



GIP Receptor Agonism Attenuates GLP-1 Receptor Agonist-Induced Nausea and Emesis in Preclinical Models

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Glucagon-like peptide 1 receptor (GLP-1R) agonists decrease body weight and improve glycemic control in obesity and diabetes. Patient compliance and maximal efficacy of GLP-1 therapeutics are limited by adverse side effects, including nausea and emesis. In three different species (i.e., mice, rats, and musk shrews), we show that glucose-dependent insulintropic polypeptide receptor (GIPR) signaling blocks emesis and attenuates illness behaviors elicited by GLP-1R activation, while maintaining reduced food intake, body weight loss, and improved glucose tolerance. The area postrema and nucleus tractus solitarius (AP/NTS) of the hindbrain are required for food intake and body weight suppression by GLP-1R ligands and processing of emetic stimuli. Using single-nuclei RNA sequencing, we identified the cellular phenotypes of AP/NTS cells expressing GIPR and GLP-1R on distinct populations of inhibitory and excitatory neurons, with the greatest expression of GIPR in γ -aminobutyric acid-ergic neurons. This work suggests that combinatorial pharmaceutical targeting of GLP-1R and GIPR will increase efficacy in treating obesity and diabetes by reducing nausea and vomiting.

Long-acting agonists targeting the glucagon-like peptide 1 receptor (GLP-1R) are highly efficacious at normalizing glycemia and reducing food intake and body weight in both obesity and type 2 diabetes (T2DM), as previously reviewed

(1–3). However, all existing U.S. Food and Drug Administration-approved GLP-1-based therapeutics elicit nausea and vomiting in a significant percentage of patients, which represent primary reasons for treatment discontinuation (4). Since there is a necessity to both enhance weight loss and glycemic control, while concurrently reducing adverse side effects, research efforts to treat obesity and T2DM strive to develop novel combinatorial therapies for GLP-1R agonists.

Glucose-dependent insulintropic polypeptide (GIP), a hormone released in the proximal intestine shortly after meal onset, regulates postprandial glucose levels by augmenting insulin secretion via activation of GIP receptors (GIPR) expressed on pancreatic β -cells (5). While GLP-1R agonists have been developed and used with success for T2DM and obesity treatment, data surrounding GIP analogs are limited and controversial, as previously reviewed (6–8). GIPRs are expressed in central nervous system regions implicated in energy balance regulation (9); however, few studies have investigated the central actions of GIP ligands on feeding behaviors (9–12), finding minor anorectic effects of GIPR monotherapy compared with the profound hypophagia produced by GLP-1R agonists.

GIPR/GLP-1R dual agonism has yielded promising results in preclinical models and clinical trials by providing greater body weight loss and superior glycemic control compared with GLP-1R agonism alone (13–17). Importantly, GIPR activation may have antiemetic effects, as a

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recent patent application reports GIPR agonism to reduce cisplatin-induced vomiting in ferrets (18). In this context, the nucleus tractus solitarius (NTS) and area postrema (AP) of the hindbrain express GIPR (9,19,20) and are required for the intake and body weight-suppressive effects of GLP-1R ligands (21) as well as control of emesis (22), yet the role of hindbrain GIPR in modulating hypophagia and malaise induced by GLP-1R ligands has never been investigated. To this end, we identify the cellular phenotypes of AP/NTS GIPR- and GLP-1R-expressing cells by using unbiased single-nuclei RNA sequencing

(snRNAseq) as well as report biobehavioral analyses following systemic or hindbrain delivery of GIPR agonists alone or in combination with GLP-1R agonists in mice, rats, and musk shrews.

RESEARCH DESIGN AND METHODS

Experimental Models

All procedures were approved by the Institutional Care and Use Committee of the University of Pennsylvania and Eli Lilly and Company. Adult male C57BL/6 mice (Taconic)

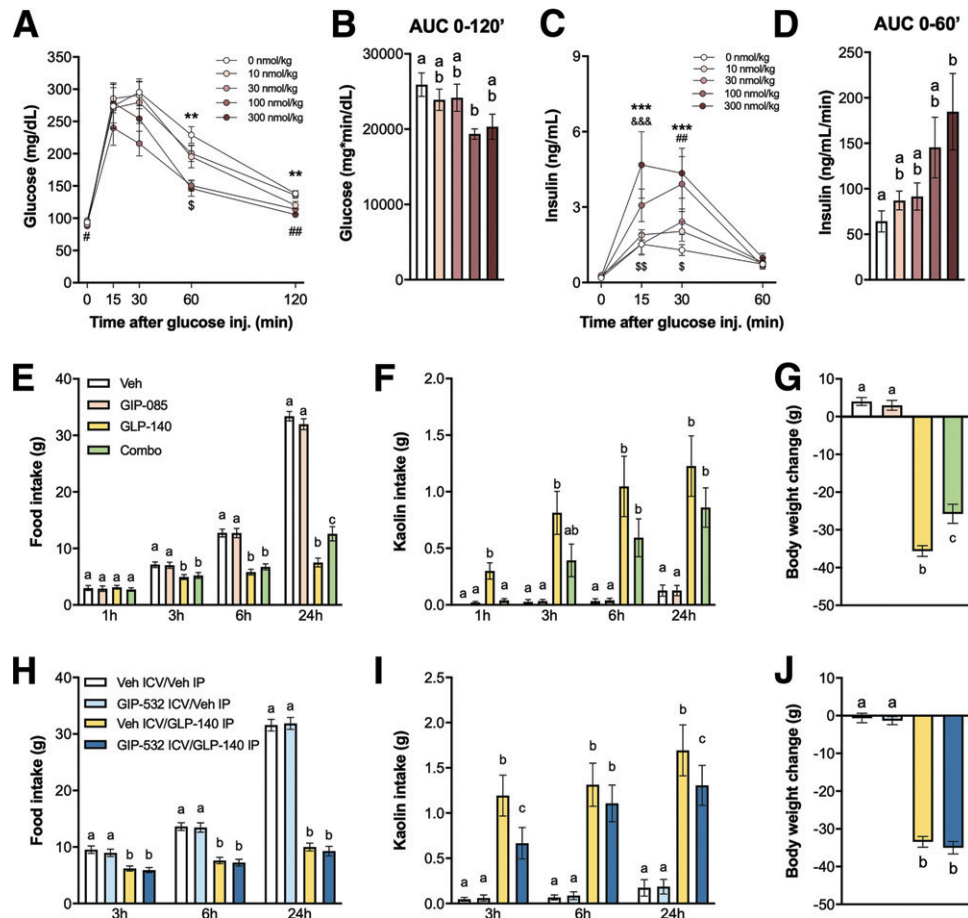


Figure 1—GIP agonism enhances glucoregulation and attenuates GLP-1-induced illness behaviors in rats. **A:** GIP-085 (10, 30, 100, and 300 nmol/kg, SC) dose-dependently suppresses BG levels following an IPGTT (2 g/kg, IP) in lean rats ($n = 6$). Vehicle (Veh) vs. 300 nmol/kg: $**P < 0.01$; Veh vs. 100 nmol/kg: $\$P < 0.05$; 30 nmol/kg vs. 300 nmol/kg: $\#P < 0.05$, $\#\#\#P < 0.01$. **B:** Glucose AUC from 0 (i.e., postglucose bolus) to 120 min after treatment ($n = 6$ per group). **C:** GIP-085 (10, 30, 100, and 300 nmol/kg, SC) dose-dependently stimulates insulin secretion ($n = 6$ per group). Veh vs. 300 nmol/kg: $***P < 0.001$; Veh vs. 100 nmol/kg: $\#\#\#P < 0.01$; 300 nmol/kg vs. 30 nmol/kg: $\&\&\&P < 0.001$; 300 nmol/kg vs. 10 nmol/kg: $\$P < 0.05$, $\$\$\$P < 0.01$. **D:** Insulin AUC from 0 (i.e., postglucose bolus) to 60 min after treatment ($n = 6$ per group). **E:** The anorectic effect of the long-acting GLP-1R agonist GLP-140 is reduced by GIP-085 combination (combo) treatment (GIP-085: 300 nmol/kg; GLP-140: 1,000 nmol/kg, IP; $n = 18$ per group). Indeed, GIP-085/GLP-140 treatment led to significantly ($87 \pm 20\%$) higher 24-h food consumption compared with GLP-140 alone. **F:** GIP-085 cotreatment attenuates kaolin intake (a validated proxy for nausea/emesis in rats) induced by GLP-140 ($n = 18$ per group). **G:** Body weight change following GLP-140, GIP-085, and combo treatments ($n = 18$ per group). **H:** Intracerebroventricular (ICV) infusion in the fourth ventricle (4th ICV) of the potent GIPR agonist GIP-532 (0.3 nmol, 1 μ L) does not affect GLP-140-induced anorexia (GLP-140: 1,000 nmol/kg, IP). **I:** GIP-532 4th ICV attenuates kaolin intake induced by systemically delivered GLP-140 (GLP-140: 1,000 nmol/kg, IP; GIP-532: 0.3 nmol; $n = 15$ per group). **J:** Body weight change following GLP-140, GIP-532, and combo treatments ($n = 15$ per group). All data are expressed as mean \pm SEM. Data in **A**, **C**, **E**, **F**, **H**, and **I** were analyzed with repeated-measures two-way ANOVA, followed by the Tukey post hoc test. Data in **G** and **J** were analyzed with repeated-measures one-way ANOVA, followed by the Tukey post hoc test. Data in **B** and **D** were analyzed with one-way ANOVA, followed by the Tukey post hoc test. Means with different letters are significantly different from each other ($P < 0.05$).

weighing ~20 g at arrival ($n = 84$), adult male Sprague-Dawley rats (Charles River Laboratories) weighing ~250–270 g ($n = 93$), and adult male shrews (*Suncus murinus*) weighing ~50–80 g ($n = 118$ total) were housed under a 12-h:12-h light/dark cycle in a temperature- and humidity-controlled vivarium.

All animals were naïve to experimental drugs and tests prior to the beginning of the experiment. For most in vivo experiments, injections were administered using a within-subjects design. See the Supplementary Text for more details.

Peptide Synthesis, In Vitro Characterization, and Pharmacokinetic Analysis

Long- (GIP-085) and short-acting (GIP-532) agonists of the GIPR and the long-acting GLP-1R agonist GLP-140 were synthesized at Eli Lilly and Company. GIP-085 and GLP-140 were dissolved in 40 mmol/L Tris HCl buffer (pH 8) 0.02% Tween-80. Exendin 4 (Ex4) and LiCl (0.3 mol/L) were dissolved in saline. The pharmacokinetics of GIP-085 and GLP-140 were evaluated in rats following a single intravenous or subcutaneous (SC) dose of 50 nmol/kg. See the Supplementary Text for more details.

Figure 2—Transcriptomic identification of rat AP and NTS cell types by snRNAseq and FISH. *A*: A total of 19 transcriptomically distinct cell types were identified. *B*: Neuronal and nonneuronal cell types were identified by known transcriptional markers. Avg. Exp., average expression; Pct. Exp., percentage expression. Highlighted Uniform Manifold Approximation and Projections (UMAPs) identifying *Gipr*⁺ (*C*) and *Glp1r*⁺ (*D*) cell types. Most of the neurons positive for either receptor are limited to a small number of cell types. *E*: A highlighted UMAP showing that the *Gipr*⁺ and *Glp1r*⁺ neurons are largely independent. *F* and *G*: Representative FISH images showing *Gipr*⁺, *Glp1r*⁺, and *Gad*⁺ cells in AP and in the adjacent portion of the NTS (~250- μ m rostral to the obex). Scale bar, 50 μ m.

Effects of GIP-085 Systemic Delivery on Ex4-Conditioned Flavor/Taste Avoidance in Mice

The saccharin two-bottle test was performed as described elsewhere (23). See the Supplementary Text for more details.

GIP-085 in Glycemic Control, Food and Kaolin Consumption, and Body Weight in Rats

Rats ($n = 6$ per group) were injected with GIP-085 (10, 30, 100, 300 nmol/kg) or vehicle 16 h before glucose administration (2 g/kg intraperitoneal [IP]). At 0, 15, 30, and 60 min, extra tail blood was collected for the analysis of circulating insulin levels. Blood was collected in EDTA-coated tubes. Rats ($n = 18$, 300–350 g) for intake and body weight experiments received GIP-085 (300 nmol/kg IP), GLP-140 (1,000 nmol/kg IP), GIP-085/GLP-140 combination, or vehicle. In a separate cohort of rats ($n = 15$), a short acting, unlipidated GIPR agonist, GIP-532 (18) (0.3 nmol in 1 μ L), was infused centrally into the fourth ventricle, while GLP-140 or vehicle was administered peripherally. See the Supplementary Text for a complete description.

Effects of GIP-085, GLP-140, and GIP-085/GLP-140 on Glycemic Control, Energy Balance, Emesis, and Neuronal Activation in Shrews

IP glucose tolerance tests (IPGTT) were performed in shrews to capture blood glucose (BG) measurements. Food intake and body weight were measured after GIP-085, GLP-140, and GIP-085/GLP-140 treatments. The emetogenic properties of different doses of GIP-085 and GLP-140, as well as GIP-085/GLP-140 cotreatment, were also investigated. The immunohistochemistry protocol used for c-Fos quantification was adapted from previous studies (24,25). Procedures were performed as previously published (26). See the Supplementary Text for more details.

AP/NTS Transcriptome Profile of Single Nuclei and Characterization of GIPR Neurons in the AP/NTS via Fluorescent In Situ Hybridization in Rats

Tissue collection, isolation of nuclei, 10 \times Genomics library preparation and sequencing, QC and clustering were performed similar to published reports (27). Fluorescence in

situ hybridization (FISH) protocol was adapted from a previous study (28). See the Supplementary Text for complete description.

Statistical Analysis

All biobehavioral parameters were analyzed using ordinary or repeated measures one-way or two-way ANOVAs, followed by Tukey post hoc tests. For the analysis of c-Fos expression, an ordinary one-way ANOVA was used, followed by Tukey post hoc tests. BG levels and BG areas under the curve (AUC) were analyzed using ordinary or repeated-measures two-way ANOVA, followed by the Tukey post hoc test. All data are expressed as mean \pm SEM. For all statistical tests, $P < 0.05$ was considered significant. All data were analyzed using GraphPad Prism 9 software (GraphPad Software, San Diego, CA).

Data and Resource Availability

snRNAseq data are available at the National Center for Biotechnology Information Gene Expression Omnibus (GEO) under accession number GSE167981.

RESULTS

Generation and In Vitro Characterization of GLP-140 and GIP-085 Peptides

We developed acylated (C-20) long-acting, potent, and selective GIP (GIP-085) and GLP-1 (GLP-140) receptor agonists (Supplementary Fig. 1A–E). Having two separate molecules instead of a single dual GIP/GLP-1 analog or a hybridized GLP-1/GIP monomolecule allowed us to evaluate the effects of each individual component separately and to modify and optimize dose selection for combination treatments. Pharmacokinetics of GIP-085 and GLP-140 are shown in Supplementary Fig. 1F and G and Supplementary Table 1.

GIPR Agonism Attenuates GLP-1RA-Induced Illness Behaviors in Rats via Central Mechanisms

As a proof of concept that our GIP-085 compound shows the expected glucoregulatory response in vivo, we first tested whether GIP-085 reduces BG following an IPGTT in lean rats 16 h after drug administration. Rats treated with

group). *D*: GLP-140 (1,000 nmol/kg, IP) induces profound anorexia in shrews ($n = 7$). *E*: GLP-140-induced anorexia is accompanied by body weight loss ($n = 7$). *F*: GLP-140 causes profound emesis during 120 min after injection in a dose-related fashion in shrews ($n = 9$). The number of animals exhibiting emesis, expressed as a fraction of the total number of animals tested, is indicated above each treatment group. *G*: Latency to the first emetic episodes of shrews that exhibited emesis following GLP-140 treatment. *H*: Heat maps showing latency, number, intensity, and frequency of emesis following different doses of GLP-140 for each individual animal across time ($n = 9$). *I*: GIP-085 (3, 30, 300, 3,000 nmol/kg, IP) dose-dependently suppressed BG levels following glucose administration (2 g/kg, IP). Veh vs. 3,000 nmol/kg: $*P < 0.05$, $***P < 0.001$; Veh vs. 300 nmol/kg: $\#P < 0.05$; 3,000 nmol/kg vs. 30 nmol/kg: $\$P < 0.05$ ($n = 10$ per group). *J*: AUC from 0 (i.e., postglucose bolus) to 120 min ($n = 10$ per group). *K*: AUC from 0 to 60 min ($n = 10$ per group). *L*: GIP-085 (300, 3,000 nmol/kg, IP) induces anorexia in a dose-dependent fashion in shrews ($n = 10$ per group). *M*: GIP-085 treatment dose-dependently leads to body weight loss ($n = 10$ per group). *N*: No significant emesis occurred following GIP-085 (300, 3,000 nmol/kg, IP) treatment during 120 min after injection ($n = 10$ per group). The number of animals exhibiting emesis, expressed as a fraction of the total number of animal tested, is indicated above each treatment group. All data are expressed as mean \pm SEM. Data in *A*, *D*, *E*, *I*, *L*, and *M* were analyzed with repeated-measurements two-way ANOVA, followed by the Tukey post hoc test. Data in *B*, *C*, *F*, *J*, *K*, and *N* were analyzed with repeated-measurements one-way ANOVA, followed by the Tukey post hoc test. Means with different letters are significantly different from each other ($P < 0.05$).

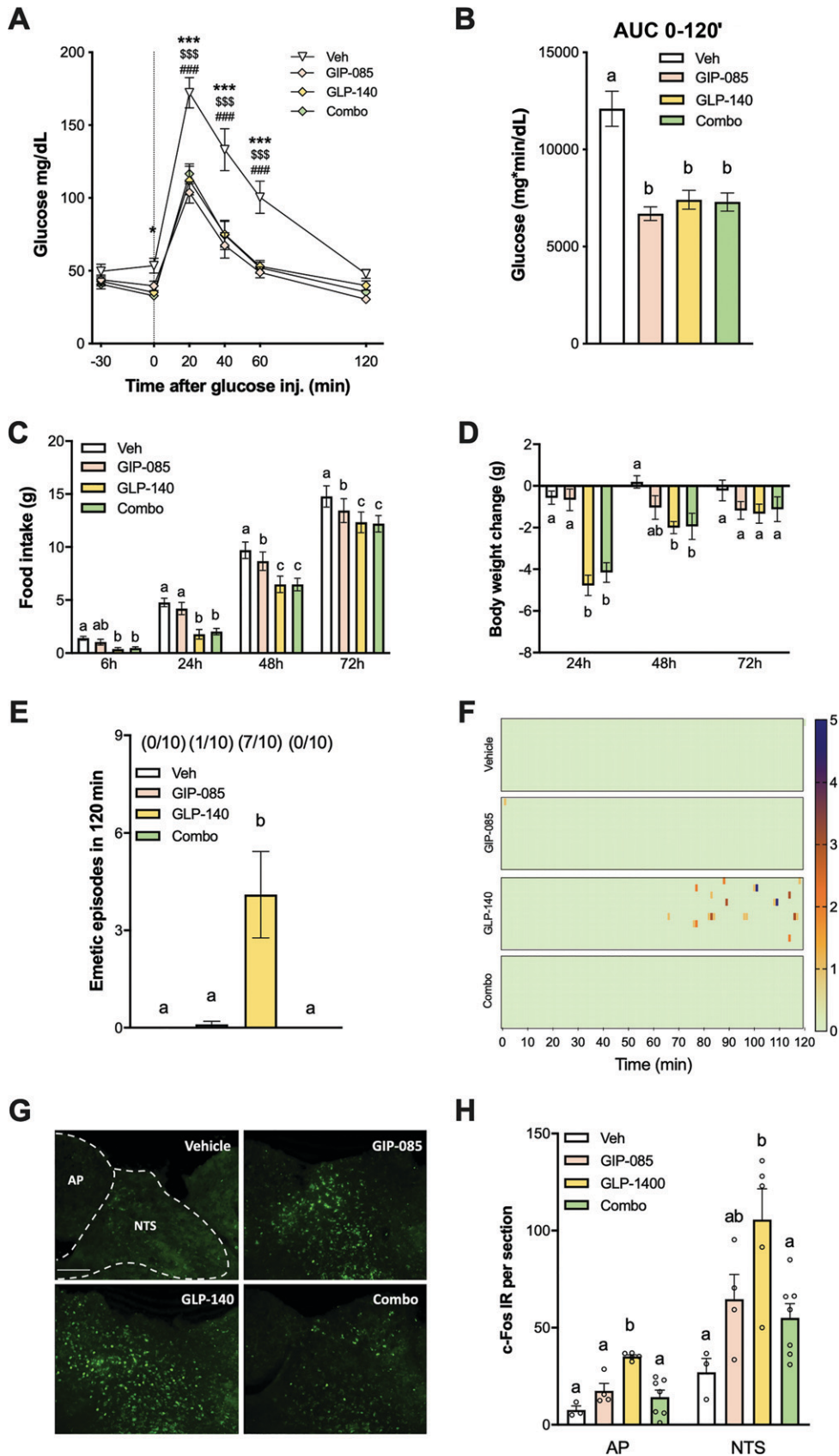


Figure 4—GIP-085 cotreatment retains GLP-140 metabolic and feedings effects and feeding but completely prevents GLP-140-induced emesis in shrews. **A:** In an IPGTT, GIP-085 (300 nmol/kg), GLP-140 (1,000 nmol/kg), and combination (combo) treatment showed similar potency in suppressing BG levels after glucose administration (2 g/kg, IP) compared with saline. Vehicle (Veh) vs. combo: * $P < 0.05$, *** $P < 0.001$; Veh vs. GIP-085: ### $P < 0.001$; Veh vs. GLP-140: \$\$\$ $P < 0.001$ ($n = 15$ per group). **B:** AUC analysis from 0 (i.e., postglucose bolus) to 120 min. All

GIP-085 showed improved glucose clearance following glucose administration compared with controls (Fig. 1A and B). Additionally, GIP-085 dose-dependently increased circulating insulin levels, providing clear evidence of the insulin-stimulating actions of GIP-085 (Fig. 1C and D).

In species that lack the emetic reflex, such as laboratory rodents, pica behavior (i.e., ingestion of nonnutritive substances such as kaolin) is used as a validated proxy for nausea/malaise (29) in response to treatments that induce nausea and vomiting in humans, including GLP-1 analogs. Similar to other GLP-1Rs (30), GLP-140 treatment induced anorexia and body weight loss (Fig. 1E–G). Rats treated with GLP-140 consumed significant quantities of kaolin already at the first measured time point, preceding the onset of the anorectic response (Fig. 1F). GIP-085 treatment alone did not show effect, but remarkably, when coadministered with GLP-140, was able to reduce the acute pica behavior induced by GLP-1R activation (Fig. 1F). Furthermore, GIP-085/GLP-140 treatment led to significantly higher 24-h food consumption compared with GLP-140 and a consequent attenuation of body weight loss (Fig. 1E–G). Since it is well established that GLP-1Rs expressed in the central nervous system, particularly in the hindbrain, mediate the illness-like behaviors of systemically delivered GLP-1R agonists (30), it is plausible that the reduced anorectic effects observed following GIP-085 coadministration are due to an attenuation of centrally mediated GLP-1R-induced malaise. Indeed, infusion of the short-acting GIPR agonist (i.e., nonlipidated GIP-532) into the fourth ventricle (only targeting hindbrain GIPR-expressing cells) was able to attenuate kaolin consumption induced by systemic GLP-1R agonist administration in rats (Fig. 1H–J). These results recapitulate the effects of systemic GIPR agonist administration and therefore point to the hindbrain as a crucial player for the GIPRs in antiemetic action. Additionally, these results are also consistent with supplementary data showing that GIPR agonism is sufficient to attenuate conditioned taste avoidance in mice to saccharin induced by the GLP-1 analog Ex4 (30) (Supplementary Fig. 2).

Single-Nuclei Transcriptomic Phenotyping of GLP-1R and GIPR-Expressing Cells in the NTS and AP of Rats

Recent studies have begun to characterize the phenotype of hindbrain neurons (19,20); however, a systematic

characterization of the cellular phenotype of hindbrain GIPR-expressing cells in rats has not been conducted. The snRNAseq data identified transcriptomically distinct populations of excitatory, inhibitory, and cholinergic neurons (clusters 1–9; Fig. 2A and B) as well as nonneuronal populations (clusters 10–19). The majority of *Gipr*⁺ neurons were identified in two clusters of *Gad1*⁺ inhibitory neurons (clusters 2 and 3; Fig. 2C) and a cluster of *Slc17a6*⁺ excitatory neurons (cluster 5). While the majority of *Glp1r*⁺ neurons were identified in the same inhibitory and excitatory neuron clusters (clusters 2 and 5; Fig. 2D), only a handful of dual *Gipr*⁺ *Glp1r*⁺ neurons were identified (Fig. 2E and F). FISH analyses support this notion (Fig. 2F and G and Supplementary Fig. 3), expanding previous findings in mice (19,20) and suggesting the presence of unique and distinct neuronal circuitries within the AP/NTS for GIPR- and GLP-1R-expressing cells. These data also suggest that the ability of GIPR activation to attenuate illness-like behaviors following GLP-1R activation is not due to potentially competing intracellular signaling processes from the ligands directly acting on the same neuron. Instead, these findings suggest that GIPR signaling may exert a downstream modulation of GLP-1R expressing neuron activation.

GLP-140 Dose-Dependently Lowers BG Levels, Reduces Food Intake, Reduces Body Weight, and Induces Profound Emesis in Shrews

The house musk shrew (*Suncus murinus*) is a vomiting mammal that shows hypoglycemia, anorexia, and emetic sensitivity to several existing GLP-1R agonists (24,25). We first confirmed the ability of GLP-140 to reduce BG following an IPGTT in this model (Fig. 3A–C). Further, although less robust than observations in rats, systemic administration of GLP-140 produced a hypophagic and body weight loss in shrews (Fig. 3D and E). Lastly, our results clearly demonstrate that GLP-140 dose-dependently induced emesis, with most of the shrews experiencing emesis (Fig. 3F) within minutes after administration (Fig. 3G). The emetic profiles of each animal following administration of different doses of GLP-140 are represented in Fig. 3H.

GIP-085 Administration Dose-Dependently Reduces BG Levels, Food Intake, and Body Weight, Without Inducing Emesis in Shrews

Similar to what we observed in rodents, GIP-085 dose-dependently enhanced glucose clearance following an

treatments similarly reduced AUCs compared with vehicle ($n = 15$). C: GIP-085 (300 nmol/kg), GLP-140 (1,000 nmol/kg), and combo treatment reduced food intake compared with vehicle ($n = 10$ per group). D: GLP-140 and combo treatments induce body weight loss in shrews ($n = 10$ per group). E: The profound emesis induced by GLP-140 treatment (1,000 nmol/kg) is completely blocked by GIP-085 (300 nmol/kg) cotreatment ($n = 10$ per group). The number of animals exhibiting emesis, expressed as a fraction of the total number of animal tested, is indicated above each treatment group. F: Heat maps showing latency, number, intensity, and frequency of emesis following treatments for each individual animal across time ($n = 10$ per group). G: Representative immunofluorescent images showing c-Fos⁺ cells in the NTS and AP (~250- μ m rostral to the obex) 3 h after GIP-085 (300 nmol/kg IP), GLP-140 (1,000 nmol/kg IP), or combo treatment. H: Quantification of c-Fos⁺ neurons in the medial NTS and in the AP ($n = 3$ –7 per group). IR, immunoreactive. All are data expressed as mean \pm SEM. Data in A, C, D, and H were analyzed with repeated-measurements two-way ANOVA, followed by the Tukey post hoc test. Data in B and E were analyzed with repeated-measurements one-way ANOVA, followed by the Tukey post hoc test. Data in H were analyzed with one-way ANOVA, followed by the Tukey post hoc test. Means with different letters are significantly different from each other ($P < 0.05$).

IPGTT (Fig. 3I) and induced improvement in the plasma glucose clearing rate, indicative of a retained gluco-regulatory potency of GIP-085 in shrews (Fig. 3J and K). In addition, GIP-085 produced anorexia (Fig. 3L) and body weight loss (Fig. 3M) in the shrews. Importantly however, GIP-085 was well-tolerated in shrews, with virtually no emesis after administration (Fig. 3N). Overall, GIP-085 and GLP-140 share similar gluco-regulatory and body weight-reducing effects in the shrew despite substantial differences in the therapeutic index relative to rodents.

GIP-085 Cotreatment With GLP-140 Retains GLP-140-Mediated Glycemic and Anorectic Profiles but Completely Prevents GLP-140-Induced Emesis in Shrews

GIP-085 and GLP-140, alone or in combination, improved glucose clearance following an IPGTT compared with vehicle injections (Fig. 4A and B). Similarly, GIP-085/GLP-140 cotreatment did not enhance the hypophagic and/or body weight-lowering effect (Fig. 4C–D). Remarkably, however, GIP-085 cotreatment was able to completely prevent GLP-140-induced emesis (Fig. 4E). Given the striking result, the same experiment was repeated in another cohort of shrews, yielding similar outcomes (Supplementary Fig. 4). Overall, these results demonstrate the ability of GIP-085 to completely counteract emesis induced by the GLP-1R agonist GLP-140, likely via hindbrain-mediated mechanisms. Figure 4G and H shows that systemic GLP-140 induces robust *c-Fos* expression, a marker of neuronal activation, in the AP and NTS of shrews. A significant attenuation of *c-Fos* expression in the AP and NTS occurred following GIP-085 cotreatment with GLP-140 compared with the robust *c-Fos* activation by GLP-140 treatment alone (Fig. 4G and H), supporting our hypothesis of a central antiemetic action of GIP-085.

DISCUSSION

Compared with GLP-1 monotherapies GIP/GLP-1 dual agonists improve clinical outcomes beyond those achieved by a selective GLP-1 receptor agonist, and importantly, show a reduction in the incidence of gastrointestinal-related adverse events compared with GLP-1 monoagonist treatments when doses were corrected/matched for efficacy (14–17,31,32). It is, however, important to mention that nausea and emesis were still present in healthy volunteers and patients with T2DM treated with GIP/GLP-1 dual agonists (16,17,32). One possible explanation could be that the dose range and/or the administration regimen used in these clinical trials was suboptimal. Another possible explanation could lie in the pharmacodynamic profile and intrinsic properties of the monomolecular dual agonists compared with the individual profile of the two single separate components (33). Overall, however, there is no doubt of the beneficial effects of targeting both incretin systems to provide enhanced effects on glucose and weight management as well as to offer a valuable

opportunity of increasing the therapeutic window/index via dose modifications with reduced incidence of nausea/emesis adverse events (6,7).

Our data here in three preclinical species show that GIPR activation blocks emesis and attenuates illness-like behaviors (i.e., pica, conditioned taste avoidance) elicited by GLP-1R activation, while remarkably maintaining food intake and body weight suppression as well as improved glucose tolerance. Importantly, the hindbrain is mediating, at least in part, the antiemetic effects of GIPR signaling. Our findings support the hypothesis that these GIPR-expressing γ -aminobutyric acid-ergic neurons may be acting as local inhibitory neurons that modulate the emetic responses elicited by GLP-1R activation, while not preventing the anorectic or glycemic effects of GLP-1R ligands. Given the striking ability of GIPR activation to attenuate the emetic side effect profile of GLP-1R activation, combinatorial pharmaceutical targeting of GLP-1R and GIPR could increase efficacy in treating obesity and diabetes by reducing nausea and vomiting, thereby increasing patient retention and potentially the therapeutic index for GLP-1R agonists.

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Author Contributions. T.B., C.E.G., S.M.F., R.C., J.A.-F., M.D., S.D., M.J.S.-N., R.M.L., J.G., A.W., A.B., M.Y.G., H.J.G., R.C.C., and B.C.R. performed experiments. TB, H.J.G., R.C.C., B.C.R., M.A., R.J.S., B.C.D.J., and M.R.H. analyzed the data. T.B., M.A., R.J.S., B.C.D.J., and M.R.H. conceived and designed the experimental approach. T.B., M.A., R.J.S., B.C.D.J., and M.R.H. prepared the manuscript. All authors edited the manuscript. M.R.H. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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