POINT

A Contemporary Rationale for Agonism of the GIP Receptor in the Treatment of Obesity

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In combatting the obesity crisis, leveraging mechanisms that lower body weight is critical. The finding that treatment with tirzepatide, a glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1) receptor agonist, produces profound weight loss highlights the value of activating the incretin receptors. Supporting this, recent studies have revealed mechanisms by which GIP receptor (GIPR) activation is beneficial in pancreatic islets, the central nervous system (CNS), and adipose tissue. Paradoxically, a hypothesis has emerged that GIPR antagonism could be an additional option in treating obesity. This concept stems from concern that GIP facilitates lipid uptake and storage in adipose tissue, although the lipid-buffering capacity of adipocytes versus other cell types is metabolically favorable. In this article, we highlight the natural physiology of the incretins, noting GIP as the primary incretin. In the CNS, GIPR agonism attenuates nausea and suppresses appetite, features that also help GLP-1 receptor agonism promote a negative energy balance. Further, we provide rationale that, in protecting against ectopic fat distribution and augmenting substrate utilization to promote insulin sensitivity, GIPR activity in adipose tissue is advantageous. Collectively, these attributes support GIPR agonism in the treatment of obesity and metabolic disease.

EMERGENCE OF GIPR AGONISM

The case for agonists of the glucose-dependent insulinotropic polypeptide receptor (GIPR) in treating obesity is supported by compelling evidence at the intersection of metabolic physiology and translational pharmacology: the long-established role of GIP as an incretin hormone and recently reported findings from pharmacology studies revealing the consequences of activating the GIPR in the brain and adipose tissue, along with historical precedence where other peptide hormones have served as templates for therapeutic agonists. In drug discovery, taking direction from Mother Nature to engineer molecules that possess pharmacological characteristics similar to those of naturally occurring ligands has often been a successful therapeutic approach—perhaps best exemplified by agents targeting members of the class B1 family of G-protein–coupled receptors (GPCRs), the phylogenetic classification that includes the GIPR (1). Most of the class B1 GPCR systems were characterized nearly three decades ago (2), and several native ligands for these receptors have been foundational for developing therapeutic agonists to treat a variety of conditions. These include parathyroid hormone for osteoporosis (3), growth hormone (GH)-releasing hormone for GH deficiency (4), glucagon-like peptide 2 for short bowel syndrome (5), and glucagon-like peptide 1 (GLP-1) for type 2 diabetes (T2D) and obesity (6–8). For GIP, counter to the aforementioned ligands, the pursuit of medicines containing GIP receptor agonist pharmacology took longer to materialize.

Although GLP-1 and GIP were both shown to be nutrient-stimulated hormones from the gastrointestinal tract that cooperate to augment postprandial insulin secretion, only GLP-1 receptor (GLP-1R) agonists were initially sought after. This was largely due to findings from early infusion studies demonstrating that native GLP-1 lowered hyperglycemia in patients with T2D, whereas GIP showed a comparably weaker effect (9). The lack of interest was further perpetuated when the physiological basis underlying the inability of *Gipr* null mice to develop obesity was misinterpreted in the initial report (10)—a phenomenon now known to result from thermal stress. However, the narrative around GIPR agonism finally pivoted when it was demonstrated that sensitivity to GIP could be partially

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restored upon an improvement in glycemic control (11), prompting interest in investigating the therapeutic potential of GIPR agonism. Soon thereafter, the interest in GIPR activation came to fruition when a number of patents disclosed the discovery of various molecules containing GIPR agonist activity, where both GIPR monoagonists and dual GIP and GLP-1 receptor agonists were described (12–17) (Fig. 1).

During this time, there were reports from studies that the weight loss effects of GLP-1R activation can be enhanced by coadministration of a GIPR agonist (18), a complement to the earlier finding that sensitivity to GIP for insulin secretion is recovered in response to improved metabolic control. Furthermore, this effect on body weight was recapitulated in studies of single-agent dual GIP and GLP-1 receptor agonists (18,19). For one molecule, the newfound efficacy translated into the clinic as studies of the GIP and GLP-1 receptor agonist tirzepatide showed substantial improvements in glycemic control and chronic weight management in patients with T2D and obesity (20). The imbalanced pharmacology of tirzepatide, favoring activity for the GIPR over the GLP-1R (21), may account for its efficacy. As such, the importance of the GIPR activity of tirzepatide in relation to these treatment outcomes prompted new interest in understanding how activation of the GIPR provides therapeutic benefits (22).

GIPR AGONISM IN THE PANCREATIC β-CELL ENHANCES INSULIN SECRETION

Studies performed >40 years ago showed how incretin hormones enhance insulin secretion to manage the postabsorptive state (23–26). The pancreatic β-cell is among the few cell types that express receptors for GIP and GLP-1 (27,28). Notably, the severe glucose intolerance manifested in mice lacking both receptors ($Gipr^{-/-}$:$Glp1r^{-/-}$) emphasized the crucial role of the incretin system (29). In humans, the incretin effect is impaired in T2D (30), owing to decreases in incretin concentrations, reduced β-cell responsiveness, or a combination of both (11,31,32). The impaired incretin system is believed to be a consequence of the disease pathology (33), and thus as originally hypothesized (34), treatment with GLP-1R agonists has proven effective at improving glycemic control.

Emerging evidence points to GIP as the predominant incretin (35,36), emphasizing the physiologic relevance of incorporating GIPR agonist pharmacology into therapeutic approaches. From a mechanistic perspective, a lack of tachyphylaxis in GIP-induced insulin secretion underlies the potential of GIPR agonism to sustain glycemic control (37). Further support for GIPR agonism comes from a clinical study where participants with T2D were administered either the selective GLP-1R agonist semaglutide or tirzepatide (Fig. 1). Tirzepatide treatment led to 27%–46% of

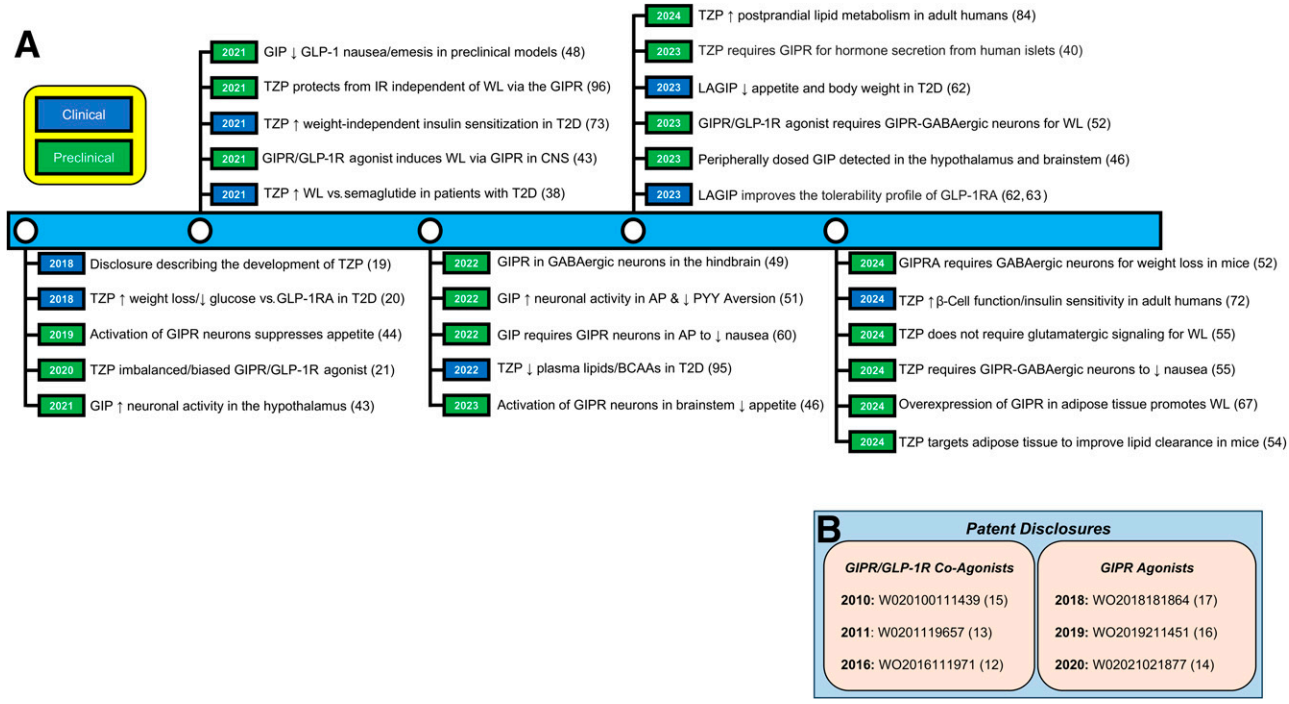

Figure 1—The case for GIPR agonism is founded on the natural incretin actions of native GIP and bolstered by new findings showing agonist-driven effects in the brain and adipose tissue. *A*: Key clinical studies and preclinical mechanistic findings are indicated, highlighting discoveries since the initial report of the GIP and GLP-1 receptor agonist tirzepatide in 2018. *B*: Patent publications describing the discovery of compounds containing GIPR activity. GIP, glucose-dependent insulinotropic polypeptide; GIPRA, GIP receptor agonist; IR, insulin resistance; LAGIP, long-acting GIP; TZP, tirzepatide; WL, weight loss.

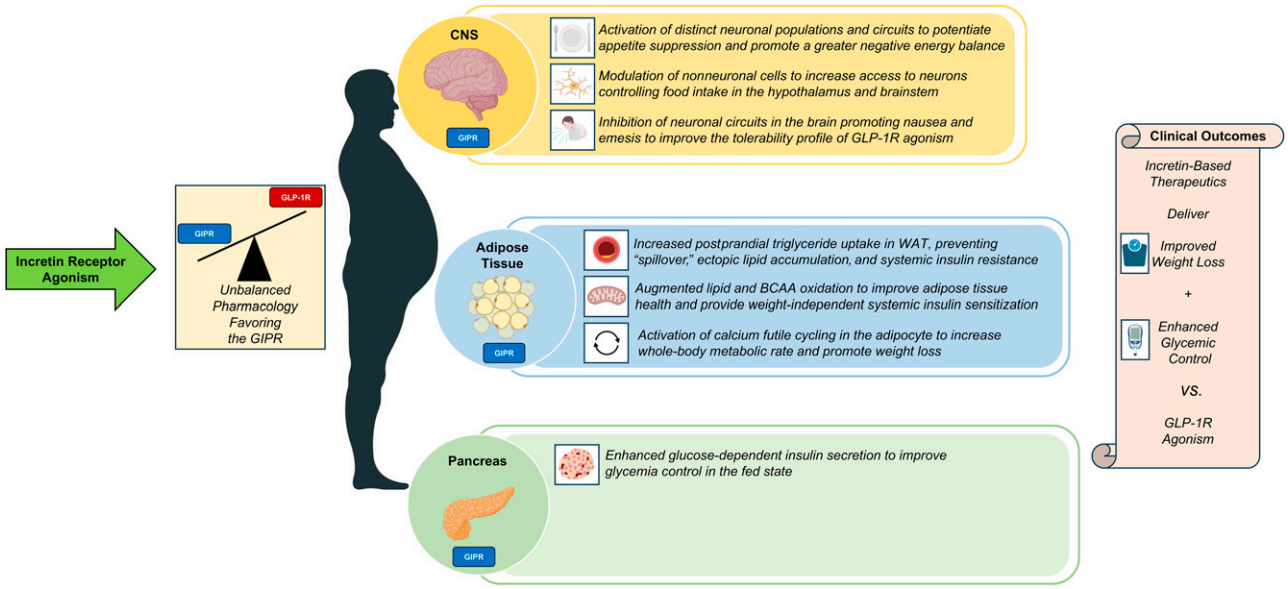

Figure 2—Potential mechanisms by which GIPR agonism may contribute to the efficacy of multireceptor agonism in weight management. In the CNS, GIPR agonism is implicated in the attenuation of nausea and the suppression of appetite, promoting a negative energy balance for sustaining weight loss. In adipose tissue, GIPR agonism improves lipid handling and augments BCAA catabolism, both of which are insulin sensitizing. Further, recent data from transgenic mice point to potential GIPR-mediated effects on energy expenditure via futile calcium cycling. GIPR, glucose-dependent insulinotropic polypeptide receptor; GLP-1R, glucagon-like peptide 1 receptor.

patients achieving normoglycemia (HbA_{1c} <5.7%), compared with 19% for patients treated with semaglutide (38). For tirzepatide, the benefit of GIPR agonism may be due to an "additive" pharmacological effect of targeting both receptors, prompting a more robust insulinotropic response. Alternatively, the impact of GIPR agonism could also result from heterogeneity in incretin receptor activity across patients, where having both GLP-1R and GIPR agonist pharmacology can accommodate a spectrum of incretin sensitivity. Precedence for the latter is supported by studies in humans where variable sensitivity to GLP-1 for insulin secretion was reported (39), and ex vivo experiments of human islets that show variation in the insulinotropic responses of GIPR versus GLP-1R agonism across donor samples (40) (Figs. 1 and 2). The phenomenon of heterogeneity in the incretin axis needs to be broadly investigated across different groups of patients, but from the perspective of looking at agents that offer the potential to enhance the insulinotropic function of pancreatic β-cells, the pharmacological choice of agonism of the GIPR seems strong.

GIPR AGONISM IN THE BRAIN MODULATES APPETITE SUPPRESSION

Similar to improvement in glycemic control, dual agonism of the incretin receptors delivers greater weight loss than GLP-1R monoagonism (41), highlighting the benefit of GIPR activation on weight loss. This has sparked major interest in understanding how next-generation medicines with GIPR pharmacology for excess adiposity mediate their efficacy (22). In comparison with the established actions of GLP-1R agonists to suppress appetite (42,43), there was little understanding of how activation of the GIPR in the central nervous system (CNS) contributes to weight loss (44). Consequently, ideas were inspired on how modulation of the GIPR in the brain potentiates the anorectic activity of GLP-1R agonism. Below, we highlight key findings that fuel new hypotheses (Fig. 2), together supporting the case for GIPR agonism in the brain.

During the past 6 years, several laboratories have investigated whether GIPR activity in the brain is required for the full weight loss efficacy of multifunctional agents (Fig. 1). The GIPR is expressed by several cell types (e.g., neurons, oligodendrocytes, endothelial, mural, and vascular smooth muscle cells), in hypothalamic (e.g., the arcuate nucleus) and brainstem (e.g., area postrema [AP]) nuclei (45–47). A major observation was the finding that the GIPR has a separate and distinct expression profile in comparison with the GLP-1R (46), with only a subset of cells expressing both of the incretin receptors in the hypothalamus and hindbrain (48). The GLP-1R is predominantly found in glutamatergic neurons (49), while the majority of GIPR-expressing neurons in the hypothalamus and brainstem are GABAergic (48,50,51).

Consistent with their central mode of action, peripherally administered GIPR-based therapeutics can be detected in the hypothalamus (e.g., median eminence [ME] and arcuate nucleus) and brainstem (AP and nucleus of the solitary tract) (45,48,52) and stimulate neuronal activity (cFOS) in these areas (45,53). Further, chemogenetic activation of $GIPR^{+}$ neurons in the hypothalamus and brainstem suppresses food intake in mice (46,48). In addition, central and

peripheral administration of a GIPR agonist alone reduces food intake via enhanced satiation (e.g., reduced meal size), and works in combination with an array of satiety agents (e.g., GLP-1R agonists and PYY mimetics) to provide synergistic weight loss (45,53–55). Deletion of the GIPR in the CNS attenuates the weight loss efficacy of GIPR monoagonism and dual incretin receptor agonism (45), highlighting that activation of the GIPR is required for the full weight loss efficacy of multireceptor agonism. Notably, hypothalamic GIPR signaling is not required for the additive effects of GIPR and GLP-1R agonism in inducing weight loss (48)—whereas other knockout studies have shown that GIPR activity is necessary in GABAergic neurons (52) but not glutamatergic neurons (56), to inhibit food intake and reduce body weight. Collectively, the GIPR is expressed by several cells found in the hypothalamus and brainstem that can extinguish appetite. Also, weight loss from GIPR agonism may be driven by the recruitment of unique neuronal populations and/or downstream neuronal circuitry, in comparison with the activation of the GLP-1R.

A barrier to realizing the benefits of GLP-1R agonist therapy is the occurrence of nausea and emesis that can be induced by these medicines (57,58). Thus, leveraging mechanisms that offset the tolerability issues associated with incretin therapy, without negatively impacting their anorectic activity, can offer therapeutic value (57,59). Reports from studies in ferrets, dogs, and shrews that GIPR agonism prevents emesis (60) have led to the hypothesis that GIPR agonism alleviates the nauseating activity of GLP-1R agonists (22,59). Indeed, GIPR agonist therapies have been shown to potentiate the suppression of appetite induced by various anorexigenic agents (e.g., GLP-1R agonists and PYY), while attenuating nausea and emesis, across multiple species (e.g., mice, rats, ferrets, shrews, and dogs) (50,51,53). These effects do not require vagal signaling (60) but are lost in the absence of GIPR activity in GABAergic neurons (56) and following ablation of GIPR-expressing neurons in the AP (61). The translational relevance of these findings is highlighted by studies in people with obesity and T2D showing that GIPR agonism reduces body weight and attenuates nausea and emesis induced by a GLP-1R agonist (62,63). From a mechanistic perspective, the simultaneous anorectic and antiemetic actions of GIPR agonism align with the neuroanatomy of the GIPR, where it is expressed by GABAergic inhibitory neurons that project locally to inhibit glutamatergic excitatory neurons in the AP, thereby reducing activation of a neural circuit that progresses through from the AP to the nucleus of the solitary tract, lateral parabrachial nucleus, and central nucleus of the amygdala. We note, however, that further exploration is required to fully elucidate the specific neuronal substrates facilitating the suppression of caloric intake/prevention of nausea.

Since GLP-1R agonists target the GLP-1R in the brain via circumventricular organs (e.g., the ME and AP) (64), it is notable that expression of the GIPR is enriched in oligodendrocytes of the ME and in tanycytes lining the third ventricle that function to regulate the access of circulating factors to the medial basal hypothalamus (46,65). Treatment of mice with a GIPR agonist has been shown to augment the uptake of selective GLP-1R agonists to anorexigenic neuronal populations that express the GLP-1R (66). Consistent with this, negating GIPR signaling in oligodendrocytes prevented a GIPR agonist from delivering synergistic weight loss that is normally observed in combination with GLP-1R agonism in obese mice (66). These findings suggest that, in addition to directly potentiating the anorectic action of GLP-1R agonism, stimulation of the GIPR in nonneuronal cells (e.g., oligodendrocytes and tanycytes) in the CNS may increase the uptake and access of multifunctional agents targeting the incretin receptors, thereby facilitating greater suppression of appetite (66).

GIPR AGONISM IN ADIPOSE TISSUE IMPROVES INSULIN SENSITIVITY

Recent human genetic analyses and clinical findings showing that blockade of the GIPR may promote weight loss (67,68) have fueled the hypothesis that GIP is an obesogenic factor (69). However, it is important to recognize that GIP does not increase food intake or reduce metabolic rate to promote a positive energy balance (44). By contrast, treatment of preclinical models and humans with GIP-based mimetics suppresses appetite to stimulate weight loss and augment lipid clearance to improve systemic insulin sensitivity (70), effects that are metabolically favorable in the management of excess adiposity.

As noted above, treatment with tirzepatide delivers better glycemic control in patients with T2D versus GLP-1R agonist monotherapy (38). Whereas this improvement is associated with enhanced insulin secretion and reduced insulin resistance secondary to weight loss (71), there is also evidence suggesting that a component of the insulin-sensitizing efficacy of tirzepatide treatment is weight independent (72), and it has been hypothesized that activation of the GIPR in adipose tissue is responsible for this (22). Subcutaneous white adipose tissue (WAT) plays a key physiological role in maintaining whole-body insulin sensitivity by functioning as a daily buffer of dietary lipid, storing excess lipids in the fed state, and releasing stored energy in the fasted state (73,74). Hence, exceeding the energy storage capacity of the adipocyte is at the forefront of the links of excess adiposity, systemic insulin resistance, and the development of T2D (75–78). The GIPR is expressed by multiple cell types in adipose tissue (e.g., endothelial cells, mesothelial cells, pericytes, and a subset of adipocytes) (79,80–82). In addition to its insulinotropic effects, GIP is a nutrient-induced factor that coordinates the storage of dietary fat in adipose tissue (83–85), with infusion studies in humans showing that GIP reduces plasma triglycerides by promoting their disposal in WAT (69,86–88). By contrast, pharmacology studies have demonstrated that blockade of GIP signaling in the fed state increases circulating triglycerides in rodents

and humans (83,85), along with ectopically increasing hepatic lipid content in obese rodents (85). Recent clinical studies have shown that tirzepatide improves postprandial lipid clearance in patients with T2D (70). Mechanistically, GIP facilitates the healthy storage of dietary lipids by enhancing adipocyte-specific insulin sensitivity (89), increasing the activity of lipoprotein lipase (LPL), augmenting WAT perfusion, and promoting glucose uptake in WAT (55,79,90–92). Notably, the role of GIP as a regulator of postprandial lipid homeostasis has fueled the hypothesis that therapeutic activation of the GIPR in the fat cell may improve adipose tissue health and function to safely store excess energy, prevent lipid "spillover," and curb the development of systemic insulin resistance (22) (Figs. 1 and 2).

In obesity, several factors are postulated to underlie the link of excess weight gain, adipose tissue dysfunction, and systemic insulin resistance: hyperlipidemia/lipotoxicity, impaired branched chain amino acid (BCAA) catabolism, inflammation, endoplasmic reticulum stress, and mitochondrial dysfunction (76,93–95). In clinical studies of tirzepatide for the treatment of T2D, patients have shown an improvement in insulin sensitivity that is accompanied by reductions in circulating lipids and BCAAs/branched chain keto acids, along with elevated biomarkers that are indicative of improved adipose tissue health (72,96). Consistent with these findings, peripherally dosed tirzepatide or a GIPR agonist to rodents can be detected in adipose tissue (55), and both have been shown to stimulate cAMP-dependent modulation of carbohydrate, lipid, and amino acid metabolism in murine and human adipocytes (55,79,85). Furthermore, chronic treatment of obese, insulin-resistant mice with GIPR agonist–containing ligands has been shown to reduce circulating lipids/BCAAs/branched chain keto acids, increase the catabolism of BCAAs and oxidation of lipids in WAT and brown adipose tissue, and increase plasma levels of the insulin-sensitizing adipokine adiponectin (55,94,97). From the perspective of looking at therapeutic end points, GIPR agonism ameliorates hepatic steatosis, augments glucose disposal in peripheral tissues, and improves systemic insulin sensitivity alone and in combination with known insulin sensitizers (e.g., the thiazolidinedione rosiglitazone) in obese rodents without changes in body weight (55,94,98). Knockout mouse studies indicated that GIPR-based pharmacotherapies require engagement of the GIPR to deliver the weight-independent insulin sensitization in obese mice (97). Overexpression of the GIPR in adipocytes activates futile calcium cycling to promote the combustion of excess calories, helping to promote weight loss (79). Furthermore, this method of adipocyte GIPR activation triggers a metabolic memory effect, which maintains weight loss after the transgene has been switched off (79). Together, there are several pathways engaged by GIPR agonism in adipose tissue that can potentially drive improved metabolism and protection against insulin resistance; future studies are required to further disentangle how GIPR agonism regulates adipose tissue health and function.

DISCUSSION

Conceptually, the design of therapies that restore incretin action, help reduce caloric intake, and properly partition lipid storage would be beneficial for treating metabolic disease, especially since obesity increases the risk of developing diabetes (99). As described above, in recent years, there has been a surge of evidence indicating that each of these attributes can be realized with use of ligands activating the GIPR. However, as sometimes occurs in intensely studied areas of science, there is not unanimity on the pharmacological approach for targeting the GIPR. Whereas there is little argument about whether satiety-promoting effects in the CNS are desirable, debate surrounds the most advantageous pharmacological strategy for the GIPR in the periphery. In our view, therapeutic mechanisms that improve the insulinotropic response and also enhance insulin sensitivity are most compelling because such treatments target the major disease impairments. Likewise, opposing approaches such as GIPR antagonism could run the risk of exacerbating one or both of these pathologies, especially in large, heterogeneous populations such as those with obesity where two-thirds of individuals may have prediabetes (100). Therefore, we advocate the case for agonism of the GIPR, where such an approach enhances insulin secretion while also warding against ectopic fat distribution. Furthermore, the central effects of GIPR agonism uniquely complement the anorexigenic actions of GLP-1R agonists, thereby synergistically facilitating weight loss. In short, the choice of agonism of the GIPR is appealing, since it improves glycemic control and reduces adiposity—both beneficial in combating metabolic disease.

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