GIP in the Regulation of GLP-1 Satiety and Nausea

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Abstract

Gastric inhibitory peptide (GIP) is best known for its role as an incretin hormone in control of blood glucose concentrations. As a classic satiation signal, however, the literature illustrates a mixed picture of GIP involvement with an at best weak anorectic response profile being reported for GIP receptor (GIPR) signaling. Not surprisingly, the pursuit of exploiting the GIP system as a therapeutic target for diabetes and obesity has fallen behind that of the other gastrointestinal-derived incretin glucagon-like peptide-1 (GLP-1). However, recent discoveries highlighted here support potential therapeutic advantages of combinatorial therapies targeting GIP and GLP-1 systems together, with perhaps the most surprising finding that GIPR agonism may have antiemetic properties. As nausea and vomiting are the most common side effects of all existing GLP-1 pharmacotherapies, the ability for GIP agonism to reduce GLP-1-induced illness behaviors but retain (if not enhance) weight loss and glycemic control may offer a new era in the treatment of obesity and diabetes.
**Introduction: The intersection of satiety and nausea**

Hunger, satiety, nausea, and emesis are all points along the spectrum of ingestive behavior. This perspective is illustrated in Figure 1 where arbitrary units of positive- and negative-affect are ascribed to each of these subjective feelings. Assuming ingestion begins due to energy need (i.e., from internal physiological drive), hunger is clearly a negative-affect, one often referred to as hunger-pain. But, rapidly upon ingestion, if the ingredients of the meal are deemed palatable, there is undoubtedly a feed-forward positive hedonic response that drives further meal taking. As the meal progresses, various components of the meal (e.g., macronutrient composition, pH, osmolarity, and total volume) give rise to a multitude of gastrointestinal (GI)-derived satiation signals being released from specialized endocrine cells along the GI tract ((1; 2) for review). The collective milieu of these satiation signals transmits an orchestrated within-meal intake inhibitory signal to the brain via the vagus nerve and through direct humoral action. If the animal is appropriately responding to these satiation signals, satiety will eventually be achieved and thus meal termination would in theory end with a modest state of positive-affect. Humans of course, as is evident in the power of the obesogenic environment pervading society at large, can override internal satiation signals with the inclusion of novel highly palatable foods as drivers for continued consumption during the ongoing meal (i.e., dessert)(3). Meal consumption continues to progress and delay meal termination, but as we pass that balancing point of negative/positive affect with the subjective feeling of fullness, the meal begins to take on a difficult to define, but clear state of malaise and nausea(4). Ultimately, persistent meal-taking beyond comfort could easily lead to emesis as an unmistakable state of negative-affect. Importantly, many anti-obesity drugs are designed to shift this ingestive behavior curve to the right by either mimicking a satiation signal and/or by engaging the neurotransmitter systems downstream of satiety signaling. Not surprisingly, nausea, emesis and GI-related adverse events are among the most prevalent side effects of anti-obesity pharmacotherapies. The clinical need to prevent negative-affect and noxious events for patients seeking to lose weight requires a more inclusive consideration of the neural circuitry governing nausea and emesis than has been devoted in the past. Interestingly, as discussed in more detail below, some surprising new discoveries are showing that the body may already hold a secret in combating illness-like behaviors with a GI-derived hormone, gastric inhibitory peptide (GIP), that is rapidly secreted during the early phases of meal consumption.

**Neural substrates mediating nausea and emesis**
Nausea and vomiting are among the most frequently occurring symptoms in a myriad of diseases and treatments related to metabolic disorders. Given their prevalence and the severe negative impact on nutritional balance, quality of life, and disease prognosis\(^5\); \(^6\), improved understanding and long-term control of nausea and vomiting remain an unmet need in many medical fields such as obesity, diabetes, and oncology. Emesis and nausea are largely controlled by the central nervous system (CNS)(\(^6\)-\(^10\)). Three critical nuclei are the nucleus tractus solitarius (NTS), the area postrema (AP) and dorsal motor nucleus of the vagus (DMV): adjacent nuclei in the hindbrain collectively termed the dorsal vagal complex (DVC) that is essential in the control of nausea, emesis, food intake, cardio-respiratory function, and gastrointestinal motility (2; \(^6\)). That so many divergent behaviors and physiological functions are regulated by this overlapping neurocircuitry has surprising led to a paucity of advancement in understanding the CNS neural substrates regulating nausea and vomiting. This is due in part to the use of classic antiemetics targeting the serotonin type-3 receptor (5-HT3R) and neurokinin-1 receptor (NK1R)(\(^11\)). Indeed, the 5-HT3 receptor antagonist ondansetron (Zofran) and the NK1R antagonist aprepitant (Cinvanti) are both prescribed treatments for chemotherapy induced nausea and vomiting(\(^6\)). Unfortunately, for many disease and physiological states that can drive nausea and emesis (e.g. cancers, diabetes, cystic fibrosis, pregnancy) it is clear that the 5-HT3R and NK1R antagonists are suboptimal for the total control of malaise (12-14), suggesting that there are other underlying neural substrates involved in the control of nausea and emesis. To that end, recent discoveries are now shedding light on the role of the GIP receptor (GIPR) system in the DVC as playing a role in processing nausea and vomiting. One critical question is whether the same neurons are engaged at different levels of excitation / inhibition, or is there parallel circuitry in the same nuclei?

**GIP in glycemic control and energy balance and metabolism**

GIP is a hormone released from the enteroendocrine cells in the small intestine early during meal ingestion(\(^15\)). Together with GLP-1, these two incretin hormones serve an important role in priming the beta cells of the pancreas to augment insulin secretion to regulate post-prandial glucose levels (16-18). While pharmacotherapy targeting the GLP-1 system have been widely successful for the treatment of T2DM and obesity, the potential use of GIP analogs as monotherapies have been largely underwhelming in preclinical and clinical studies and even produced some controversial findings ((\(^19\); \(^20\) for review). As such, GIP analogs were initially not pursued as monotherapies to treat diabetes or obesity due to the perception of an overall
weak biological effect, in part because of early findings suggesting a GIP resistance in the diabetic condition (21) alongside incongruent results on its hypophagic and body weight lowering effects (19; 22-26). Nonetheless, there is now convincing evidence that the increase in glucose-stimulated insulin secretion following administration of exogenously applied GIP is mediated by direct activation of GIP receptors (GIPR) expressed on pancreatic β-cells (15; 27). Additional work is also showing that GIPR signaling has positive actions in bones (i.e. promoting mineral density and inhibiting bone reabsorption) (28), modulates thermogenesis (via direct actions on brown adipose tissue) (29), directly influences fat metabolism (by modulating lipid storage and lipolysis in the white adipose tissue) (30) and contributes to the optimal level of postprandial glucagon secretion via direct alpha cell actions (31). These unique actions of GIP, as well as those in combination with GLP-1 described in more detail below, are collectively increasing the exploration of GIP as a therapeutic target.

**GLP-1-GIP co-agonists: Improving glycemic control and weight loss while reducing nausea and emesis**

Approximately 30 years ago, the discovery was made that a compound in the venom-laced saliva of the Gila monster shared similar properties to human GLP-1, but unlike the endogenous active form of GLP-1 (i.e., GLP-1(7-36)), this compound was resistant to enzymatic degradation by dipeptidyl peptidase IV (DPP-IV). This finding initially led to exendin-4 (Ex4; exenatide) (32), a human GLP-1 receptor agonist. Thereafter, a lipidated GLP-1R agonist, liraglutide, was also introduced for the treatment of diabetes and obesity (18). Not surprisingly, the glycemic and energy balance beneficial effects of Ex4 and liraglutide inspired the creation of second generation GLP-1 receptor agonists for treating T2DM, that include but are not limited to dulaglutide and semaglutide (33). These developments yielded substantial overall metabolic improvements in patients compared to first generation GLP-1R agonists that include superior and longer lasting hypoglycemic actions and greater body weight loss.

Importantly, however all first- and second-generation GLP-1R agonists are still accompanied by a high incidence of illness-like behaviors as a principal side-effect that include nausea and vomiting (34-36). A wealth of literature indicates that a significant portion of the hypophagic effects of current GLP-1R agonists are mediated by GLP-1Rs expressed in the CNS, in particular those in the AP/NTS (37-42). Perhaps not surprising, this hindbrain site-of-action, is also responsible for
mediating the illness-like behaviors (e.g. nausea, conditioned taste avoidance, emesis) of systemically delivered GLP-1R agonists (43). Accumulating evidence highlights nausea and emesis as the principal reported side effects of existing GLP-1 therapeutics(44). Industry leaders in the field are also clearly aware of this concern, as a recent report from GlaxoSmithKline concluded that “Patients reported that GI-related issues “Made me feel sick” (64.4%) and “Made me throw up” (45.4%) as their top reasons for discontinuation” (12). Consistent with other diseases, there are clear “disparities between patient experiences and physician perceptions” with a clear need to improve “gaps in physician–patient communication” with regard to GLP-1-therapeutics and incidence of illness. Despite the common dismissive comment to the contrary, these effects are not transient nor insignificant as they lead to discontinuation of treatment in ~6-10% and reduced dose tolerance in another ~15% of T2DM patients (45-52). Thus, using conservative numbers, greater than 20% of patients with type 2 diabetes in the USA cannot benefit fully from existing FDA-approved GLP-1 therapeutics. Thus, finding an ability to attenuate the nausea/emesis adverse events of GLP-1R agonists without affecting action on beta cells or satiety circuits will not only lead to better patient compliance, but may also allow for greater therapeutic tolerability of higher concentrations of GLP-1R agonists to potentially further enhance weight loss and glycemic control. As GLP-1R agonism is now being investigated as a potential pharmacotherapy for an ever-growing number of non-metabolic diseases affecting the CNS (e.g., cognitive impairments, neurodegeneration and substance abuse), achieving greater BBB penetrance will be imperative with higher concentrations of GLP-1R agonists that can be tolerated if nausea/emesis are blocked so as to enrich GLP-1R ligand access to CNS regions not currently accessed by existing approved dosing regiments.

**GIP as an anti-emetic**

GIPR activation may have surprising antiemetic effects, as recently described in a patent application filed by Tekada (53). This finding may contribute in part to the explanation for why the combination of agonists targeting both the GIP and GLP-1 systems has yielded promising results in pre-clinical models and clinical trials, providing greater body weight loss and better glycemic control than GLP-1R agonism alone(25; 54-57). Indeed, in cynomolgus monkeys, GIP/GLP-1 co-agonism was shown to be superior in reducing blood glucose levels and increasing plasma insulin compared equimolar doses of liraglutide (58). The same report showed a reduction in the incidence of gastric-related adverse events for the co-agonist compared to GLP-1 monotherapy.
These data are further supported by our recent discovery that GIPR agonism was sufficient to block the emetic events by a GLP-1R agonist in the musk shrew (59).

The mechanism(s) mediating the anti-emetic actions of GIPR agonism are not known, despite recent work describing the phenotype of GIPR-expressing neurons in the various CNS nuclei involved in the control of energy homeostasis, including the AP and NTS (60; 61). Using single nuclei RNA-sequencing of murine AP/NTS tissue, these two recent independent publications (60; 61), generated the full transcriptome profile of each individual neuron. Intriguingly, a significant portion of Gad1 and Gad2 expressing neurons (responsible for GABA synthesis), also expressed Gipr, while only a few neurons expressed GLp1r and Gipr (60). These data suggest the presence of two unique and very distinct neuronal circuitries within the AP and highlight the hypothesis of a local inhibitory network within the caudal hindbrain that could be exploited via GIPR activation to reduce hindbrain GLP-1R-mediated emesis and nausea.

Conclusions

That the GIP system was initially not heavily pursued as an obesity or diabetes target is not completely surprising given the conflicting literature briefly discussed here. However, the recent discovery that GIPR agonism can block nausea and emesis of GLP-1R agonists should set a precedent to consider whether GIPR agonism can block other drivers of malaise. Indeed, as recently described (53), GIPR agonism was capable of reducing emetic responses that usually occur following gut peptide PYY and cisplatin administrations in beagles and ferrets, respectively. These discoveries should also prompt the field as a whole to re-evaluate whether other GI-derived hormones that also appeared to be lack-luster in metabolic effects as monotherapies may show promise in food intake / glycemic control / anti-emetic potential as a combinatorial target. At least for the GIP system, there is clearly a lot of important unanswered questions with regard to the ability of GIPR agonism to treat nausea and emesis while improving glycemic control.

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Figure legends:

Figure 1: Conceptual graph illustrating that hunger, satiety, and nausea can all be viewed as interconnected points on the same curve of positive / negative affect during a meal.

Figure 2: Overview of the beneficial effects of GIPR agonism in combination with GLP-1-based therapeutics for the treatment of T2DM and obesity. GIP/GLP-1 dual treatment improves gluco-regulation, while simultaneously promoting sustained body weight loss over time. Additionally, GIPR activation may counteract GLP-1-induced malaise via direct modulation of the AP/NTS circuitry. Given the inhibitory nature of the GIPR-expressing neurons, one can speculate the existence of a local inhibitory network within the caudal hindbrain that could be exploited via GIPR activation to reduce hindbrain GLP-1R-mediated emesis and nausea, thus offering a valuable opportunity of dose modifications increasing the therapeutic window/index.

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Hunger, Satiety, Nausea: Points on the Same Curve of Ingestive Behavior

Anti-Obesity Drugs Designed to Augment Endogenous Satiation Signals

Affect Index

Positive

Negative

Time

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