Therapeutic Targeting of the GIP Receptor—Revisiting the Controversies

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Current and emerging strategies to therapeutically target weight management include pairing agonism of the glucagon-like peptide 1 receptor (GLP-1R) with either agonism or antagonism of the glucose-dependent insulinotropic polypeptide receptor (GIPR). On the surface, these two approaches seem contradictory, yet they have produced similar effects for weight loss in clinical studies. Arguments that support the rationale for both approaches are made in these point-counterpoint articles, founded on preclinical studies, human genetics, and clinical outcomes. Here, we attempt to reconcile how two opposing approaches can produce similar effects on body weight by evaluating the leading hypotheses derived from the available evidence.

The point-counterpoint articles published in this issue of *Diabetes* deliberate the rationale for agonizing the glucose-dependent insulinotropic polypeptide receptor (GIPR) (1) or antagonizing the GIPR (2) in consideration of therapeutic approaches to treating obesity. The case for agonism is founded on substantial preclinical and clinical data, bolstered by the clinical efficacy of tirzepatide (3,4), a co-agonist for both the GIPR and glucagon-like peptide 1 receptor (GLP-1R) (5). The authors point to the actions of GIPR agonism to enhance insulin secretion, improve insulin sensitivity, and reduce inflammation in adipose tissue, as well as independent and combined effects with GLP-1R agonism in the brain to reduce food intake and decrease aversive responses, as supporting evidence for GIPR agonism.

On the other side, support for GIPR antagonism comes from loss-of-function genetics in mice and human studies of *GIPR* variants with impaired activity that associate with reduced body mass, along with preclinical studies and emerging human data demonstrating that chronic GIPR antagonism resists weight gain and enhances the weight-lowering effects of GLP-1R agonism. The conundrum that we attempt to resolve is how two diametrically opposing pharmacological approaches can produce the same outcome of reducing body weight. Layered into this discussion are the factors beyond weight loss that should be considered in deciding the relative merits of these two approaches. Resolving some of these unanswered questions will require additional experimentation, as well as the results of forthcoming clinical trials. Herein, we discuss GIPR agonism versus antagonism in the context of metabolic disease therapeutics.

The current major focus for comparing the results of GIPR agonism versus antagonism is weight loss. GIPR monoagonism reduces food intake and body weight in preclinical models (6) and in humans (7). Studies in mice reveal that GIPR agonism requires engagement with GIP receptors within the central nervous system (CNS) to lower body weight (8). Interestingly, deletion of GIPR alone in the mouse CNS also provides protection against diet-induced obesity (8), recapitulating the phenotype exhibited by the high-fat diet–fed whole-body–*Gipr* knockout mouse (9). Collectively, these observations capture the confusion in directional targeting of the GIPR, with both gain- and loss-of-function strategies decreasing body weight.

To establish precisely where the key GIPR-dependent signaling cascades occur within the CNS that are coupled with reduction of food intake, further resolution is required, with potential targets including neurons in the hypothalamus, hindbrain, and nonneuronal populations that

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potentially govern activity in these areas (10–14). Whether GIPR agonism and antagonism in each of these areas differentially suppress food intake through overlapping or distinct pathways remains unclear. One focus of particular interest is the collection of GABAergic neurons in the hindbrain. Here, GIPR agonism elicits antiaversive effects in the context of a range of noxious or aversive stimuli, including GLP-1R agonism (Fig. 1*A*) (12,15,16). These antiaversive effects target populations of neurons different from those transducing anorectic signals and appear to translate to healthy human participants treated with a single dose of a long-acting GIP analog together with liraglutide (17). This points to an inhibitory tone originating from GIPR$^+$ neurons to dampen the activity of GLP-1R neurons responsible for transducing aversive signals. Alternatively, GIPR agonism may attenuate aversive responses downstream of GLP-1R neurons. Interestingly, deletion of *Gipr* in GABAergic neurons enhances the activity of GLP-1R agonism to reduce food intake and body weight and these GABAergic neurons are also critical for the enhanced weight loss activity of dual incretin agonists in comparison with GLP-1R monoagonism (14). In these same studies loss of the antiaversive properties of GIPR agonism in GABAergic neurons was also reported. Hence, we can surmise that one potential mechanism of basal GIPR activity in the hindbrain is to inhibit the satiating effects of GLP-1R agonism. Reducing this inhibitory tone, potentially through naturally occurring human GIPR variants with reduced signaling properties, or via pharmacological GIPR antagonism, could enhance the activity of anorectic GLP-1R signaling pathways, thereby increasing the sensitivity to and effectiveness of endogenous GLP-1 or pharmacological GLP-1R agonism (Fig. 1*B* and *C*). This hypothesis aligns with reports of effective weight loss with bispecific molecules that simultaneously block GIPR while activating the GLP-1R (18–20). Theoretically, this approach of using GIPR antagonism might reduce the

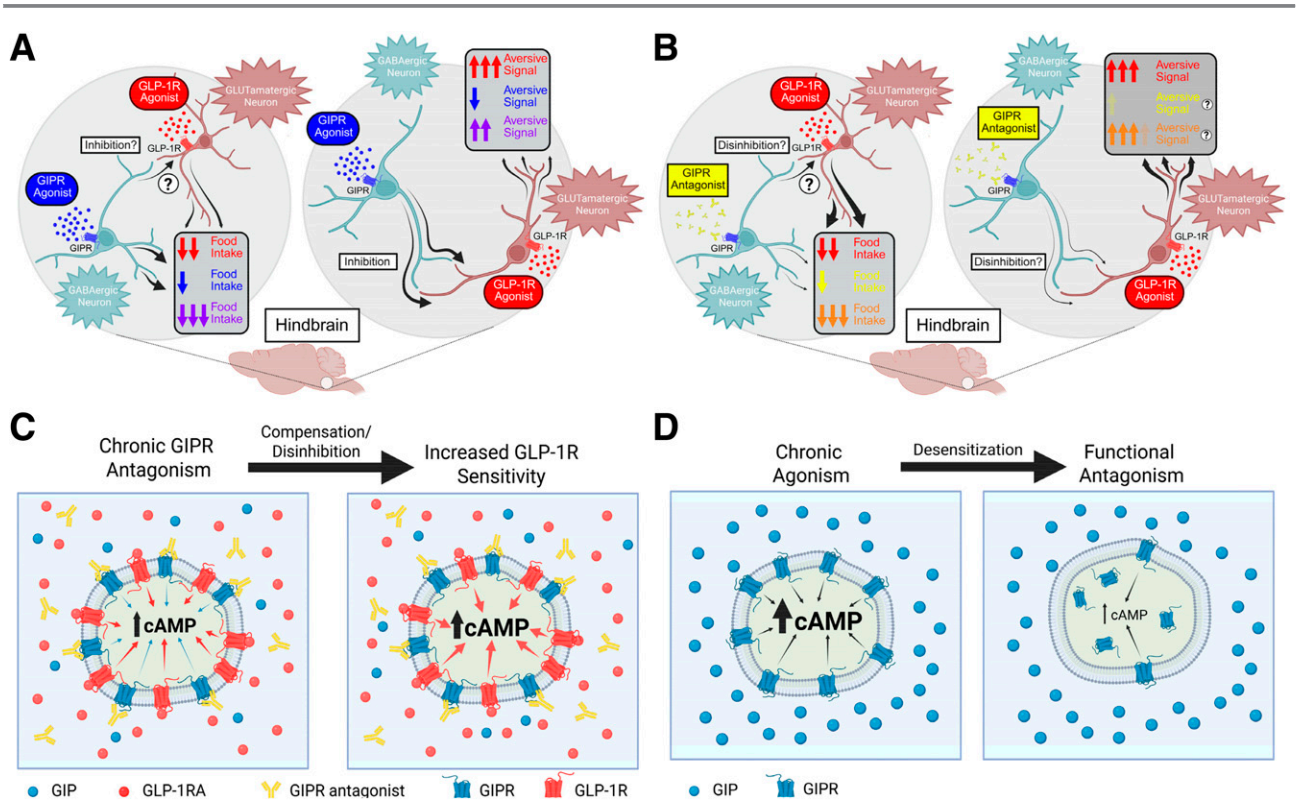

Figure 1—Hypotheses on how GIPR agonism or antagonism regulates body weight. *A*: GIPR agonism increases the activity of GABAergic inhibitory neurons in the hindbrain regions of the CNS. The increase in inhibitory tone may decrease food intake, independently adding to the actions of GLP-1R agonism. GIPR$^+$ neurons have also been shown to project onto, and inhibit, GLP-1R$^+$ GLUTamatergic neurons that produce the aversive effects in response to GLP-1R agonism. *B*: GIPR antagonism may decrease the activity of GABAergic inhibitory neurons, leading to disinhibition of the GLP-1R$^+$ neurons in the hindbrain that decrease food intake. As a result, GIPR antagonism increases the effectiveness of GLP-1R agonism to decrease food intake. *C*: Chronic loss of GIPR activity, potentially achieved by either genetic or pharmacological loss of function, produces an increase in GLP-1R sensitivity. In β-cells, which express both GIPR and GLP-1R, this may theoretically occur in a cell-autonomous manner. As very few neuronal populations express both receptors, this mechanism is more likely explained by a decrease in the interaction between distinct GIPR$^+$ and GLP-1R$^+$ neurons in the CNS. Loss of GIPR neuronal activity disinhibits GLP-1R$^+$ neurons, increasing their activity. *D*: Chronic agonism of the GIPR drives desensitization to result in loss of function that resembles antagonism. Although this hypothesis would provide a harmonious explanation to reconcile the effects of GIPR agonism and antagonism, there is currently no evidence to suggest that tirzepatide attenuates activity in GIPR$^+$ neurons that regulate food intake. GLP-1RA, GLP-1 receptor agonist.

tolerability of simultaneous GLP-1R agonism (Fig. 1*B*), a hypothesis currently being examined in clinical trials with maritide, a GIPR antagonist antibody conjugated to two peptide GLP-1R agonists.

Two complementary studies provide further evidence linking attenuation of GIPR signaling to augmentation of GLP-1R pathways in the CNS. Gutgesell et al. (21) demonstrate a requirement for GLP-1R signaling to achieve the maximal effects of GIPR antagonism for reduction of food intake and body weight in mice. Furthermore, the anorectic actions of GIPR antagonism were preserved in mice with selective deletion of the *Gipr* in CNS GABAergic neurons or deletion of *Gipr* in the peripheral nervous system within peripherin-expressing neurons. Interestingly, gene expression profiles in hindbrain CNS neurons, notably, pathways linked to regulation of synaptic plasticity, exhibited similar patterns of modulation after acute GIPR antagonism versus GLP-1R agonism. Collectively, these findings, together with data from Wean et al. (14), highlight roles for the GLP-1R in the transduction of CNS signals emanating from genetic loss of GIPR signaling or pharmacological GIPR antagonism.

Liu et al. (22) studied the actions of bispecific antibodies that blocked the GIPR, while simultaneously activating the GLP-1R, in mice with CNS neuronal deletion of the *Gipr* using synapsin-Cre, or reduction of neuronal *Glp1r* expression using Wnt1-Cre2. Remarkably, the anorectic and weight loss effects of the bispecific GIPR-Ab/GLP-1 antibody were partially diminished in both lines of mice, implicating an important role for both CNS GLP-1R and GIPR for transducing the full weight loss effects of molecules such as maritide, the investigational human GIPR-Ab/GLP-1 antibody now under assessment in phase 3 clinical trials. Furthermore, greater weight loss was achieved with the GLP-1 medicine dulaglutide in mice with inactivation of the CNS GIPR, whereas the extent of weight loss in mice treated with dulaglutide plus GIPR-Ab was attenuated in CNS GIPR knockout mice. Collectively, these studies highlight critical roles for both the CNS GIPR and GLP-1R in transducing the maximal weight loss effects of medicines like maritide and suggest that loss of CNS GIPR signaling sensitizes CNS circuits to both endogenous and pharmacological GLP-1R agonism.

Interestingly, there are no data for addressing whether selective agonism of these GIPR$^+$ GABAergic neurons suppresses the ability of GLP-1R agonists to reduce food intake. Clearly, more resolution of relevant GIPR signaling pathways, and their interactions with GLP-1R$^+$ circuits, is needed to identify the specific cellular sites and actions of GIPR in the various CNS regions that express the receptor. Moreover, studies are needed to determine which of these regions are accessible to or indirectly activated or inhibited by structurally distinct GIP-based therapeutics including peptides, antibodies, and eventually small molecules that may have different levels of brain penetration. Finally, it is important to mechanistically refine our understanding of the relative contribution(s) of GIPR activity in different regions of the CNS for weight control, which may be difficult to accomplish in humans. Studies in mice reveal important roles for CNS circuits as targets for GIPR agonism/antagonism in the control of body weight; however, whether mechanisms outside of the brain partially contribute to modulation of anorectic GIPR-regulated CNS pathways in humans is not established.

As the debate between agonism and antagonism continues, it is important to extend this conversation beyond the control of body weight to include important considerations of the biological actions of GIPR and interaction with GLP-1R circuits beyond the CNS. We must be careful not to fall into the trap of extending observations gained from studies where GIPR agonism was used to infer that the opposite biology will occur with GIPR antagonism, or vice versa. For instance, as mentioned above, loss of GIPR in GABAergic neurons relieves the inhibitory tone on GLP-1R$^+$ neurons and increases the effectiveness of GLP-1R agonism to reduce food intake. On one hand, this aligns with the data supporting that GIPR agonism in GABAergic neurons inhibits the aversive effects of GLP-1R agonism. However, whether GIPR agonism in GABAergic neurons also inhibits the effectiveness of GLP-1R neurons to reduce food intake remains unclear and doubtful. This phenomenon can be potentially explained by the reports of two distinct populations of GLP-1R$^+$ neurons within the hindbrain, one driving satiety and one driving aversion (14,23). On the other hand, loss-of-function outcomes in studies of incretin receptor biology do not always translate to the opposite effect with gain-of-function approaches, as genetic deletion or pharmacological blockade of the GLP-1R is also associated with resistance to weight gain in mice (24–26).

GIPR agonism exerts multiple important actions beyond the CNS, including enhancement of insulin and glucagon secretion to control postprandial metabolism (27,28), positive effects on adipose tissue (29,30) and bone metabolism (31–33), reductions in the activity of inflammatory pathways (34–37), and increases in insulin sensitivity (38,39). How many of these beneficial actions are negatively impacted by GIPR antagonism in humans with type 2 diabetes and/or obesity, if any at all? Importantly, are the putative negative metabolic consequences of GIPR antagonism in peripheral organs dwarfed by the beneficial actions of simultaneous and robust GLP-1R agonism? Use of careful approaches to identify the specific effects of GIPR agonism in each of these areas, including the cellular localization of the GIPR that is technically challenging to ascertain (40), can set expectations for outcomes that may be impacted by pharmacological antagonism. It is possible that none of these are meaningfully impacted by GIPR antagonism, especially since this approach will usually be paired with GLP-1R monoagonism and potentially other mechanisms. Nevertheless, GIPR antagonism alone is also being explored in the clinic. Hence, it is essential to consider and explore all clinically relevant

outcomes, including and beyond weight control, in considering targeting GIPR with either agonism or antagonism.

There are several additional factors that can potentially contribute to the debate of agonism versus antagonism. First, there is an increasing appreciation for the importance of biased agonism at G-protein–coupled receptors, including the incretin receptors. Mounting evidence that G-protein–biased GLP-1R agonists are superior to full agonists that recruit β-arrestin proteins (41,42) has fostered interest in understanding the implications of biased signaling at the GIPR (43). Whether the outcomes of this pursuit can meaningfully impact the directional biology and effect size pursuant to GIPR agonism remains to be seen. However, it is interesting to consider whether the same degree of tunability, evident in using a biased agonist, might be possible in pursuing GIPR antagonism.

Second, it has been postulated that chronic agonism of the GIPR drives a level of desensitization that results in loss of function that mimics functional antagonism (44), with either adipocytes (45) or β-cells (46) used as examples. This hypothesis (Fig. 1*D*) would be unifying to explain how both agonism and antagonism support weight loss, but it is not yet bolstered by substantial evidence for desensitization of CNS GIPR activity in one or more neuronal populations.

Although GIPR desensitization has been demonstrated for adipocytes (45), analyses of GIPR expression, combined with genetic targeting experiments, suggest that adipocytes do not appear to be the predominant $GIPR^+$ cell type within adipose tissue in vivo. In much of the literature investigators use induced 3T3-L1 adipocytes (47,48), induced preadipocytes from human tissue (29), or genetic overexpression of GIPR to study adipocyte GIPR activity (30). These adipocyte-focused models contrast with reports that most of the GIPR signal in adipose tissue in vivo originates from nonadipocytes (49), illustrating that inducible or cell culture models may not faithfully capture the landscape of primary adipocytes in vivo. Similarly, the lack of tachyphylaxis in quantifying the insulinotropic actions of GIP in humans without diabetes would argue against meaningful desensitization in β-cells (50). It is likely that the use of different GIPR agonists, with varied receptor pharmacology, may underlie some of these divergent results. Furthermore, we must always consider the contribution of species differences between rodents and humans, which has already proven to be impactful for understanding of the mechanism of GIPR agonism with tirzepatide, a weak GIPR agonist at the mouse GIPR (51). Incorporating these important biological details in future experimental design is a requirement for continued interrogation of this hypothesis.

Finally, a new class of emerging GLP-1 medicines includes the development of small molecules to address concerns about injections, the substantial costs of manufacturing peptide-based therapies, a limiting supply of pens, and a cold chain to deliver therapy for the duration of a patient's lifespan. This opportunity, together with advances in molecular resolution of the structure of the GLP-1R, has led to the development of several GLP-1R small-molecule agonists now in clinical development (52,53), with testing of small-molecule GIPR antagonists also in the clinic. Simultaneously, antibody-based GIPR antagonist–GLP-1R agonists such as maritide that are suitable for monthly dosing, potentially providing some level of durability for body weight following cessation of treatment, are also under investigation. It is an exciting time to follow the development of these agents on several fronts.

Beyond weight loss, GLP-1R agonists reduce the rates of myocardial infarction, stroke, cardiovascular death, kidney disease, and all-cause mortality in people with type 2 diabetes (54), actions recapitulated by semaglutide in people with obesity (55). Moreover, GLP-1 medicines decrease the severity of metabolic liver disease and heart failure with preserved ejection fraction and produce clinical improvement in people with obstructive sleep apnea or knee osteoarthritis. While a subset of these benefits are likely reflective of the weight loss achieved in many of these trials, it seems likely that weight loss–independent benefits, perhaps ensuing from the anti-inflammatory mechanisms of GLP-1 action, also contribute (56). While scrutiny of the extrapancreatic actions of sustained GIPR signaling in humans is limited, preclinical studies support an anti-inflammatory action for GIPR agonism, whereas loss of GIPR signaling is associated with increased inflammatory tone (35,36,57). In forthcoming safety and outcome studies in individuals with type 2 diabetes and/or obesity, scrutiny is merited of the extent to which gain or loss of GIPR signaling, alone or in combination with GLP-1R agonism, will potentiate or exacerbate, respectively, the anti-inflammatory actions and favorable outcomes detected with GLP-1R agonism.

Resolving the complexity of GIPR agonism versus antagonism for both control of body weight and improvement in cardiometabolic outcomes mandates that we remain focused on understanding relevant mechanisms of action linked not only to weight loss but also to sustained improvement in human health. Although considerable progress has been made in the past several decades on the underlying science of GLP-1–based and, more recently, GIP-based therapies, there is much to learn. An argument can be made that we are not yet able to resolve the debate between GIPR agonism and antagonism simply because so many of the key questions remain unanswered. Fortunately, studies of the merits of both gain– and loss–of–GIPR signaling approaches, together with GLP-1R agonism, will soon be further informed by the results of large safety and outcome studies. Ultimately, the magnitude and durability of patient benefit across a wide range of clinical indications will be the deciding factor in evaluating the relative strengths or limitations of different GIP-based therapies. It seems likely that there will be room and

justification for both GIPR agonism and antagonism as partners in the expanding universe of GLP-1 medicines.

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