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Review Article

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Gastric Inhibitory Polypeptide (GIP) Receptor: Structure, Mechanism, and Therapeutic Implications in Weight Management

Imran Badshah
Hollywood Private Hospital, Perth, 6009, Nedlands
E-mail: *Badshah.endo@gmail.com*

Abstract

When fatty foods are consumed, the upper gut secretes gastric inhibitory polypeptide, or glucose-dependent insulinotropic polypeptide (GIP).Mounting evidence shows GIP‘s pharmacological and physiological significance in obesity. Both Inhibiting natural GIP or its receptor and administering exogenous GIP agonistsin obesity leads to weight loss through mechanisms including altered energy expenditure(e.g., increased lipolysis) and/or lower energy intake(e.g., reduced appetite).This complex therapeutic potential of GIP is mediated by the brain regulating the energy balance. This review examines the structure, mechanisms, and therapeutic applications of GIPR manipulation, emphasizing its potential to enhance weight loss and glycemic management.

Keywords: Obesity, GIP Agonists, Glycemic management.

1. Introduction

Obesity is a major problem in developed and developing nations, contributing to increased morbidity and mortality. According to the 2022 NHS survey in Australia, 65.8% of adults were overweight or obese (Australian Bureau of Statistics, 2022). Obesity has led to increased co-morbidities such as type 2 diabetes, cancer, and cardiovascular disease, making it a significant concern for modern medicine. While bariatric surgery is the most helpful intervention for achieving sustained and substantial weight reduction (20-30%) (Sjöström et al., 2007), its accessibility and suitability are limited as it entails restructuring the digestive tract. The mechanism includes restricting the quantity of food eaten in one sitting, lowering the patient's appetite and increasing the production of gut hormones that produce fullness to cut in appetite (le Roux et al., 2006). This has drawn interest in creating pharmaco-therapies targeting these gut hormones, providing a less intrusive treatment option for a larger population. Among these, the glucose-dependent insulinotropic polypeptide and its receptor, GIP and GIPR, have become important players in regulating metabolism, directly increasing the metabolism of carbohydrates, which lowers glycemia in people with type 2 diabetes. The majority of obese people who cannot afford, cannot have, or will not have bariatric surgery are particularly interested in these gut hormones (Davies & Tan, 2023). This review will concentrate on the role of GIPR modulation in weight management, examining the current therapeutic strategies and future direction. The review will begin with a quick summary of history. The main body will examine how combining GIP receptor agonists and antagonists may improve weight reduction results.

2. Historical Perspective

In the early 1900s, it was discovered that intestinal mucosa-produced factors could stimulate the release of endocrine pancreatic chemicals, lowering blood glucose levels. These substances, known as incretins, are responsible for between 50% and 70% of the insulin released following oral glucose. The first known incretin hormone was gastric inhibitory polypeptide (GIP), which inhibited stomach acid production in dogs. GIP was later identified as a glucose-dependent insulinotropic polypeptide and potentiated sugar-stimulated insulin production (Fisman & Tenenbaum, 2021).

GLP-1 is a second incretin hormone discovered after sequencing and cloning mammalian proglucagon genes and cDNAs. These two peptides enhance glucose-stimulated insulin secretion in a compounding fashion, possibly contributing to the incretin effect. Combined, they can explain the increasing effect on people (Baggio & Drucker, 2007).

3. GIPR Structure and Expression

GIPR is a member of the G protein-coupled receptor (GPCR) family. It has an N-terminus extracellular domain(ECD), a C-terminal ECD, seven transmembranes (TM) domains with G-protein α, β, γ helices, and activated intracellular transmembrane helix 6(TM6) (Usdin et al., 1993). Figure 1 shows the structure of the G-Protein coupled GIPR-GIP complex. The structure creates a ligand binding site in the plasma membrane that allows signal transmission via transmembrane helices. The N-terminal at the top of the receptor interacts directly with the GIP ligand, and through the C-terminus, the receptor interacts with other proteins. GIPR is expressed in various tissues, including pancreatic α-, β-, and δ-cells, white and brown adipose tissues (Beaudry et al., 2019; Campbell et al., 2022), and regions of CNS (Zhang et al., 2021; Adriaenssens et al., 2019;Kaneko et al., 2019). In pancreatic αand β cells, GIPR activation stimulates glucagon and insulin secretion (Boylan et al., 1999). Beyond its insulinotropic effects, GIP affects lipid metabolism by directing lipid storage in adipocytes. Likewise, GIP receptors in the CNS have a complex role in maintaining energy balance, as evidenced by their involvement in controlling hunger and body weight (Fukuda, 2021).

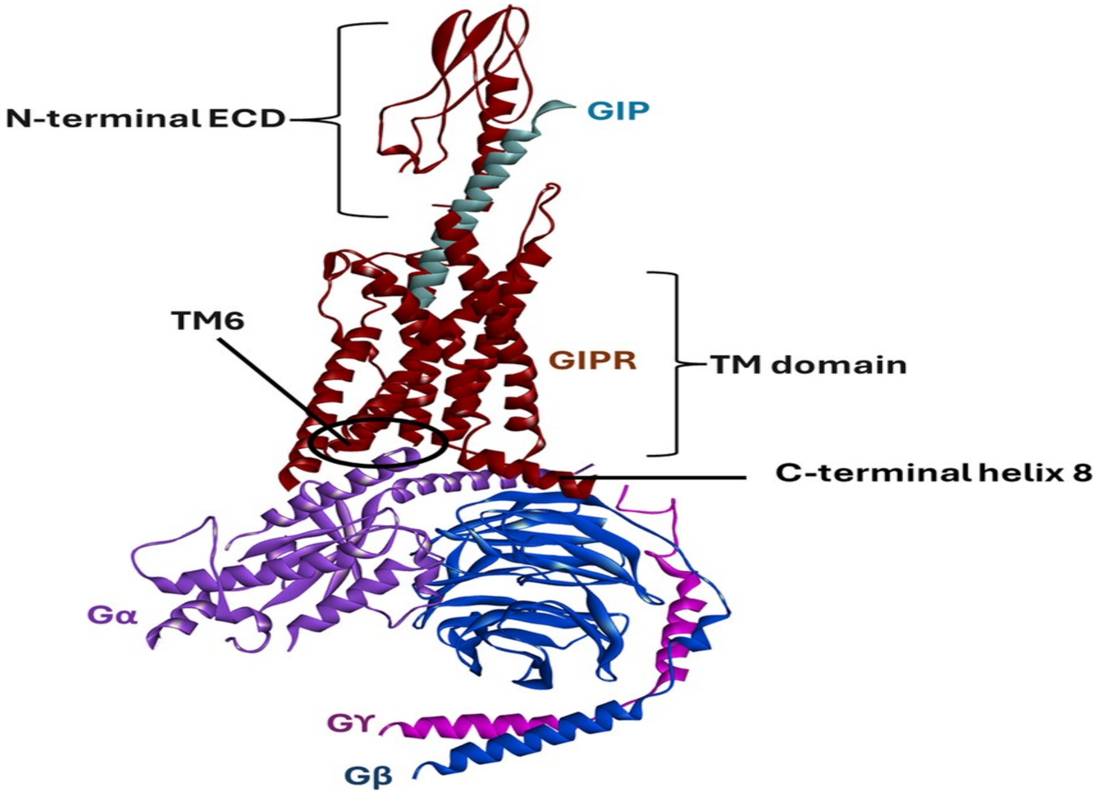

Figure 1: Structure of G protein-bound GIPR complexed with GIP (Aksu et al., 2024)

4. Mechanism of Action

Figure 2 shows the mechanism of action of GIPR, primarily involving the activation of the GIP hormone in the beta cell. GIP targets class II G-protein-bound receptors. These receptors mainly use the activation of phospholipase C/protein C and adenylate cyclase/protein kinase A (PKA) cascades as their signalling mechanism. The pancreatic islets' β-cells have a high quantity of GIP receptors. Insulin exocytosis and calcium ion concentration rise due to GIP binding to its receptor, raising intracellular cAMP levels. cAMP acts as a second messenger and activates Protein Kinase- A (PKA), Exchange Protein Directly Activated by cAMP 2 (EPAC2), and Mitogen-Activated Protein Kinase (MAPK) pathway. These activated pathways increase glucose-stimulated insulin secretion. Sodium ions (Na+) influx and potassium ions (K+) efflux leads to membrane depolarization essential for insulin secretion. MAPK and ERK1/2 maintain β cell mass.AKT/PKB (Protein Kinase B) and B-cell lymphoma two protein (BCL2) inhibit apoptosis. CREB and TORC2 transcribe gene expression for β- cell function. AMP-stimulated protein kinase (AMPK) modulates insulin secretion with SURI, a potassium channel (Mayendraraj et al., 2022). Dipeptidyl peptidase 4 (DPP-4) cleaves GLP-1 and quickly deactivates GIP. However, compared to GLP-1, GIP inactivates more slowly, resulting in a half-life of 5–7 minutes. These important pathways regulate insulin secretion, lipid metabolism, and energy homeostasis (Gupta & Raja, 2022).

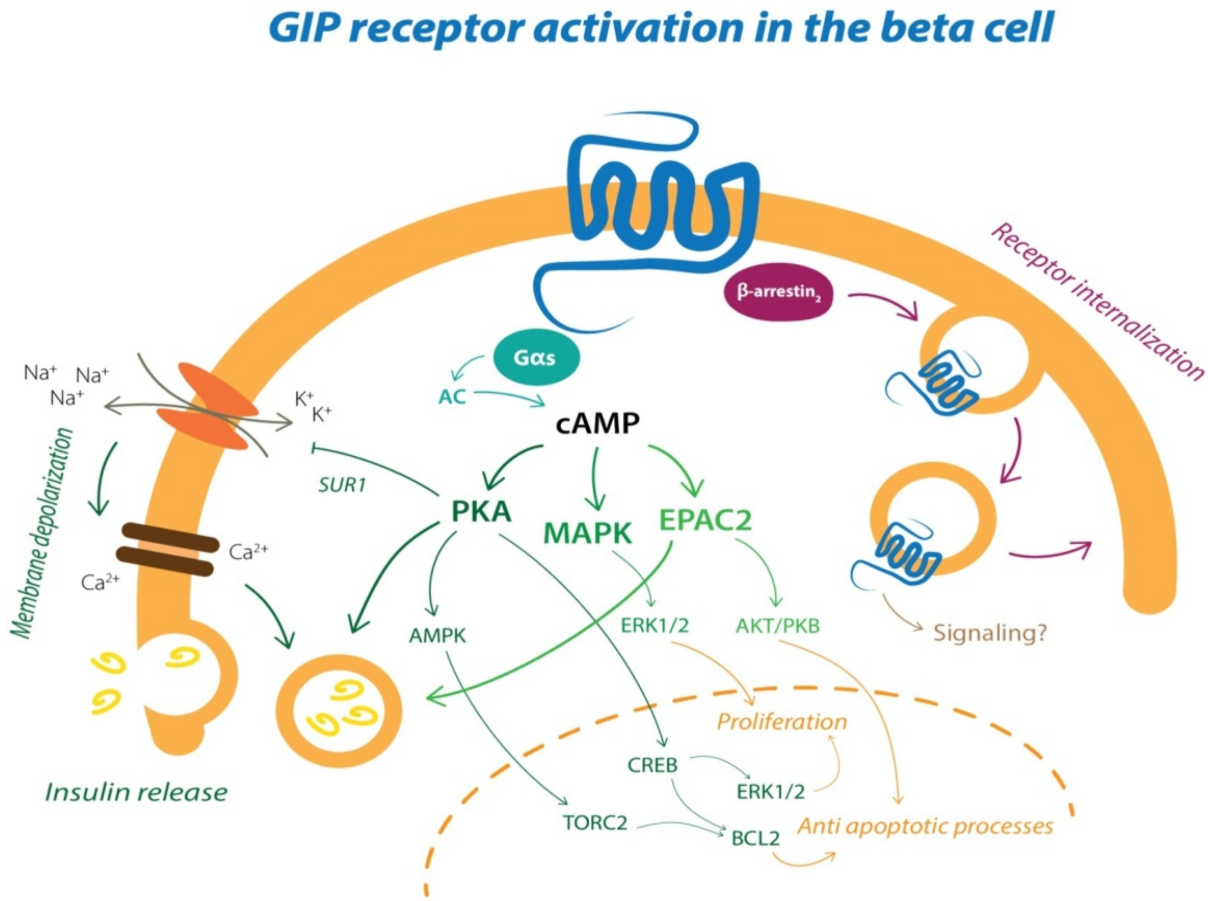

Figure 2. Glucose-dependent insulinotropic polypeptide (GIP) receptor activation in the beta cell (Mayendraraj et al., 2022).

5. GIPR and GLP-1 Agonists

Tirzepatide is a hybrid receptor agonist of the GIP and GLP-1 receptors, suitable for once-weekly subcutaneous injection. GLP-1 receptor agonists have varied effects on obesity control, depending on factors like glucose tolerance and baseline body weight. Tirzepatide has been linked to higher weight loss in T2DM subjects and non-diabetic people, with a mean weight loss of 20% after 72 weeks. Combining stimulation of GIP and GLP-1 receptors may have more significant appetite regulation impacts (Ciardullo et al., 2024). Tirzepatide engages with both receptors. However, the coagonist dramatically alters post-receptor actions of the GLP1 receptor (b-arrestin recruitment and internalization) compared to single agonists (Willard et al., 2020). The GIP-antibody GLP-1 complex has been shown to produce higher cAMP responses (activating both Gas and adenylate cyclase receptors) than single agonists. GIP and GLP-1 receptors create dimers when stimulated (Lu et al., 2021). Insulin signalling, glucose uptake, and the conversion of glucose to glycerol are all improved by GIPR agonism, but lipolysis is increased when insulin is absent. This implies that GIPR agonism over time may alter adipose tissue metabolism in distinct ways when fed and while fasting (Alcaino et al., 2024). Similarly, Liraglutide, one of the approved drugs for obesity, reduces appetite by targeting brain areas that regulate food intake (Müller et al.,2019). In the same way, Semaglutide, a second-generation GLP-1RA, reduce weight by up to 20% at higher doses (Wilding et al., 2021).

6. Multi-Receptor Agonists for the GIPR and GLP-1R

Better clinical results could be obtained by developing medications that combine GLP-1R action with additional hormonal triggers (Campbell et al., 2022). The hypothesis was confirmed by discovering a monomolecular, comparably sized coagonist that combines glucagon receptor (GCGR) action and GLP-1R agonism (Day et al., 2009). This dual agonist outperformed a GLP-1R mono agonist regarding metabolic and weight advantages in preclinical settings. The body has multiple sites where the GIPR is expressed, which may affect the metabolic mechanisms governing body weight and glycemic regulation. Interestingly, body weight drops and hypothalamic leptin signalling increases when an antibody against the GIPR is administered intracerebro ventricularly (Mentis et al., 2011). Through the CNS's GIPR expression, GIPR agonism does decrease dietary intake (Zhang et al., 2021). Hypothalamic nerves that inhibit food intake and hindbrain nerves that have an anti-emetic impact are two hypothesized explanations for this (Adriaenssens et al., 2019). By promoting healthy fat storage and preventing ectopic storage in less efficient storage locations like the liver or muscles, GIPR agonism in adipose tissue strengthens the lipid buffering capacity of white adipose tissue (Samms et al., 2020), enhances insulin sensitivity, and slows the development of insulin resistance linked to Obesity (Klein et al., 2022). Moreover, when GLP-1R and GCGR agonism are combined, energy expenditure is increased to optimize weight reduction. It may address nonalcoholic fatty liver disease by utilizing the lipid oxidative characteristics of glucagon in hepatocytes (Jiang et al., 2022). Additionally, several glucagon/ GLP1 coagonist formulations are advancing through clinical trials in individuals with obesity and diabetes (Table 1), evaluating the translational perspective of this initial multi-receptor agonist (MRA) strategy.

Table 1: Ongoing clinical trials for multi-receptor agonists (Campbell et al., 2023).

Compound	Stage	Published Results
GLP1R/GCGR		
LY3305677	phase 1b	Jiang et al., 2022
Cotadutide	phase 2b	Nahra et al., 2021
BI-456906	phase 1	-
Efinopegduite	phase 2	Alba et al., 2021
ATL-801	phase 1	-
GLP1R/GIPR		
Semaglutide + GIPR agonist	phase 1	-
GLP1R/GIPR/GCGR		
SAR441255	phase 1	-
LY3437943	phase 2	Coskun et al., 2022
HM15211	phase 2	-
GLP1R/amylin		
Semaglutide + cagrilintide	phase 1b	Enebo et al., 2021

7. GIPR Antagonists

In diet-induced obesity, leptin sensitivity is often impaired, limiting its effectiveness in suppressing appetite. Moreover, GIPR overstimulates insulin release and enhances fat deposition in adipose tissue (Gögebakan et al., 2015). GIPR activation also increases the expression of SOCS3, a protein that inhibits leptin signalling, which results in increased hunger and weight gain. Blocking GIPR can reverse these effects by reducing SOCS3 expression and restoring leptin sensitivity. For instance, infusion of GIPR antagonist Gipg013 results in appetite reduction and weight loss. Chronic GIPR antagonist treatment has also enhanced insulin sensitivity (Killion et al., 2018). However, this effect may be due to the weight reduction rather than the GIPR antagonist's direct effects (Davies & Tan, 2023). GIPR antagonist Pro3 GIP has been shown to restore insulin sensitivity, increase glucose tolerance, and treat islet hypertrophy and cell hyperplasia linked to Obesity (Gault et al., 2005). The peptide-based GIPR antagonist AT-7687 holds great promise for the treatment of obesity. With the GLP-1 analogue liraglutide, AT-7687 reduced weight more than a placebo and enhanced metabolic markers like LDL cholesterol and glycemic control without sacrificing tolerability (Jensen et al., 2024). Amgen is also a GIPR antagonist in conjunction with GLP-1 R agonist. For example, AMG133, a GLP-1 R agonist/GIPR antagonist antibody, induced a sustained weight loss of almost 8 kg over 100 days after a single injection. Monthly administrations of 420 mg of this particular peptide resulted in over 15% weight loss after 90 days, surpassing tirzepatide's 8% weight reduction at 12 weeks. Over a 120-day monitoring period, there was no noticeable weight gain after discontinuing injections (Lu et al., 2021). Table 2 summarizes the examples of more such GIPR antagonists and their impacts on body weight and other relevant parameters.

Table 2: Summary of the effects of different interventions targeting the GIP/GIPR on body weight and compositions (Campbell, 2021)

Specific Manipulation	Diet/Background	Effect on Body Weight/ Composition	Other Effects
(Pro3)GIP (Antagonist)	HFD	Reduces gain (fat mass)	
(Pro3)GIP (Antagonist)	Obese/ob/ob	Decreased weight (fat mass)	
GIP(3-30) (Antagonist)		No impact	
Acyl GIPR antagonist		No impact	
Gipg013 (Antibody, IP)	HFD	Reduced gain (fat mass)	Reduced food intake
Gipg013 (Antibody, IP)	Obese	No impact	Reduced food intake
Gipg013 (Antibody, ICV)	Obese	Reduced weight (fat and lean mass)	Reduced food intake
Mu-GIPR-Ab (Antibody)	HFD	Reduced gain (fat mass)	Reduced food intake
Mu-GIPR-Ab (Antibody)	Obese	Decreased weight (fat mass)	Reduced food intake

*Note.*HFD: high-fat diet; RT: room temperature; BMT: bone marrow transplant; IP: intraperitoneal; ICV: intracerebroventricular.

8. Potential Adverse Effects

Therapeutic agents targeting GIPR, including agonists, antagonists, and multi-receptor agonists, enhance insulin secretion, improve glycemic control, and cut body weight. However, the dual role of GIPR in metabolic regulation presents the challengeof receptor desensitization. *In vitro* GIPR desensitization from chronic GIPR activation mimics GIPR antagonism (Davies & Tan, 2023). As seen in 3T3-L1 adipocytes, this desensitization is thought to be caused by decreased GIPR regenerating to the cell-membrane periphery after initial activation and internalization. (Mohammad et al. 2014). Gastrointestinal side effects have also been reported. Nausea, vomiting, and diarrhoea are common, limiting long-term efficacy (Killion et al., 2020a).

9. Conclusion

The Glucose-Dependent Insulinotropic Polypeptide Receptor (GIPR) has become a key target in dealing with obesity and associated metabolic disorders. Its role in glucose metabolism, energy balance, and lipid storage reflects its therapeutic prospects. Meanwhile, GIPR agonists, antagonists, and multi-receptor agonists improve glycemic control, increase insulin sensitivity, and contribute to weight reduction. However, these therapies are not without challenges, including gastrointestinal side effects, receptor desensitization, and patient response variability. These findings draw attention to the need for patient-specific strategies and demonstrate the intricacy of GIPR pathways. By addressing these issues, GIPR-targeted treatments may help in the battle against obesity.

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