformin over 40 weeks. HOMA2-B increased by 96.9–120.4% with tirzepatide (5, 10, and 15

Table 1. Comparison of tirzepatide and semaglutide.

	Tirzepatide	Semaglutide
Molecular properties		
Type	Dual GIP/GLP-1 agonist	Selective GLP-1 agonist
Peptide length	39 AA (GIP-based backbone)	31 AA (GLP-1-based analogue)
DPP-4 resistance	Aib at positions 2, 13	Aib at position 8
Acylation	C20 eicosanedioic acid at Lys20	C18 octadecanedioic acid at Lys26
Half-life	116.7 h (~5 days)	165 h (~7 days)
GIPR activity	Comparable to native GIP; Tyr1 critical (~20-fold loss if mutated)	None
GLP-1R affinity	~20% of native GLP-1; biased agonism (cAMP > β -arrestin)	Full agonist
Dosage	5, 10, or 15 mg/week SC	1.7 or 2.4 mg/week SC
Clinical efficacy (SURMOUNT-5, 72 weeks)		
Body weight	–20.2% (95% CI –21.4 to –19.1)	–13.7% (95% CI –14.9 to –12.6)
Waist circumference	–18.4 cm	–13.0 cm
≥25% weight loss	32%	16%
GI discontinuation	2.7%	5.6%
HOMA2-B	Increased 97–120%	Increased 84%
HOMA2-IR	Decreased 15.5–24%	Decreased 5.1%
Metabolic mechanisms		
Fat oxidation	Increased beyond prediction; RQ 0.85–0.80	No substrate-shifting effect observed
Adipose tissue	Lipid buffering; adiponectin +26%; prevents adiposity	No direct activation; only proportional loss with body weight
CNS effects	GIPR + GLP-1R in hypothalamus; area postrema → reduced nausea	GLP-1R only; higher nausea-related discontinuation
Cross-species considerations		
Human evidence	SURMOUNT-5; SURPASS 1–5; Ravussin (metabolic chambers, limited n)	STEP 1–4; SUSTAIN 1–10; well-characterized
Preclinical evidence	Primarily rodent (3T3-L1, GIPR ^{–/–} mice)	Validated across rodent and human models
Translation caveat	Direct translation limited. Species differ in adipose distribution, brown fat, and metabolic rate. GIPR ^{–/–} may cause developmental compensation. Agonism-vs-antagonism paradox unresolved.	Stronger translational evidence; well-established human pharmacology.

Note: Clinical efficacy data from the SURMOUNT-5 trial [6] and SURPASS post hoc analyses [17,18]. Metabolic data from [7,8]. Molecular data from [15,16]. AA, amino acids; Aib, α -aminoisobutyric acid; CI, confidence interval; CNS, central nervous system; GI, gastrointestinal; GIPR, glucose-dependent insulinotropic polypeptide receptor; GLP-1R, glucagon-like peptide-1 receptor; HOMA2-B, homeostatic model assessment of β -cell function; HOMA2-IR, homeostatic model assessment of insulin resistance; RQ, respiratory quotient; SC, subcutaneous.

mg) versus 84.0% with semaglutide, while HOMA2-IR decreased by 15.5–24.0% with tirzepatide compared to only 5.1% with semaglutide. Fasting glucagon also fell more with tirzepatide across all doses. The glycated hemoglobin A1c (HbA1c) and weight loss held consistently regardless of where patients started in terms of β -cell function or insulin resistance. This indicates that dual agonism benefits patients across the spectrum of disease severity. Tirzepatide improved HOMA2-IR by 3–5 times more than semaglutide, and this difference was only partly explained by the greater weight loss, supporting a direct metabolic effect of GIPR co-activation on peripheral insulin sensitivity [18].

SURMOUNT-5 is a strong study, but several limitations should be considered. The open-label design may

have influenced more subjective outcomes such as appetite and self-reported side effects. Its 72-week duration also limits conclusions about long-term durability and safety beyond two years, given the well-documented tendency for weight regain after GLP-1 receptor agonist discontinuation [10]. In addition, comparing maximum tolerated doses of structurally different molecules makes strict dose equivalence difficult to interpret.

GIPR Agonism

With tirzepatide's clinical effects established, the next question concerns the role of GIPR activation: what does GIPR activation specifically contribute? The focus is on

the biology, including signaling, tissue-specific effects, and metabolic pathways, rather than on tirzepatide. This distinction matters because tirzepatide activates both receptors simultaneously, making it difficult to attribute any single outcome to one pathway alone. Accordingly, this section draws on preclinical studies characterizing GIPR function in isolation, clinical data where tirzepatide's effects exceed what GLP-1R activation alone would predict, and the Ravussin metabolic study as the most direct human evidence. Separating the effects of GIP from those of GLP-1 in a drug that activates both receptors simultaneously is inherently difficult.

GIPR Biology and Signaling

The GIP receptor is a class B1 G-protein-coupled receptor in the secretin receptor family. Structurally, it features a large extracellular N-terminal domain for ligand binding, a seven-transmembrane helical domain for signal transduction, and an intracellular C-terminal domain that engages downstream effectors. GIP is a 42-amino acid peptide derived from a distinct 153-amino acid preprohormone. It binds the receptor, activating G α s, leading to stimulation of adenylyl cyclase and raising intracellular cAMP. Elevated cAMP engages two parallel effectors that amplify glucose-stimulated insulin secretion. The first effector, PKA, does not close K_{ATP} channels directly; it sensitizes them to the ATP/ADP ratio generated by glucose metabolism. This reduces the depolarization threshold so that a given glucose stimulus produces a larger secretory response. PKA also enhances L-type calcium channel conductance and phosphorylates exocytotic machinery including synaptotagmin and SNARE complex proteins to accelerate granule fusion. At the transcriptional level, PKA phosphorylates cAMP response element-binding protein (CREB) to drive expression of β -cell survival genes, including insulin receptor substrate 2 (IRS2) and B-cell lymphoma 2 (Bcl-2), linking the same signal to both acute secretion and long-term β -cell maintenance. The second effector, Epac2, operates independently of PKA: it mobilizes calcium from ER stores via ryanodine and IP₃ receptors and promotes granule priming through Rim2 and Munc13-1. Pharmacological studies have shown that inhibiting both PKA and Epac simultaneously abolishes the incretin effect almost entirely. Inhibiting either alone reduces it by only 40–60%, confirming their parallel and complementary contributions. The entire cascade remains strictly glucose dependent. Without elevated glucose, K_{ATP} channels stay open, and there is no baseline secretory event to potentiate [5,13,14].

Beyond acute insulin release, GIPR activation has trophic effects on β -cell mass. GIP promotes proliferation through phosphoinositide 3-kinase/protein kinase B (PI3K/Akt)-mediated phosphorylation and inactivation of forkhead box O1 (FoxO1), relieving its repression of the cell cycle, while concurrently upregulating pancreatic and

duodenal homeobox 1 (PDX-1), a master transcription factor for β -cell identity and insulin gene expression. On the survival side, PKA phosphorylates the pro-apoptotic protein Bad at serine 112, sequestering it in an inactive complex with 14-3-3 proteins and preventing caspase activation. These trophic effects have been demonstrated in cell culture and rodent models and may be relevant to T2D, in which progressive β -cell failure is driven by glucolipotoxicity and ER stress [5,13]. GIPR is also expressed in white and brown adipose tissue, bone, the CNS, and the cardiovascular system, where GIP's metabolic roles are discussed in the following sections (Fig. 1).

The GIP Paradox in Type 2 Diabetes

In healthy individuals, GIP's greater contribution to the postprandial insulin response has been demonstrated by studies using the selective GIPR antagonist GIP (3-30). Healthy volunteers received oral glucose with and without co-infusion of GIP (3-30): blocking GIP action reduced postprandial insulin secretion by approximately 50–60%, while the GLP-1R antagonist exendin (9-39) reduced it by only 20–30%. The loss of this effect in T2D was characterized using hyperglycemic clamp studies, where patients received graded GIP infusions at plasma glucose clamped at 8–10 mmol/L: unlike controls, T2D patients showed markedly blunted C-peptide responses even at 5–10 times physiological GIP concentrations, while GLP-1's responsiveness was preserved at supraphysiological doses. GIPR downregulation under chronic hyperglycemia, impaired receptor-G-protein coupling, and glucolipotoxicity-induced desensitization of downstream signaling underlie this loss of responsiveness. Improving glycemic control may partially restore the β -cell's responsiveness to GIP, which points to functional desensitization rather than permanent receptor loss [5]. With tirzepatide, higher levels of GIP receptor stimulation appear to overcome this reduced sensitivity [15]. GIPR activation also exerts important metabolic effects in peripheral tissues, such as adipose tissues.

In preclinical models, both GIP receptor agonism and antagonism promote weight loss, an observation that should not be possible if GIP has a clear and consistent metabolic role [21]. That contradiction is the GIP agonism-versus-antagonism paradox, and it remains one of the most unresolved questions in incretin biology.

How can activating and blocking the same receptor produce the same outcome? Three compelling explanations, as summarized in Table 2 (Ref. [5,15,21]), may resolve this paradox. Receptor desensitization offers an answer: flood the GIPR with sustained stimulation, and it may stop listening; β -arrestin-mediated internalization progressively silences the very receptor being activated, so that chronic agonism ends up functionally resembling blockade [21]. A second proposed mechanism is tissue specificity: GIP exerts different effects in fatty tissues, the pancreas,

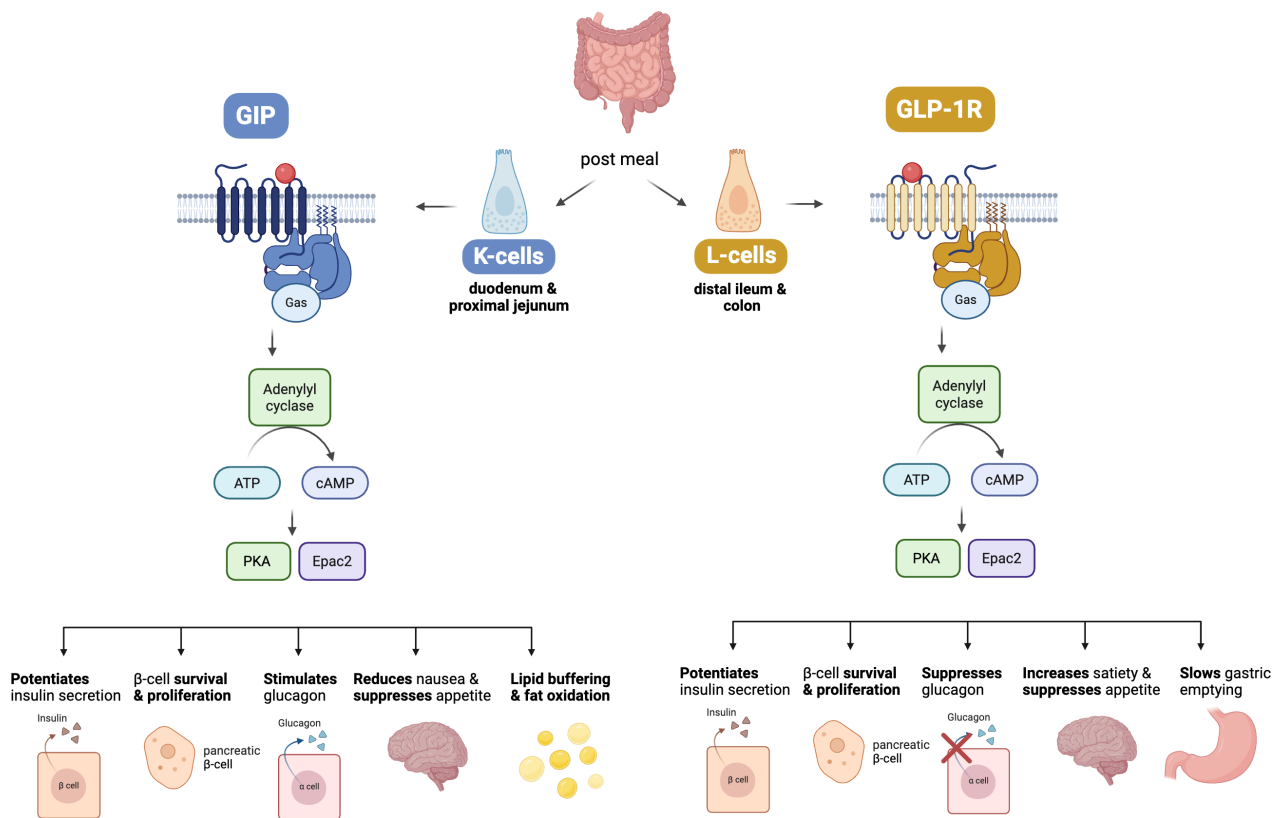


Fig. 1. Comparative signaling pathways and physiological effects of GIP and GLP-1. GIP (left) is secreted from intestinal K-cells and activates GIPR, engaging the cAMP/PKA/Epac2 cascade to potentiate glucose-stimulated insulin secretion, promote β -cell survival, enhance lipid buffering and fat oxidation in adipose tissue, and suppress appetite while attenuating nausea via the CNS. GLP-1 (right) is secreted from L-cells and activates GLP-1R through the same cAMP/PKA pathway, potentiating insulin secretion, suppressing glucagon, slowing gastric emptying, increasing satiety, and promoting β -cell survival. Both pathways are strictly glucose-dependent. Created in BioRender (<https://BioRender.com/nrdb9u5>). GIP, glucose-dependent insulintropic polypeptide; cAMP, cyclic adenosine monophosphate; PKA, protein kinase A; Epac2, exchange protein directly activated by cAMP 2.

and the brain, and the whole-body outcome is a net sum of these divergent actions, meaning both agonism and antagonism could produce weight loss simply by winning in different tissues [15]. A third possibility looks at the problem in the disease itself: GIP signaling in obesity and T2D is not the same system as in lean physiology; receptor expression is altered, downstream pathways are rewired, and what works in a healthy mouse may simply not translate [5,21]. None of these explanations is fully satisfactory on its own, and that may be precisely the point. If we cannot agree on what GIP receptor activation does, therapeutic development rests on uncertain ground, and choosing incorrectly between agonism and antagonism could have major consequences for the next generation of drugs.

GIPR Agonism in Adipose Tissue

GIPR is highly expressed in white adipose tissue, initially complicating our understanding of GIP's role in obesity. Early work characterized GIP as a lipogenic hormone: it stimulates triglyceride synthesis, lipoprotein lipase

activity, and insulin-stimulated glucose transport through GLUT4 translocation, and drives de novo lipogenesis [8]. These effects were first demonstrated *in vitro* using differentiated 3T3-L1 adipocytes, where GIP (1–100 nM) induced dose-dependent increases in LPL mRNA expression and enzymatic activity, promoted GLUT4 translocation (assessed by subcellular fractionation), and enhanced lipogenesis measured by ^{14}C -acetate incorporation [5,8]. *In vivo*, GIP receptor knockout mice (GIPR $^{-/-}$) gained approximately 40% less weight than wild-type littermates when fed a high-fat diet over 20 weeks, accompanied by reduced visceral adipose tissue mass, which initially cemented GIP's reputation as a pro-obesity hormone [5]. However, these knockout models develop compensatory metabolic adaptations from early life, so their phenotype may not accurately reflect acute GIPR modulation in adult physiology [15].

A more nuanced picture has since emerged, one that reframes GIP's adipose tissue effects as metabolically protective rather than harmful. GIPR activation in subcutaneous adipose tissue promotes safe lipid storage, limiting

Table 2. Proposed mechanistic explanations for the GIP agonism-versus-antagonism paradox [5,15,21].

Explanation	Key evidence	Limitation
Receptor desensitization	Chronic GIPR stimulation may trigger β -arrestin-mediated internalization, making prolonged activation functionally resemble blockade	Not demonstrated in humans
Tissue-specific signaling	GIPR mediates distinct effects in adipose tissue, β -cells, and CNS; agonism and antagonism may produce similar outcomes through different tissue-level pathways	Relative tissue contributions unquantified
Developmental compensation	Germline GIPR knockout mice adapt from birth, potentially exaggerating apparent benefits of receptor deletion	Knockout phenotypes $\neq$ acute pharmacological blockade in adults

free fatty acid spillover into the liver, skeletal muscle, and visceral compartments, where ectopic deposition fuels insulin resistance and systemic inflammation [7]. In addition, GIP stimulates adiponectin secretion, an insulin-sensitizing adipokine that boosts fatty acid oxidation in muscles and curbs hepatic glucose output [7]. Clinical data are consistent with these effects: tirzepatide has been shown to raise circulating adiponectin by up to 26% at the 10 mg dose [15].

Instead of promoting fat accumulation, GIPR agonism redirects fat metabolism in a way that increases systemic insulin sensitivity and reduces cardiometabolic risk. Despite tirzepatide causing some loss of lean mass during weight loss, evidence suggests that approximately 74% of weight loss comes from fat and 26% from lean mass, comparable to other weight loss methods [20]. Since lean mass also includes water and other non-muscle tissues, this does not translate directly into a proportional loss of skeletal muscle. The long-term implications for muscle strength and function remain unclear and require further investigation.

Increased Fat Oxidation: The Ravussin Study

The study by Ravussin and colleagues [7], published in *Cell Metabolism* in 2025, provided human-level evidence for the metabolic effects of dual incretin agonism. This metabolic substudy recruited adults with obesity and used whole-room indirect calorimetry, metabolic chambers, the gold standard for measuring energy expenditure and substrate oxidation. These are airtight rooms where participants live for 24 hours while sensors continuously track oxygen consumption (VO₂) and carbon dioxide production (VCO₂); from these values, the respiratory quotient (RQ, VCO₂/VO₂) is calculated, showing whether the body is primarily oxidizing carbohydrates (RQ near 1.0) or fats (RQ near 0.7). Participants underwent 24-hour assessments before and after tirzepatide treatment, allowing precise tracking of changes in total energy expenditure, resting metabolic rate, and how the body was dividing its fuel use between fat and carbohydrate.

The key finding was that tirzepatide significantly increased fat oxidation beyond what would be expected from weight loss alone [7]. This is important because weight loss is typically accompanied by metabolic adaptation, including a disproportionate decline in resting metabolic rate

(adaptive thermogenesis), reduced fat oxidation, and hormonal changes that favour weight regain. In contrast, tirzepatide did not appear to exacerbate these responses. Total energy expenditure and resting metabolic rate declined in proportion to changes in body mass, with no evidence of excess adaptive thermogenesis. Specifically, the 24-hour respiratory quotient decreased from approximately 0.85, indicating mixed substrate utilisation, to around 0.80, reflecting a greater reliance on fat oxidation. This reduction was larger than those predicted by standard models of metabolic adaptation based on changes in body composition [7]. This points to a move toward greater fat use, which could help explain improvements in body composition, insulin sensitivity, and longer-term weight control. The investigators proposed that GIPR signalling may contribute to this effect because of GIP's recognised role in adipose tissue lipid metabolism. Since tirzepatide is a dual GIP/GLP-1R agonist, the contribution of GIPR activation cannot be determined from this study alone. Thus, tirzepatide's biased agonism at the GLP-1 receptor may also play a role in these metabolic effects.

Central Nervous System Effects

In addition to peripheral effects on fat metabolism, GIPR activation also exerts significant effects in the central nervous system. GIPR is expressed in several hypothalamic nuclei involved in appetite regulation, including the arcuate nucleus, paraventricular nucleus, and ventromedial hypothalamus, as well as the area postrema and nucleus of the solitary tract [8]. These expression patterns partially overlap with GLP-1R distribution, suggesting that dual agonism is involved in a broader network of appetite-regulatory circuits than either agonist alone [6,8]. One hypothesis is that GIPR activation in the area postrema may dampen GLP-1R-mediated nausea by modulating the emetic reflex. This aligns with the clinical observation in SURMOUNT-5 that GI adverse events leading to treatment discontinuation occurred approximately half as often with tirzepatide compared to semaglutide [6,10]. Overall, the CNS effects of GIPR agonism appear to contribute to both greater appetite suppression and improved tolerability, thereby supporting long-term treatment adherence.

Discussion

The evidence in this review supports the conclusion that dual GIP/GLP-1R agonism is an advance over selective GLP-1R agonism. The SURMOUNT-5 data showed a 6.5 percentage point weight loss advantage for tirzepatide, with superior results across every threshold measured and clinically significant improvements in waist circumference [6]. These clinical numbers are backed by a coherent mechanistic framework: Dual GIP/GLP-1R agonism is associated with enhanced fat oxidation without worsening metabolic adaptation, promotes healthy lipid buffering in adipose tissue and adiponectin-mediated insulin sensitization [7], and provides complementary CNS appetite suppression through circuits that GLP-1 alone does not fully engage [6,8,10]. The SURPASS program data show that tirzepatide improves β -cell function and insulin sensitivity through mechanisms only partly explained by weight loss, suggesting additional GIPR co-activation contribution [17,18]. These headline numbers also obscure an important nuance: women lost roughly 6 percentage points more weight than men in SURMOUNT-5. This disparity is consistent with the broader GLP-1 receptor agonist literature, yet its underlying mechanisms remain poorly understood, and with tens of millions of patients now receiving these drugs, it can no longer be treated as a peripheral concern.

In addition, most of what we know about GIPR signaling at the cellular and tissue levels still comes from rodent models, and mice are not simply miniature humans. Their adipose tissue distribution, metabolic rate, and receptor expression patterns differ in ways that matter, and the GIPR knockout mouse, one of the most cited models in this field, develops without GIP signaling from birth. Whatever leanness these animals display may reflect a lifetime of metabolic rewiring, not what happens when you block the receptor acutely in an adult with obesity. The Ravussin study provides the closest available direct evidence in humans and is therefore particularly valuable. However, the small sample size and use of tirzepatide, a dual agonist, make it impossible to cleanly attribute the fat oxidation findings to GIP alone [7]. SURMOUNT-5 adds another layer of complexity: because neither participants nor investigators were blinded to treatment, subjective outcomes such as nausea and gastrointestinal symptoms may have been shaped by expectation [6].

The safety picture is promising but incomplete. Both drugs were well tolerated overall, with gastrointestinal side effects, including nausea, vomiting, diarrhea, and constipation, being the most commonly reported events, mostly during dose escalation. Severe adverse events were rare and balanced between groups. Only one confirmed case of pancreatitis emerged in the semaglutide arm, and no cardiovascular deaths, thyroid malignancies, or pancreatic cancers were observed [6]. Although reassuring, 72 weeks is a relatively short observation window for a drug that patients

may take for decades. The absence of a signal is not the same as proof of safety, and the long-term consequences of sustained dual incretin receptor activation on the pancreas, thyroid, gallbladder, and beyond remain open questions that only larger, longer trials can answer. One additional signal warrants attention: a recent network meta-analysis in adults with overweight or obesity found that both drugs modestly increased resting heart rate relative to placebo: Tirzepatide by about 2 bpm and semaglutide by 3–4 bpm. Although this increase is not considered clinically meaningful in isolation, it warrants monitoring in patients with pre-existing arrhythmias or heart failure [22].

The paradox of GIP agonism-versus-antagonism remains a central unresolved issue in the field. Both pharmacological activation and blockade of GIPR reduce body weight in animal models [15]. Several explanations have been proposed, including dose-dependent receptor desensitization, tissue-specific signaling, and context-dependent metabolic effects [9,15]. If GIPR antagonism can produce weight loss, then dual-acting approaches combining GLP-1R agonism with GIPR antagonism may represent a potential therapeutic strategy [9].

The field is advancing rapidly, and several questions warrant priority. Although 72 weeks is sufficient to establish efficacy, it is too short to determine the long-term durability of weight loss, cardiovascular outcomes, or rare safety risks associated with continuous use [6]. Triple receptor agonists targeting GIP, GLP-1, and glucagon receptors are already moving through clinical development; retatrutide, for instance, has shown up to 24% weight loss in early trials, with the glucagon component enhancing hepatic lipid oxidation and thermogenesis [23]. Perhaps most exciting is the prospect that genetic and biomarker profiling could identify which patients are most likely to benefit from dual versus single agonism, shifting treatment from a one-size-fits-all model toward personalized metabolic medicine [9,10]. At the most fundamental level, human studies of selective GIPR agonists and antagonists are needed to disentangle the effects of GIP from those of GLP-1, a question that, as this review highlights, remains surprisingly unresolved.

The clinical translation of incretin-based therapies has reshaped how we manage diabetes and obesity. Semaglutide (Ozempic/Wegovy) and tirzepatide (Mounjaro/Zepbound) are now among the most widely prescribed drugs in endocrinology, and for the first time, pharmacological treatments are reliably producing weight losses of 15–20%, approaching the range of some bariatric surgical procedures, without the surgical risks [6,13]. In addition, these drugs tackle glycemic control and weight management simultaneously, a dual benefit that was historically challenging with older medications [10].

Tirzepatide and semaglutide represent some of the most important advances in metabolic medicine in decades, yet the patients who stand to benefit most, those in low- and

middle-income countries, where 95% of projected diabetes growth will occur by 2050, are the least likely to ever receive them [1,2]. In the United States alone, list prices exceed \$1000 per month, and supply shortages, driven partly by off-label cosmetic use, have left patients with genuine clinical need unable to access treatment [10]. A drug that works brilliantly but remains accessible only to a wealthy minority cannot solve a global health crisis. Pricing reform, accelerated generic development, and coordinated global health policy are not optional; they are essential if these therapies are to realize their full potential.

Other difficult questions are emerging. What does it mean for patients to remain on treatment indefinitely, knowing that discontinuation will likely reverse its benefits? Weight regain after withdrawal is well-documented, and the prospect of lifelong pharmacological dependency, together with its cumulative financial burden, raises serious questions about sustainability for both patients and health-care systems [4]. At the same time, the widespread off-label use of these drugs for cosmetic weight loss is impossible to ignore. When semaglutide and tirzepatide are used for modest cosmetic weight loss while patients with T2D or severe obesity cannot access them because of shortages and cost, the allocation of a scarce medical resource has clearly failed [9]. There is also the question of who funds the evidence base. The SURMOUNT trials were sponsored by Eli Lilly and the STEP trials by Novo Nordisk, the same companies that stand to profit from their findings. Although these studies met rigorous regulatory standards and there is no implication of misconduct, industry sponsorship creates a structural conflict of interest that the field has not fully confronted [5,6]. Progress without accountability is incomplete, and these concerns warrant the same scrutiny as the clinical data.

Conclusion

Dual incretin agonism represents an advance in the treatment of obesity and type 2 diabetes. The SURMOUNT-5 trial demonstrated that tirzepatide produces greater weight loss than semaglutide with better tolerability and superior outcomes across every threshold measured. GIPR co-activation contributes through enhanced fat oxidation, adipose tissue lipid buffering, adiponectin-mediated insulin sensitization, and complementary CNS appetite suppression through circuits that GLP-1 alone does not fully engage. Improvements in insulin sensitivity observed in the SURPASS program appear to exceed those attributable to weight loss alone, suggesting that GIPR activation may exert direct metabolic effects independent of weight reduction. The GIP agonism-versus-antagonism paradox remains unresolved, much of the mechanistic evidence remains preclinical, and 72 weeks is not sufficient to answer questions about durability, rare safety signals, or the consequences of treatment discontinuation. These are

not minor caveats but central questions for the next generation of trials. The incretin story is far from complete. From Bayliss and Starling's discovery of secretin in 1902 to today's dual and triple agonists, this field has repeatedly defied expectations.

Availability of Data and Materials

Not applicable.

Author Contributions

LW performed the literature review, identified and analyzed the key articles, drafted the manuscript, created the BioRender figure, and was responsible for the visualization. JLL conceived the initial idea and was responsible for the conceptualization, supplied essential source materials, and critically revised the manuscript. LX conceived the initial idea of the figure and was responsible for the conceptualization and critical revision of the manuscript. All authors gave final approval of the version to be published. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

Jun-Li Liu was the Editor-in-Chief of this journal at the time of acceptance. Jun-Li Liu had no involvement in the peer review of this article and has no access to information regarding its peer review. The other authors declare no conflict of interest.

Declaration of Generative AI and AI-Assisted Technologies in Manuscript Preparation

During the preparation of this manuscript, the author used Claude to obtain feedback on writing, improve clarity, and enhance readability. Grammarly was used to identify and correct grammatical, spelling, and punctuation er-

rors. After using AI-assisted tools, the authors thoroughly reviewed, verified, and revised the manuscript to ensure the accuracy, originality, and integrity of its content.

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