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Regulation of energy metabolism through central GIPR signaling

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ABSTRACT

In recent years, significant progress has been made to pharmacologically combat the obesity pandemic, particularly with regard to biochemically tailored drugs that simultaneously target the receptors for glucagon-like peptide-1 (GLP-1) and the glucose-dependent insulinotropic polypeptide (GIP). But while the pharmacological benefits of GLP-1 receptor (GLP-1R) agonism are widely acknowledged, the role of the GIP system in regulating systems metabolism remains controversial. When given in adjunct to GLP-1R agonism, both agonism and antagonism of the GIP receptor (GIPR) improves metabolic outcome in preclinical and clinical studies, and despite persistent concerns about its potential obesogenic nature, there is accumulating evidence indicating that GIP has beneficial metabolic effects via central GIPR agonism. Nonetheless, despite growing recognition of the GIP system as a valuable pharmacological target, there remains great uncertainty as to where and how GIP acts in the brain to regulate metabolism, and how GIPR agonism may differ from GIPR antagonism in control of energy metabolism. In this review we highlight current knowledge on the central action of GIP, and discuss open questions related to its multifaceted biology in the brain and the periphery.

1. Introduction

The gut-brain axis constitutes a bidirectional communication system that links the gastrointestinal tract and the central nervous system (CNS) through neuronal and hormonal signaling pathways to control energy metabolism [1]. Emphasizing the relevance of this gut-to-brain communication, we have witnessed over the last decades the identification of a plethora of gut hormones which are excreted from the gut and its adjacent organs in response to food intake, and that signal to the brain to affect systemic energy and glucose metabolism, such as leptin, adiponectin, ghrelin, amylin, growth/differentiation factor 15 (GDF15), peptide YY (PYY), fibroblast growth factor 21 (FGF21), insulin, glucagon, and glucagon-like peptide-1 (GLP-1) [1]. The latter is of particular importance, since the therapeutic potential of GLP-1R agonism expands well beyond the regulation of glucose metabolism. Most notably, GLP-1 and its long-acting analogs (GLP-1RAs) decrease body weight via centrally-mediated inhibition of food intake [2]. They further improve renal function by increasing natriuresis and diuresis, stimulate bone remodeling, improve cardiovascular (CV) function, protect from ischemic injury and myocardial infarction, decrease inflammation and apoptosis, and have neuroprotective effects in selected patient cohorts [1]. The ability to decrease body weight through inhibition of food intake is one of the therapeutically most relevant non-glycemic effects of GLP-1RAs, and has been demonstrated in rodents, birds, pigs, non-human primates and humans [1].

GLP-1RAs decrease food intake via their action in the CNS, although with mechanistic differences depending on the species, the used molecule and the route of administration [1]. Both liraglutide [3] and semaglutide [4] reach the hypothalamus and the hindbrain via the circumventricular organs. In the hypothalamus and hindbrain, they induce cFOS neuronal activation, while directly stimulating hypothalamic POMC/CART neurons [3,4]. Antagonization of central GLP-1R using exendin(9−39) dampens food intake inhibition of i.p. administered liraglutide and exendin-4 [5], and liraglutide inhibition of food intake is attenuated in mice with neuronal loss of GLP-1R [6], hence emphasizing the relevance of central GLP-1R action for control of food intake. But food intake inhibition through long-acting GLP-1RAs shows notable differences relative to endogenous GLP-1. While long-acting GLP-1RAs directly act on hypothalamic feeding centers [3,4], but don't depend on vagal afferents or the hindbrain to inhibit food intake [3], GLP-1 is produced in a subset of neurons within the nucleus tractus solitarius (NTS) [7], and its infusion into the hepatic portal vein

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increases cFOS neuronal activity in the NTS and area postrema (AP), but not the hypothalamus [8]. Infusion of native GLP-1 stimulates vagal afferents in rats [9], and GLP-1-induced inhibition of food intake prevails in rats with subdiaphragmatic vagal deafferentation after intravenous (i.v.) infusion into the portal vein [8,10], but not when administered intraperitoneally (i.p.) [10]. Depending on the species and route of administration, GLP-1RAs hence differ in their ability to decrease food intake via CNS mechanisms, with long-acting GLP-1RAs decreasing food intake via the hypothalamus, and endogenous GLP-1 lowering food intake via vagal afferent-dependent and -independent mechanisms. But while the potential of GLP-1R agonism to decrease food intake is well acknowledged, uncertainty remains if and how pharmacological targeting of the GIP system affects systemic energy metabolism, and if GIP receptor (GIPR) signaling should be amplified or inhibited to improve metabolic outcome. In this review, we discuss the multifaceted nature of GIP's biology, and discuss how modulation of the brain GIP system affects systemic energy metabolism in rodents.

2. Clinical weight loss effects of GLP-1R mono-agonism vs. GIPR: GLP-1R co-agonism

The dose-dependent appearance of adverse effects, which are mostly transient and primarily of gastrointestinal nature, along with the requirement of higher doses relative to treatment of diabetes, constitutes a liability for the use of GLP-1RAs as anti-obesity medication. Nonetheless, in 2021, the U.S. Food and Drug Administration (FDA) approved with semaglutide 2.4 mg (Wegovy®, Novo Nordisk) the second GLP-1RA for the treatment of obesity in adults. In the STEP trials, average placebo-corrected weight loss induced by Wegovy was ~12–15% after 68-wks of treatment [11–13], and with superior potency relative to liraglutide [14], but with ~50% reduced potency in patients with T2D [11]. While it warrants clarification if and how weight loss efficacy in patients with obesity and type 2 diabetes (T2D) can further be enhanced by next generation GLP-1RAs, pharmacological weight loss >10% was until recently not thought to be safely possible [15]. The clinical success of semaglutide, with tolerable weight loss of ~15% in a significant portion of patients, hence impressively testifies how medicinal peptide chemistry, and GLP-1-based drug development specifically, advanced over recent years. Of particular merit has been the demonstration that many of the beneficial effects of GLP-1R agonism can be accelerated by either co-treatment with selected gut hormones, such as e.g. GIP, glucagon, amylin, or CCK, or through biochemically engineered poly-agonists that combine the metabolic action of several independent hormones into a single entity of enhanced potency and sustained action [1,15–17]. The most prominent example of such a GLP-1-based poly-agonist is the GIPR:GLP-1R co-agonist tirzepatide (Mounjaro®, Eli Lilly), which in the SURPASS trials decreased HbA1c with superior potency over semaglutide 1 mg [18], insulin glargine [19] und insulin degludec [20]. Depending on the dose (5, 10, or 15 mg once-weekly; QW), participants achieved a reduction in HbA1c of up to 2.59%, with placebo-corrected body weight loss of 7–14,5% after 40–52 wks of treatment [18–22]. In the SURMOUNT-1 study, mean placebo-corrected weight loss achieved by tirzepatide was 17,8% after 72 wks treatment, and with 50% of patients in the 10 mg group, and 57% in the 15 mg group, achieving weight loss >20% (relative to 3% of patients treated with placebo) [23]. The metabolic efficacy of tirzepatide and semaglutide were recently evaluated under real-world settings, utilizing data from over 41,000 patients with obesity [24]. The study used the standard doses labeled for the treatment of T2D, with dose escalation scheduled to the highest tolerated dose. Following one year of treatment, weight reduction of $\geq$ 5% was observed in 81.8% of patients receiving tirzepatide and in 64.6% receiving semaglutide. Weight loss of $\geq$ 10% was achieved by 62.1% of patients receiving tirzepatide and 38.0% of patients receiving semaglutide, with $\geq$ 15% weight loss in 42.3% and 19.3% of patients, respectively [24]. Albeit caution is warranted due to the different doses used in the study, the superiority of tirzepatide over semaglutide manifests in additional weight loss of −2.3% after 3 months, −4.3% after 6 months, and −7.2% after 12 months, without notable differences in the appearance of gastrointestinal adverse effects at any point during the study [24]. In summary, these findings underscore that the GIPR:GLP-1R co-agonist tirzepatide outperforms semaglutide at maximal approved doses to yield greater weight loss without compromising tolerability. But what makes GIPR:GLP-1R co-agonists superior over GLP-1 mono-agonism, and what is the contribution of the GIP receptor? Where and how does GIP act to enhance metabolic outcome and where and how does GIPR agonism separate from GIPR antagonism to affect systems metabolism?

3. Regulation of systemic energy metabolism by GIPR agonism and antagonism

In contrast to GLP-1, GIP is traditionally stigmatized to have little to no pharmacological value. Consistent with this is the observation that the insulinotropic action of GIP is largely dampened in patients with T2D [25–31], and that *Gipr* deficient mice are resistant to diet-induced obesity [32–35]. But while resistance to diet-induced obesity is also observed in GLP-1R deficient mice [36,37], insulin-induced near--normalization of hyperglycemia restores the insulinotropic effect of GIP in patients with T2D [38], hence indicating that GIPR agonism may hold pharmacological potential when given in adjunct to drugs that overcome hyperglycemia. Nonetheless, particularly under hyperinsulinemic conditions, GIP promotes lipogenesis and lipid deposition in cultured adipocytes via mechanisms that include enhanced action and secretion of lipoprotein lipase [39–41], stimulation of insulin-induced glucose uptake [42–44], conversion of glucose into lipids [42] and acceleration of insulin receptor affinity [42–44]. A potentially obesogenic nature of GIP is seemingly further supported by human genetic studies, which show common *GIPR* variants with decreased receptor function to the associated with decreased BMI [45–47]. Further consistent with these findings is the observation that certain GIPR antagonists decrease body weight and food intake in diet-induced obese (DIO) mice and non-human primates [48], particularly when given in adjunct to GLP-1R agonism [48,49]. However, while no GIPR antagonist has yet received federal approval, there is increasing preclinical evidence indicating the GIPR agonism is a physiological relevant entity of GIPR:GLP-1R co-agonism. Mice with overexpression of GIP show decreased body weight when fed with a high-fat diet (HFD) [50], and although GIP promotes lipogenesis in cultured adipocytes under conditions of hyperinsulinemia [39–41], it stimulates lipolysis under conditions or normo- or hypoinsulinemia in cultured adipocytes [51,52] and in patients with type 1 diabetes (T1D) [53]. When given either alone or in combination with GLP-1R agonism, long-acting GIPR agonists decrease body weight in DIO mice [16,17,54,55], and these effects vanish in mice with loss of *Gipr* in either the CNS [55] or more specifically in gamma-aminobutyric acid (GABAergic) neurons [56]. Consistent with a role of the brain GIP system in regulating energy metabolism, food intake is decreased in mice upon chemogenetic activation of either hypothalamic [57,58] or hindbrain [57] GIPR neurons, and long-acting GIPR agonists decrease body weight and food intake in DIO mice when given directly into the lateral ventricle of the brain [55]. The GIPR:GLP-1R co-agonist MAR709 further decreases body weight and food intake in DIO mice with superior efficacy relative to a pharmacokinetically matched GLP-1, but MAR709 loses superiority over GLP-1 in mice with loss of *Gipr* in either the CNS [55] or in GABAergic neurons [54]. In summary, there is ample preclinical evidence indicating that GIPR agonism is a vital constituent of GIPR:GLP-1R co-agonism and that long-acting GIPR agonists act centrally on brain feeding centers to decrease body weight through inhibition of food intake. Nonetheless, little is known about the neurocircuitries and mechanisms of how central GIPR agonism affects systemic energy metabolism, and how GIPR agonism separates from GIPR antagonism to decrease body weight. Furthermore, it warrants clarification whether these central effects of GIP translate to humans.

4. Regulation of food intake through central GIPR agonism

The hypothalamus and the brainstem are well known for their implication in control of food intake [59,60]. The hindbrain constitutes the brainstem, the cerebellum and the medulla oblongata, which connects the brainstem with the spinal cord. The dorsal vagal complex (DVC) comprises the area postrema (AP), the nucleus tractus solitarii (NTS) and the dorsal motor nucleus of the vagus nerve (DMX), which together integrate information from autonomic nervous system to control food intake [59–61]. Notably, both GLP-1R and GIPR agonists reach the hindbrain via the AP [3,4,56,57], but while GLP-1R agonists induce cFos neuronal activation in the AP and the NTS [54], GIPR agonists induce neuronal activation primarily in the AP [54,62–64]. The blood-brain-barrier (BBB) separates the bloodstream from the brain and spinal cord to restrict the passage of circulating hormones into higher brain areas. While it is unclear whether endogenous GIP is capable to cross the BBB, GIP is found in the cerebrospinal fluid of mice [65] and humans [66], and GIP has neuroprotective effects in animal models for Alzheimer's and Parkinson's disease [67–70]. But although these data suggest that GIP can cross the BBB, several studies suggest that GIP is also produced in certain brain areas [71,72]. But similar to liraglutide and semaglutide, which do not seem to cross the BBB [3,4], fluorescently-labeled GIP accumulates after single peripheral bolus administration primarily in the AP and the median eminence (ME), but not in the hypothalamic arcuate nucleus (ARC) [54,57]. Although the majority of the neuronal cell bodies within the ARC are located in the BBB protected region, some can potentially reach the ME, where they may have direct contact with peripherally secreted hormones [73].The ARC is separated from the ME by the tanycytes, which are specialized to facilitate the transport of cargo from the general circulation into the hypothalamus [74]. While tanycyte-mediated BBB transcytosis is crucial for the hypothalamic uptake and action of liraglitude [75], no such transport has yet been demonstrated for GIP and GLP-1-based poly-agonists. Arguing against a major role of the tanycytes in BBB transcytosis of GIP, *Gipr* is expressed in only a mere fraction (0.2%) of tanycytes, and with substantially lower expression relative to *Glp-1r* [76]. Nonetheless, in both the hypothalamus and the hindbrain, *Gipr* is expressed in many non-neuronal cell types, including those composing the BBB [77,78], which is formed by a layer of tightly packed endothelial cells and surrounded by mural cells and astrocytes. ScRNAseq data obtained from mice that express yellow fluorescent protein (YFP) under control of the *Gipr* promoter show that the majority of *Gipr*-expressing cells in the hypothalamus are mural cells, particularly pericytes [58,78]. In the adult murine hypothalamus, expression of *Gipr* is nonetheless only found in ∽0.5% of mural cells [76], potentially indicating enriched localization of GIPR in the ME and the BBB. While it warrants clarification if and to what extend GIPR signaling in brain mural cells affects systems metabolism, pericytes play an important role in regulating blood flow, and while GIP increases mesenteric blood flow in humans [79–82], cats [83] and dogs [84], it decreases blood flow in the pancreatic and hepatic arteries [83,84]. The observation that *Gipr* is enriched in hypothalamic and hindbrain pericytes hence indicates that GIP potentially controls brain blood flow and may thereby enhance central drug exposure by accelerating BBB transcytosis.

Expression of *Gipr* is high in the AP [62,63], but scarce in the NTS and the nodose ganglion of the vagus nerve [57,62,63]. The majority of *Gipr* cells in the NTS are of non-neuronal origin [77], which is consistent with the observation that long-acting GIPR agonists increase cFos neuronal activation in the AP [56,57,62,63,85] but only marginally in the NTS [56,62]. But GIP-induced cFos activation seems to vary depending on the used GIPR agonist, since other studies using a different GIPR agonist (GIP-085) show cFos activation in both, the AP and the NTS [57,85]. In the AP, *Gipr* is predominantly expressed in inhibitory GABAergic neurons that express the vesicular GABA transporter (*Vgat*) [77,86,87], and while GIPR agonism solidly increases cFos neuronal activation in the AP of wildtype mice, no such effect is observed in mice that lack *Gipr* in *Vgat*-expressing GABAergic neurons [56]. Even more strikingly, while chronic treatment with a fatty acid acylated (acyl)-GIP decreases body weight and food intake in DIO mice, these effects vanish in mice with lack of *Gipr* in GABAergic neurons [56]. And while the GIPR:GLP-1R co-agonist MAR709 decreases body weight and food intake with superior efficacy relative to treatment with a pharmacokinetically-matched GLP-1 control, this superiority vanishes in mice with deletion of *Gipr* in GABAergic neurons [56]. The mechanisms by which GIPR signaling in GABAergic neurons decreases body weight and food intake, as well as the role of the AP in mediating these effects, remain to be determined. The same neuronal pathways may also account for the observation that GIPR agonists act in the AP to ameliorate the emetic effects of GLP-1R agonism [64,85], an appreciable observation that might contribute to greater tolerability of GIPR:GLP-1R co-agonism relative to single GLP-1R agonism at higher doses.

The observation that peripherally injected GIPR agonists reach the brain via the circumventricular organs, but don't accumulate in brain regions shielded by the BBB [54,57], suggests that these regions harbor the 1st order signaling nodes mediating food intake inhibition through GIPR agonism. It is well known that efferent neurons that control food intake project from the AP to the NTS and parabrachial nucleus (PBN) [60], and further to the amygdala and the hypothalamus [57,62,88]. In line with the hypothesis that GIP may transmit satiety signals from the AP to these (and potentially other) brain regions, GIP increases cFos activation in the lateral PBN [57] and the hypothalamus [55,56,58] and selective chemogenetic activation of GIPR neurons in either the DVC [57] or the hypothalamus [58], or direct administration of GIP into the lateral ventricle of the brain [55], decreases food intake in mice. GIP-induced augmentation of peptide YY (PYY)-induced emesis is further associated with decreased neuronal activity in the PBN [63]. Glutamatergic neurons in the PBN, however, do not express *Gipr* [89], hence indicating that GIP modulates neuronal activity in the PBN via excitatory projections from the DVC [60]. Consistent with such assumption is the observation that GIPR neuronal projections from the DVC reach the PBN [57], and that excitatory signals from the NTS to the PBN decrease food intake in mice [90] (Fig. 1). The PBN further transmits excitatory signals to the lateral part of the central amygdala (CeA) [88], a key hub of the brain reward system, which primarily harbors GABAergic neurons that upon activation suppress hedonic food intake in rodents [91]. Treatment of mice with a long-acting GIPR agonist increases cFos neuronal activation in the CeA [63], hence indicating that GIPR agonism might decrease food intake also via projections to this area. GIP may further transmit satiety signals from the DVC to the paraventricular nucleus of hypothalamus (PVH), which contributes to the regulation of food intake via projections from the NTS [57,62,92]. Consistent with this, cFos neuronal activation is increased in the PVH following chemogenetic activation of GIPR neurons in the DVC [57], and after peripheral bolus administration of acyl-GIP [56], and this effect vanishes in mice with lack of *Gipr* in GABAergic neurons [56]. The PVH is nonetheless also targeted by neurons of the ARC, and while peripheral administration of long-acting GIPR agonists increases cFos activation in the ARC [54,55], direct administration of acyl-GIP into the lateral ventricle of the brain decreases body weight and food intake in obese mice [55]. These data are further supported by the observation that chemogenetic activation of hypothalamic GIPR neurons decreases food intake [57,58], hence indicating that GIP engages neurocircuitries in both the hypothalamus and the hindbrain to control food intake. In any case, food intake inhibition by GIPR agonism inevitably depends on functional central GIPR signaling, since GIP-induced inhibition of food intake vanishes in mice with Nestin cre-mediated neuronal loss of *Gipr* [55]. While the exact mechanisms through which GIP acts in the hypothalamus to decrease food intake remain to determined, expression of *Gipr* is only moderate in ARC and absent in PVH and (dorso-medial hypothalamus) DMH [78]. Interestingly, co-administration of GLP-1R and GIPR agonists promote greater weight loss and further inhibition of food intake relative to singular GLP-1R agonist [17,57], and this

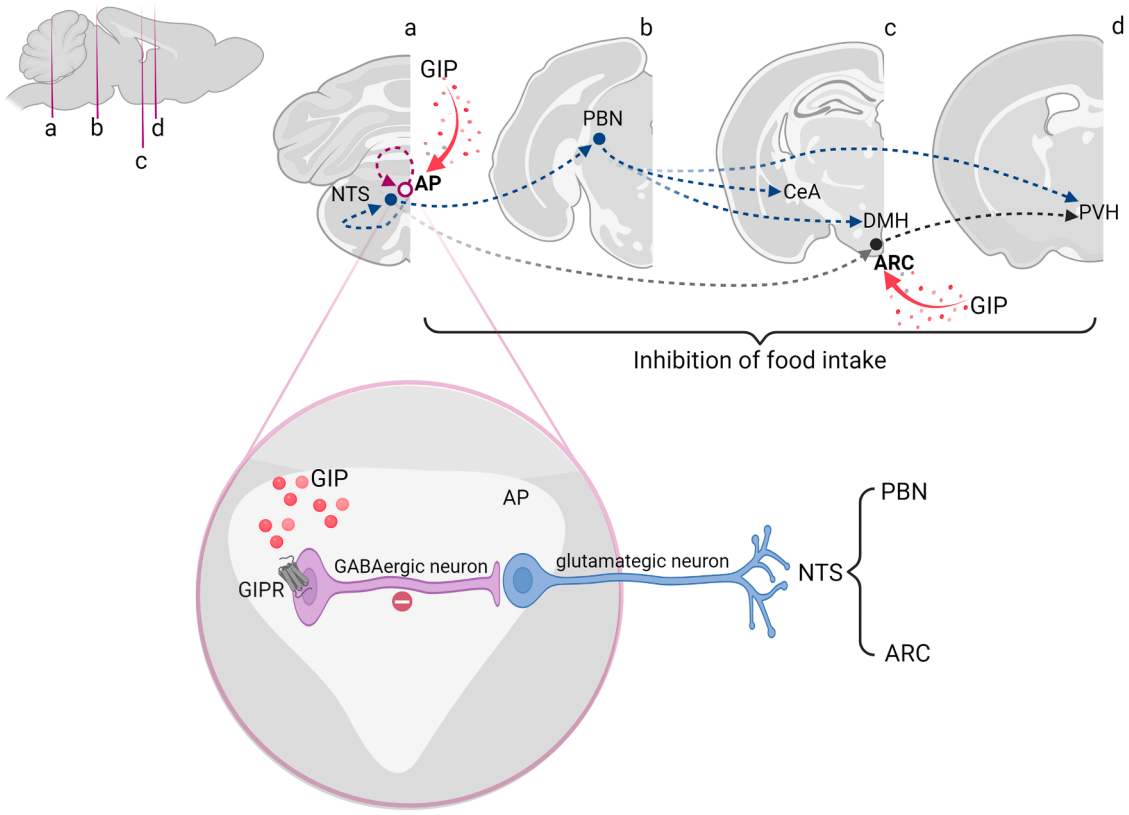

Fig. 1. Proposed model for GIPR signal distribution throughout the mouse brain. GIPR-expressing GABAergic neurons initiate signaling within the area postrema (AP) in the brainstem (magenta dotted arrows) **(A)**. Glutamatergic projections (blue dotted arrows) extend from the AP to the solitary nucleus (NTS) and further to the parabrachial nucleus (PBN) in the midbrain. Subsequently, this signaling reaches feeding-related centers, including the amygdala (central nucleus of the amygdala lateral, CeAl) and hypothalamic nuclei (dorso-medial hypothalamus, DMH, and paraventricular nucleus, PVH). Direct projections from NTS reach the arcuate nucleus of the hypothalamus (Arc) (gray dotted arrows) to regulate Arc neurons, thereby decreasing food intake. However, this pathway has not been confirmed for GIP signaling yet. The GABAergic neurons expressing GIPR are situated within the AP and regulate secondary glutamatergic neurons that project to NTS and subsequent brain regions, eliciting anorexigenic responses **(B)**.

superiority is fully preserved in mice with viral-mediated knock-down of *Gipr* in the hypothalamus [57]. While these data suggest that food intake inhibition through GIPR agonism does not depend on functional GIPR signaling in the hypothalamus, these data need to be regarded with caution, since viral-mediated knockdown is often incomplete. Nonetheless, the ARC also engages direct projections from the NTS to control food intake [93–95] and GABAergic projections from the NTS decrease body weight via inhibition of AgRP/NPY neurons in the ARC [96].

5. Lessons from *Gipr* deficient mice

The observation that *Gipr* deficient mice are resistant to diet-induced obesity (DIO) [32–35], has spurred interest to explore the potential of GIPR signal inhibition for the treatment for obesity. And indeed, GIPR antagonists lower body weight and food intake in DIO mice and non-human primates [48], particularly when given in adjunct to GLP-1R agonism [48,49]. Protection from DIO in *Gipr* deficient mice is consistent with the ability of GIP to promote adipocyte lipid storage under conditions of hyperinsulinemia [40,41,97]. But mice with targeted deletion of *Gipr* in the adipose tissue are not protected from diet-induced obesity and show no difference in body weight or fat mass relative to wildtype controls when fed with a HFD [98–100]. While the lack of adipocyte GIPR signaling can hence not explain why global *Gipr* deficient mice are protected from diet-induced obesity, mice with deletion of *Gipr* in either the CNS [55] or in GABAergic neurons [56] show decreased body weight and fat mass when fed with a HFD. Although these neuron-specific *Gipr* deficient mice not fully recapitulate the obesity-protecting phenotype seen in mice with global *Gipr* deficiency [101–104], these data nonetheless clearly indicate that the protection from obesity partially results from GIPR deficiency in the brain. Future studies will need to clarify why both the activation and inhibition of GIPR decreases body weight and fat mass in experimental animals. One widely considered hypothesis is that GIPR agonism results in GIPR desensitization, hence leading to functional GIPR antagonism [105]. This hypothesis is based on the observation that GIPR sensitivity is decreased in DIO mice and in isolated adipocytes following treatment with GIP [100]. But ligand-induced receptor desensitization has also been shown for GLP-1 in rat insulinoma INS-1 cells [106] and for GLP-1 and GIP in hamster β-cell HIT-T15 cells [107]. And chronic treatment of DIO mice with acyl-GIP does not decrease expression of *Gipr* in either the hypothalamus or the adipose tissue [55]. Although there is currently no evidence supporting the hypothesis that GIPR agonism decreases body weight through functional GIPR antagonism, it seems plausible to hypothesize that GIPR agonists and antagonists may engage different mechanisms to affect energy metabolism. And while long-acting GIPR agonists act on the brain satiety centers to decrease food intake [55–58], GIPR antagonists may compete with endogenous GIP in the periphery to inhibit the lipogenic action of endogenous GIP in adipose tissue [108]. GIPR agonism and antagonism may further differentially affect food intake via central mechanisms, with GIPR agonism decreasing food intake via activation of GABAergic neurons to decrease food intake [56], and with GIPR antagonism potentially silencing these GABAergic neurons to increase the action and signaling of glutamatergic neurons implicated in food intake control. Consistent with such assumption is the observation that GLP-1R neurons implicated in food intake control are exclusively glutamatergic [109], and while long-acting GIPR agonists

equally decrease body weight in wildtype and GLP-1R knock-out mice [55,110], GIPR antagonists primarily decrease body weight when given in adjunct to GLP-1R agonism [48,49]. GIPR agonism and antagonism might hence promote food intake inhibition via different mechanisms, with GIPR agonism decreasing food intake independent of GLP-1R agonism and with GIPR antagonism enhancing food intake inhibition through enhanced GLP-1R action.

6. Conclusion

In summary, starting with the observation that GIPR:GLP-1R co-agonism outperforms GLP-1-based monotherapies to yield greater weight loss and further inhibition of food intake in rodents [16,17], we have witnessed in recent years a rekindled interest in how GIP affects systemic energy metabolism. Numerous studies have subsequently revealed a surprising variety of GIP effects that expand well beyond its initial classification as an insulinotropic hormone, with metabolic action in the brain to decrease body weight and food intake. The question of how GIPR agonism and antagonism both act in the brain to regulate feeding behavior remains puzzling and is subject of intense ongoing investigations. Additional research is necessary to investigate whether long-acting GIPR agonists also affect food intake and body weight in humans. Undoubtedly, verifying that the impact of GIP on energy metabolism translates to humans is crucial for potentially targeting the brain GIP system using next generation anti-obesity medication.

CRediT authorship contribution statement

Arkadiusz Liskiewicz: Writing – original draft, Writing – review & editing. **Timo D Müller:** Writing – original draft, Writing – review & editing.

Conflict of Interest

TDM receives research funding from Novo Nordisk, but these funds are unrelated the here described work. TDM further received speaking fees within the last 3 years from Novo Nordisk, Eli Lilly, AstraZeneca, Merck, Berlin Chemie AG, and Mercodia.

Data Availability

No data was used for the research described in the article.

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