

# GLP-1, GIP, AND GLUCAGON: A PARADOX IN DIABETES, OBESITY AND BEYOND

Obesity and type 2 diabetes mellitus (T2DM) are rising worldwide. Central to these diseases are the hormones glucagon-like peptide-1 (GLP-1), glucose-dependent insulintropic polypeptide (GIP), and glucagon (GCG). GLP-1 receptor agonists (GLP-1RAs) have revamped pharmacological treatment through robust insulin secretion and appetite suppression, driving the development of strategies that target GLP-1R in combination with the GIP and GCG receptors (GIPR and GCGR). However, these pathways reveal a therapeutic paradox: as GLP-1 and GIP stimulate insulin secretion, GCG signaling exerts opposing effects on glucose and fat metabolism. Here, we highlight the emerging potential of these hormones and their unresolved risks linked to long-term neurological effects.

## Obesity and T2DM background

**Obesity** and **T2DM** have reached epidemic proportions worldwide. Nearly 2 billion individuals are clinically obese and more than 500 million have developed T2DM<sup>1,2</sup>. These conditions are closely linked and frequently occur together due to shared defects in metabolic regulation. Excess adiposity promotes chronic, low-grade inflammation and the accumulation of lipid intermediates in insulin-sensitive tissues, particularly liver and muscle tissues. These metabolites interfere with insulin receptor signaling, progressively reducing insulin sensitivity and driving compensatory hyperinsulinemia. As insulin resistance worsens, glucose uptake becomes inefficient, leading to chronic hyperglycemia and the development of T2DM. Obesity and T2DM consequently predispose patients to cardiovascular, renal, and neurological complications<sup>1,2</sup>.

## GLP-1/GIP/GCG signaling

**GCG** and insulin are produced in pancreatic  $\alpha$  and  $\beta$  cells, respectively, and exert opposing actions to maintain metabolic homeostasis. While insulin promotes glucose uptake by cells, lowering its levels in the blood, it also induces lipogenesis in adipocytes and inhibits GCG secretion. In contrast, GCG (via GCGR activation) stimulates lipolysis and glycogen breakdown into glucose, increasing blood glucose levels<sup>3</sup>.

Complementing this counterbalance, **GLP-1** and **GIP** are gut-produced hormones (also known as incretins) secreted in response to postprandial glucose (Fig. 1)<sup>4,5</sup>. Glucose first initiates insulin secretion by triggering  $\text{Ca}^{2+}$  influx in  $\beta$ -cells. Then GLP-1 increases intracellular cAMP and prolongs  $\text{Ca}^{2+}$  channel activity, thereby amplifying insulin exocytosis only when glucose levels are elevated<sup>4</sup>. This "volume control" mechanism explains why GLP-1RAs became such crucial therapies for treating T2DM, as glucose remains the primary "power switch" for insulin secretion<sup>4</sup>. Beyond  $\beta$  cell signaling, GLP-1 also reduces appetite through central nervous system (CNS) pathways, likely involving  $\text{Ca}^{2+}$ -dependent

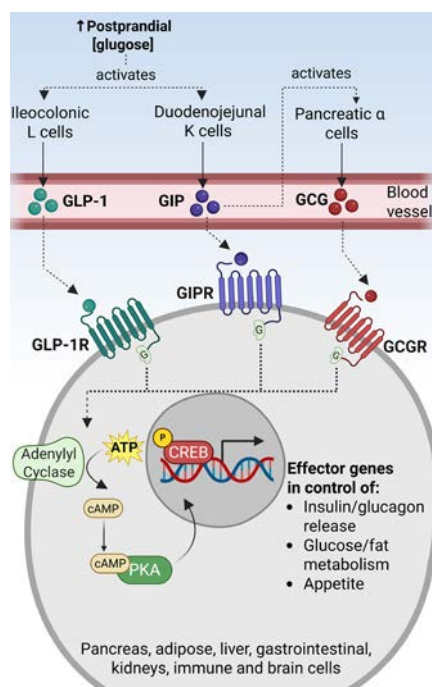


Figure 1. Overview of the CREB-dependent GLP-1R/GIPR/GCGR pathways.

modulation of GABAergic and glutamatergic neurons, although such mechanisms remain only partially defined<sup>6</sup>. GIP, on the other hand, exerts seemingly paradoxical actions. It stimulates insulin production and release in  $\beta$  cells, similarly to GLP-1, while simultaneously promoting GCG secretion from  $\alpha$  cells. This dual activity makes its net metabolic outcome difficult to predict<sup>5</sup>.

The broad distribution of **GLP-1R**, **GIPR**, and **GCGR**, and their ability to regulate genes controlling insulin/GCG secretion, lipid and glucose metabolism, and appetite, make them essential for systemic metabolic homeostasis. They are G-protein-coupled receptors that elevate intracellular cAMP levels and engage the PKA-CREB pathway to regulate genes controlling insulin/GCG secretion, glucose and lipid metabolism, and appetite regulation<sup>4,5,7,8</sup>. Balanced GLP-1R, GIPR, and GCGR activity is therefore essential for systemic metabolic homeostasis, and therapeutic modulation of these pathways has become a central focus of obesity and T2DM drug development<sup>4,5,7</sup>.

## Fine-tuning GLP-1R/GIPR/GCGR

Clinically, GLP-1RAs have demonstrated robust efficacy in T2DM. Agents such as **semaglutide** have achieved marked improvements in glycemic control, setting the stage for subsequent dual and triple receptor agonism strategies (Fig. 2). Indeed, 40 weeks of treatment reduced HbA1c levels (long-term glycemic marker) from diabetic ranges to levels below the diabetic threshold<sup>9</sup>. Beyond glycemic control, clinical trials consistently revealed a marked reduction in body weight (BW). This weight-loss effect, initially observed during T2DM treatment, led to the evaluation of higher doses, at which semaglutide induced ~14% BW loss in 68 weeks and gained approval for obesity management<sup>10</sup>. **Orforglipron**, an oral GLP-1RA, has achieved similar clinical results compared to the injectable semaglutide<sup>11</sup>. Furthermore, agonists simultaneously targeting GLP-1R and GIPR or GLP-1R, GIPR, and GCGR achieved even greater results in BW reduction. Dual GLP-1R/GIPR agonism with FDA-approved **tirzepatide** resulted in ~20% BW loss in 72 weeks<sup>12</sup>. Triple GLP-1R/GIPR/GCGR agonist **retatrutide** has produced ~24% BW reduction within 48 weeks in clinical trials<sup>13</sup>. These treatments illustrate how poly-agonism can achieve greater BW loss in a shorter time.

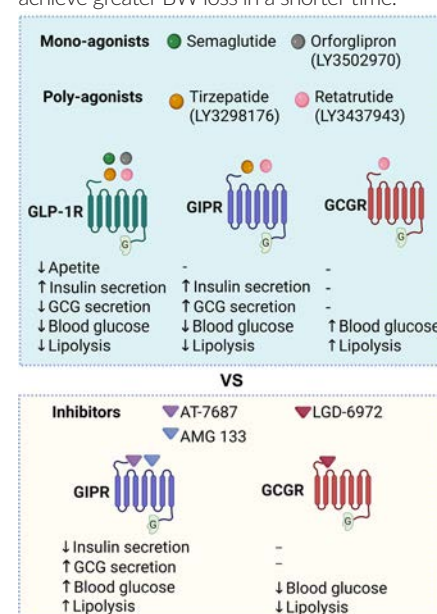


Figure 2. Agonism versus inhibition across the GLP-1R/GIPR/GCGR axis.

Despite the success of poly-agonism, emerging data showing that GIPR and GCGR inhibition can confer metabolic benefits challenge this straightforward agonism paradigm (Fig. 2). AMG-133, a GIPR antagonist fused to two GLP-1 analogue peptides, produced striking BW loss (~16% in 12 weeks) in obese humans and showed similar effects in obese mice and non-human primates (NHPs)<sup>14</sup>. This mirrors earlier findings in which GIPR knockout mice resisted diet-induced obesity<sup>15</sup>, and AT-7687 (GIPR antagonism) combined with a GLP-1RA outperformed either treatment alone in NHPs<sup>16</sup>. A similar paradox emerges for GCGR. While GCGR activation in the context of triple GLP-1R/ GIPR/GCGR agonism with retatrutide markedly reduced HbA1c levels<sup>17</sup>, GCGR antagonism alone using LGD-6972 significantly lowered fasting plasma glucose in humans<sup>18</sup>. Consistently, mice lacking GCGR display reduced food intake, improved glucose tolerance, and elevated endogenous GLP-1 levels<sup>19</sup>.

Across clinical strategies involving either receptor agonism or inhibition, adverse effects predominantly include nausea, vomiting, and/or diarrhea<sup>9-14,16,17</sup>, emphasizing the complexity of receptor modulation in therapeutic design.

These findings highlight a central challenge: defining the optimal activity of GLP-1R, GIPR, and GCGR that maximizes therapeutic benefits while minimizing adverse effects. While GLP-1R agonism reliably promotes favorable glucose and weight outcomes<sup>4</sup>, the contributions of GIPR and GCGR remain more nuanced and condition-dependent<sup>14-19</sup>, underscoring the need for continued research to resolve receptor interplay across different tissues.

## Impacts in the CNS

Beyond their metabolic roles, GLP-1R, GIPR, and GCGR are expressed in CNS cells (e.g., neurons, astrocytes, microglia, oligodendrocytes), where they regulate neuroinflammation, oxidative stress, and cell survival<sup>20</sup>. Receptor activation engages cAMP-dependent pathways, notably PKA/CREB, MAPK/ERK, and Epac, supporting anti-inflammatory, antioxidant, and pro-survival responses (Fig. 3). Anti-apoptotic signaling by these hormones involves upregulation of Bcl-2 and Bcl-xL and inhibition of BAD, p53, and FOXO1/FOXO3, while suppression of the NF-κB pathway limits chronic neuroinflammation. Together, these mechanisms promote neuroprotection<sup>20</sup>. In models of Alzheimer's and Parkinson's diseases, GLP-1R and

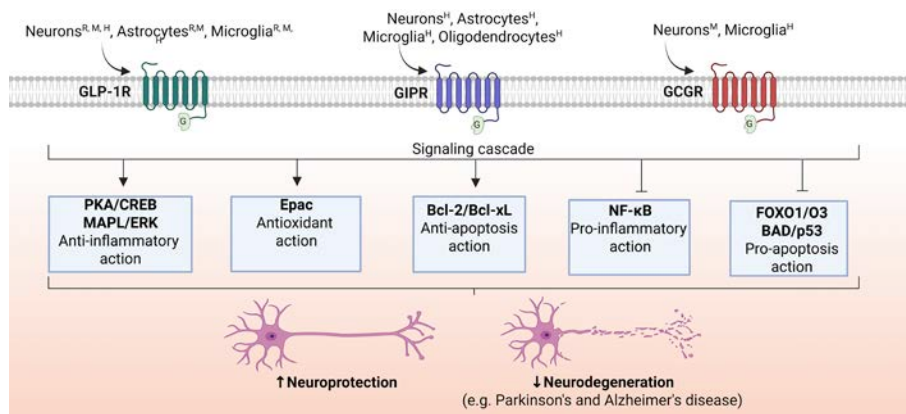


Figure 3. GLP-1R/GIPR/GCGR signaling in neuroprotection. Superscript R,M and H indicates receptor expression evidenced in rats, mice and humans, respectively. Adapted from<sup>20</sup>.

GIPR agonists reduce microglial activation, preserve mitochondrial function, and restore synaptic plasticity, leading to improved cognitive and motor outcomes<sup>21,22</sup>. These findings have been translated clinically as well, with GLP-1RAs such as exenatide, liraglutide, and semaglutide, currently being evaluated in clinical trials for neurodegenerative diseases<sup>22</sup>.

These benefits, however, come with unresolved concerns, and emerging clinical observations highlight this uncertainty: in a matched cohort of 162,253 patients, GLP-1RA treatments were associated with a 98% increased risk of psychiatric disorders, including a 195% higher risk of major depression, a 108% increased risk of

anxiety, and a 106% elevated risk of suicidal behavior<sup>23</sup>. Although mechanisms remain unclear, these findings underscore the urgent need to map long-term CNS consequences of chronic receptor engagement, particularly as increasingly potent dual and triple agonists enter clinical use<sup>23</sup>.

As therapeutic research accelerates, key questions remain unanswered: how do these receptors interact across CNS cell types? What balance of GLP-1R, GIPR, and GCGR activation is optimal and safe for the brain? And how do long-lasting agonists reshape neuroimmune communication over months or years? Addressing these gaps will require models capable of resolving receptor-specific contributions in signaling.

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## Tools for research

InvivoGen's HEK-Blue™ GLP-1R, GIPR, and Glucagon reporter cells provide robust systems to quantify receptor activation through a CREB-inducible SEAP readout. Each cell line expresses a specific human receptor, enabling precise assessment of cellular signaling. Complementing these tools, our bioactive molecules, including GLP-1, GIP, Glucagon, Semaglutide, Tirzepatide, Retatrutide, and Orforglipron, are functionally validated using HEK-Blue™ cells. Together, they offer an integrated platform for studying the GLP-1/GIP/GCG axis in research.

| PRODUCT            | CAT. CODE                |
|--------------------|--------------------------|
| HEK-Blue™ GIP      | <a href="#">hkb-gip</a>  |
| HEK-Blue™ GLP-1    | <a href="#">hkb-glp1</a> |
| HEK-Blue™ Glucagon | <a href="#">hkb-gcg</a>  |
| GLP-1 (7–36) amide | <a href="#">hlc-glp1</a> |
| GIP (1–42)         | <a href="#">hlc-gip</a>  |
| Glucagon (1–29)    | <a href="#">hlc-gcg</a>  |
| Semaglutide        | <a href="#">hlc-sema</a> |
| Retatrutide        | <a href="#">hlc-reta</a> |
| Tirzepatide        | <a href="#">hlc-tirz</a> |
| Orforglipron       | <a href="#">hlc-orfo</a> |