The evolving story of incretins (GIP and GLP-1) in metabolic and cardiovascular disease: A pathophysiologica update

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Abstract
The incretin hormones glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) have their main physiological role in augmenting insulin secretion after their nutrient-induced secretion from the gut. A functioning entero-insular (gut-endocrine pancreas) axis is essential for the maintenance of a normal glucose tolerance. This is exemplified by the incretin effect (greater insulin secretory response to oral as compared to “isoglycaemic” intravenous glucose administration due to the secretion and action of incretin hormones). GIP and GLP-1 have additive effects on insulin secretion. Local production of GIP and/or GLP-1 in islet α-cells (instead of enteroendocrine K and L cells) has been observed, and its significance is still unclear. GLP-1 suppresses, and GIP increases glucagon secretion, both in a glucose-dependent manner. GIP plays a greater physiological role as an incretin. In type 2-diabetic patients, the incretin effect is reduced despite more or less normal secretion of GIP and GLP-1. While insulinotropic effects of GLP-1 are only slightly impaired in type 2 diabetes, GIP has lost much of its acute insulinotropic activity in type 2 diabetes, for largely unknown reasons. Besides their role in glucose homoeostasis, the incretin hormones GIP and GLP-1 have additional biological functions: GLP-1 at pharmacological concentrations reduces appetite, food intake, and—in the long run—body weight, and a similar role is evolving for GIP, at least in animal studies. Human studies, however, do not confirm these findings. GIP, but not GLP-1 increases triglyceride storage in white adipose tissue not only through stimulating insulin secretion, but also by interacting with regional blood vessels and GIP receptors. GIP, and to a lesser degree GLP-1, play a role in bone remodelling. GLP-1, but not GIP slows gastric emptying, which reduces post-meal glycaemic increments. For both GIP and GLP-1, beneficial effects on cardiovascular complications and neurodegenerative central nervous system (CNS) disorders have been observed, pointing to therapeutic potential over and above improving diabetes complications. The recent finding that GIP/GLP-1 receptor co-agonists like tirzepatide have superior efficacy...
compared to selective GLP-1 receptor agonists with respect to glycaemic control as well as body weight has renewed interest in GIP, which previously was thought to be without any therapeutic potential. One focus of this research is into the long-term interaction of GIP and GLP-1 receptor signalling. A GLP-1 receptor antagonist (exendin [9-39]) and, more recently, a GIP receptor agonist (GIP [3-30] NH₂) and, hopefully, longer-acting GIP receptor agonists for human use will be helpful tools to shed light on the open questions. A detailed knowledge of incretin physiology and pathophysiology will be a prerequisite for designing more effective incretin-based diabetes drugs.

**KEYWORDS**

drug mechanism, GIP, GLP-1, GLP-1 analogue, incretin physiology, incretin therapy

## 1 | INTRODUCTION

The scientific interest in GLP-1 (glucagon-like peptide-1) has received its main motivation from the therapeutic potential for type 2 diabetes and obesity, which became obvious after the discovery of GLP-1’s function as an incretin hormone (released from the gut after nutrient ingestion and glucose-dependent stimulation of insulin secretion) in 1987, and the proof-of-principle that the insulinotropic activity is at least partially preserved (published in 1993); thus, allowing a substantial reduction, even a full normalization of plasma glucose in hyperglycaemic patients with type 2 diabetes. Later, the weight-lowering potential boosted the interest in GLP-1. GLP-1 receptor agonists with increasing effectiveness have been approved, and the latest developments led to orally active GLP-1 RAs, both as peptides with absorption enhancers and readily absorbable, small molecular compounds.

GIP (glucose-dependent insulino tropic polypeptide), the ‘neglected incretin’, had quite a different fate. It was found to be a potent incretin in animals and human subjects; however, in acute experiments even with very high, pharmacological doses of GIP, it was close to ineffective as an insulino tropic agent in subjects with type 2 diabetes. No therapeutic potential was seen, especially since GIP receptor knock out mice (GIPR-/—) were protected from weight gain induced by high fat-feeding, suggesting an obesogenic role for GIP receptor agonism. These views were held until tirzepatide, a dual GIP/GLP-1 receptor agonist in development for the treatment of type 2 diabetes, has shown superior efficacy in reducing plasma glucose and glycated haemoglobin (HbA₁c) in comparison to dulaglutide and semaglutide, two potent selective GLP-1 RAs (the latter representing the most effective compound from this class to date). Tirzepatide treatment led to more profound reductions in HbA₁c (by approximately 2%) and in body weight (often exceeding 10 kg on average). These results suggest a contribution of GIP receptor stimulation to both (a) the improvement in glycaemic control and (b) to body weight reduction. These findings have sparked a new wave of research with the aim of defining mechanisms of GIP-GIP receptor interactions explaining superior lowering of plasma glucose as well body weight and has provided recent insights, which are not at all conclusive at this moment in time, and certainly are at conflict with some of the old views on GIP. For these reasons, it is the purpose of the present review to provide state-of-the-art knowledge on the roles of the incretin hormones GIP and GLP-1 in physiology (incretin role, ileal brake function, bone remodelling), pathophysiology (type 2 diabetes, obesity, cardiovascular disease, etc.), with a view on their therapeutic potential derived from a characterization of their biological actions. Since the recent years have produced more insights into the role of GIP, there will be a relative focus on GIP. Details on incretin-based therapy will be the subject of accompanying articles in this supplement volume.

## 2 | THE INCETIN EFFECT DEFINES THE MAIN PHYSIOLOGICAL ROLE OF GIP AND GLP-1

The incretin effect describes the phenomenon that oral glucose, absorbed from the gut, leads to the stimulated secretion of both GIP and GLP-1, which in turn provides a stimulus to β-cells in the islets of Langerhans to augment their insulin secretory responses, while intravenous glucose does not raise plasma concentrations of either GIP or GLP-1, explaining the much lower stimulation of insulin secretion. The incretin effect is the difference between insulin secretory responses to oral and ‘isoglycaemic’ intravenous glucose administration (usually expressed as a percentage of the insulin secretory response to oral glucose). Its size depends on the amount of glucose ingested and can reach up to two-thirds of the total insulin secretory response to oral glucose administration. Judging by the effect size, the incretin effect is a major contributor to important mechanisms necessary to maintain a normal glucose tolerance. Reductions in the incretin effect usually are associated with impairments in oral glucose tolerance (impaired glucose tolerance or diabetes). Technical aspects of how to measure the incretin effect, and a description of variations in the incretin effect associated with various pathophysiological conditions and their therapy, have been extensively reviewed. In short, oral, but not
intravenous glucose induces secretion of GIP and GLP-1, leading to measurable rises in their plasma concentrations. The plasma concentrations reached after nutrient stimulation are instrumental in augmenting insulin secretion, if only plasma glucose concentrations are higher than typical fasting (basal) levels. This ‘insulinotropic’ action is highly dependent on plasma glucose concentrations. Therefore, high

| Tissue/Organ                  | GIP R | Details/commentary | GLP-1 R | Details/commentary |
|-------------------------------|-------|--------------------|---------|--------------------|
| **Endocrine pancreas** (islet of Langerhans) |       |                    |         |                    |
| β-cells                      | +++   | IHC (human)        | +++     | IHC (human)        |
| α-cells                      | ++    | IHC (human)        | −/ (+)  | IHC (human); Present in a small proportion of α cells (various methods) |
| δ-cells                      | +     | scRNA-seq          | −/+     | IHC (human); IHC (human) |
| PP cells (γ - cells)         | +     | IHC (human)        | −       | IHC (human)        |
| **Exocrine pancreas**        |       |                    |         |                    |
| Acinar cells                 | n.r.  |                    | (+)     | IHC (human)        |
| Ductal cells                 | n.r.  |                    | −       | IHC (human)        |
| **Liver**                    | − −   | RT-PCR (rat)       | −       | RNA-seq. (human); IHC (NHP) |
| **Skeletal muscle**          | −     | qPCR (human)       | −       | RP (mouse)         |
| **Heart**                    | +     | qPCR (human), all four chambers | + | qPCR (human), all four chambers; IHC (human/NHP), only sinoatrial node; |
| **Adipose tissue**           |       |                    |         |                    |
| Subcutaneous and visceral    | ++    | qPCR/ WB (human); Unclear whether on adipocytes or stromal-vascular cells. | + | qPCR (human); IHC (human), primarily in vascular cells |
| Brown adipose tissue         | +     | RP (mouse)         | +       | RP (mouse), only blood vessels |
| **Brain**                    |       |                    |         |                    |
| Nucleus accumbens            | ~     |                    | ++      | ISLB (non-human primate) |
| Hippocampus                  | +     | RT-PCR (rat)       | +       | In situ hybridization (non-human primate), low expression |
| Amygdala                     |       |                    | ++      | ISLB (non-human primate) |
| Substantia nigra             | +     | RT-PCR (rat)       | ++      | ISLB (non-human primate) |
| Cerebellum                   | +     | RT-PCR (rat)       | +       | ISLB (non-human primate) |
| Neocortex                    |       |                    | −       | ISLB (non-human primate) |
| Lung                         | +     | qPCR (human)       | +       | IHC (NHP), (vascular) smooth muscle cells; RP (mouse), pneumocytes |
| Kidney                       | −     | RT-PCR (rat) cortex | +       | IHC (human), smooth muscle cells in arterial vessels near macula densa |
| Blood vessels                | +     | WB (human endothelial cell line) | +       | RP (mouse) |
| Bone                         | ++    | IHC (human), cultured primary osteoblasts; (rat), tissue osteoblasts and osteocytes | −/+     | IHC (mouse/rat), absent in cultured osteoblasts; (rat) present in bone marrow stromal cells |
| Gastro-intestinal tract      | +     | qPCR (human)       | +       | IHC (human); Brunner’s glands; |
| Adrenal gland                | +     | RT-PCR (rat) cortex | +       | RP (mouse), medulla |
| Spleen                       | −     | RT-PCR (rat)       | +       | RP (mouse), blood vessel |
| Eye (retina)                 | +     | RT-PCR (rat)       | +       | IHC (human); antibody not validated for IHC |

**Note:** +, ++, ++++, present (weak, intermediate, strong signal); −, not present; ~ not reported; For GIP and GLP-1 receptor expression in the brain, see Figure 3.

**Abbreviations:** IHC, immunohistochemistry; ISLB, In situ ligand binding; RP, reporter protein; scRNA-seq, single-cell RNA sequencing; WB, Western Blot from protein extracts.
concentrations of GIP and GLP-1 do not cause hypoglycaemia. An incretin effect is observed at similar magnitude in rodents, pigs and in human subjects, but not in dogs. The relative contribution of GIP vs. GLP-1 secretion and action to the incretin effect may be subject to species differences.

3 | GIP AND GLP-1 PHYSIOLOGY: ANIMAL STUDIES

3.1 | Distribution of receptors for GIP and GLP-1 in organs, tissues and cell types

Specific seven-transmembrane G protein-coupled receptors for GIP and GLP-1 can be found in the endocrine pancreas (islets of Langerhans) (Table 1), in the brain (Figure 3), and in various other tissues, where GIP and GLP-1 exert biological activities (Figure 1). Proof that a given organ, tissue, or cell type expresses GIP and/or GLP-1 receptors is not a trivial task, since, among other reasons, commercial antisera used for immunohistochemistry often lack the required sensitivity and specificity, as recently outlined by McLean et al in a detailed, excellent review article.

Corresponding to the incretin role of GIP and GLP-1, both receptors are abundantly expressed on β-cells in the islets of Langerhans (Table 1). GIP receptors are also typically found on α-cells of the endocrine pancreas. However, discrepant findings have been reported regarding the α-cell expression of GLP-1 receptors as summarized by McLean et al. GLP-1 receptors probably are found on cell membranes of a minor (10%-15%) subpopulation of α-cells in the human and rodent pancreas. GIP receptors are also found on δ and PP cells, while the presence of GLP-1 receptors on these minor cell populations is more questionable (Table 1).

GIP and GLP-1 receptors are expressed in the heart and in blood vessels. Regarding GLP-1 receptors in the heart, mRNA has been identified in all four chambers of the heart (including human specimens), while GLP-1 receptor protein has escaped detection with the exception of being clearly expressed in the sino-atrial node. Attempts to identify GLP-1 receptors in vascular cells have been less vigorous and often involved isolated cells or cell lines. These findings are of interest in light of the cardiovascular benefits associated with GLP-1 receptor agonist treatment. A functional role has also been assigned to GIP receptors in the heart.

GIP and GLP-1 receptors in adipose tissue will be discussed in relation to their effects on triglyceride storage into adipocytes (vide infra).

Next to metabolic effects, the potential influence of GIP and/or GLP-1 on body weight regulation is another important biological activity that defines a therapeutic potential for incretin hormones. Receptors for GIP and GLP-1 have been identified in brain regions involved in the regulation of appetite, satiety, food/energy intake and energy expenditure (Figure 3). Substantial progress has been made regarding the identification of hypothalamic (arcuate, paraventricular, ventromedial, dorsomedial nuclei) and brain stem nuclei (area postrema, nucleus tractus solitarii, lateral parabrachial nucleus) and their role in

FIGURE 1 Overview on biological glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) effects at the organ/tissue level
meal initiation and termination defining energy balance and body weight regulation.27,28 GIP and/or GLP-1 receptors in other brain regions (Table 1) may be involved in anti-apoptotic effects, synaptic plasticity, memory,23,29 reward functions29 and emotional responses,29,30 with a chance for beneficial effects for a number of neuro-degenerative disorders (vide infra). Nevertheless, species differences have to be taken into account, as there are some differences in GLP-1 receptor expression in the brain between rodents and higher species.29

GIP, perhaps to a lesser degree GLP-1, elicit effects on osteoclasts and osteoblasts involved in bone remodelling, through their receptors expressed in bone tissue (vide infra).

GLP-1 receptors have been identified in testis,31 and GLP-1 receptors have been shown to ameliorate testicular inflammation and sperm quality associated with obesity in mice.32 There may be some benefit of GLP-1 receptor agonism with respect to erectile function,33 suggesting expression of GLP-1 receptors in the corpus cavernosum.

The potential presence of GLP-1 receptors in the eye (primarily in the retina) is of interest with respect to findings of the SUSTAIN-6 study documenting more eye-related clinical events (blindness, necessity for photocoagulation, intravitreal injection therapy or vitrectomy) with semaglutide (GLP-1 receptor agonist) treatment.54 One prominent study claimed the proof of retinal GLP-1 receptors55 and a related prevention of retinal neurodegeneration. However, the GLP-1 receptor antibody employed has not withstood the test of vigorous scrutiny.53 The absence of GLP-1 receptors in the eye reinforces the conclusion that the eye events cannot be explained by an interaction of semaglutide with retinal GLP-1 receptors, but rather by the rapid and substantial fall in plasma glucose and HbA1c concentrations, that is, a dramatic improvement in glycaemia control prompted by the initiation of semaglutide therapy in some patients with pre-existing advanced retinopathy.56

For further information on GIP and GLP-1 polymorphisms and variants, see Online Supplement, section 1.

3.2 | GIP and GLP-1 secretion

Incretin hormones, by definition, are characterized by low (basal) plasma concentrations in the fasting state, and substantial increments following nutrient intake.57 Both GIP and GLP-1 secretion from K and L cells, respectively, is mainly stimulated by the ingestion and absorption of carbohydrates and triglycerides or their digestion products (Table 2), and (to a lesser degree) by protein or amino acids. A notable exception may be glutamine, which preferentially stimulates GLP-1 secretion, and may be an example of a relatively specific GLP-1 secretagogue (eg, to be used in addition to inhibitors of dipeptidyl peptidase-4 [DPP-4] to boost efficacy39). Bypassing the absorptive process in the gut by intravenous administration of glucose, amino acids or lipid emulsions do not elevate GIP and/or GLP-1 secretion. Regarding the mechanisms coupling the presence of the secretagogues to the release of GIP and/or GLP-1, some are shared by K and L cells: Membrane glucose transporters SGLT-1 and GLUT2, $K_{ATP}$ channels and calcium-sensing receptors, 7-transmembrane G-protein-coupled receptors GPR 40, GPR 119, and GPR 120, inhibitory neurotransmitters like galanin (for details and references, see Table 2). Specifically for K cells and GIP secretion, insulin may play a role as part of a feedback inhibitory mechanism limiting GIP-induced insulin secretory responses.59 Unique for L cells and GLP-1 secretion are the roles of sweet taste receptors (gustducin),60,61 gastrin-releasing peptides (a stimulatory neuropeptide),62 a stimulatory function of GIP63 (only in rodents), and of the inflammatory cytokines interleukin-164 (stimulating GIP secretion) and -65 (stimulating GLP-1 secretion). The latter (muscle-derived IL-6) may stimulate GLP-1 in connection with physical exercise.66 Gut intraepithelial T lymphocytes expressing integrin-β7 and GLP-1 receptors have the ability to suppress the secretion of GLP-1, potentially leading to metabolic disturbances and accelerated atherosclerosis, which can be prevented by integrin-β7 knock-out.67

3.3 | Insulin secretion

Insulin secretion is stimulated by GIP in mice,68,69 rats,70 and pigs,71 and by GLP-1 in mice,69 rats and7 pigs.1 The evidence is less convincing in dogs72 and non-human primates.73 A remarkable feature of insulin secretion under the influence of GIP and GLP-1 is the strict glucose-dependence: GIP does not stimulate insulin secretion from the isolated perfused rat pancreas at glucose concentrations below 4 mmol/L (72 mg/dL), and the degree of augmentation of insulin secretion increases with increasing degrees of hyperglycaemia.74 Along the same lines, GLP-1 requires a permissive degree of hyperglycaemia for its insulinotropic actions.75 The main reason is the fact that GIP and GLP-1 receptors on endocrine pancreatic β-cells are coupled to G-proteins that lead to the stimulation of adenylate cyclase and the intracellular production of cyclic AMP, which in turn elicits biological effects through the stimulation of protein kinase A (PKA).76 Thus, both incretin hormones are ineffective in initiating an insulin secretory response, which requires membrane depolarization, for example, as triggered by hyperglycaemia and the subsequent closure of K-ATP channels.77 This feature is one of the important prerequisites for the low, if not absent, risk for hypoglycaemia with incretin-derived glucose-lowering medications.

3.4 | Glucagon secretion

While the stimulation of insulin secretion by GIP and by GLP-1 is characterized by extensive similarities regarding their dose-response characteristics and their glucose-dependence, there are characteristic differences with respect to glucagon secretion: While GLP-1 suppresses glucagon122 (as one important component of its potentially “therapeutic” mode of action), GIP can stimulate glucagon secretion.123 The stimulation of glucagon secretion in the isolated perfused rat pancreas by GIP depends on a low plasma glucose concentration.123 The difference with respect to the stimulation (GIP) or suppression (GLP-1) of glucagon secretion points to the fact, that the two incretin hormones have overlapping, but not identical biological roles.

For further information on intra-islet production of GIP and GLP-1 (Figure 2), see Online Supplement, section 2.
| **Table 2** Secretion of glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1): Shared features and difference |
|-----------------|-----------------|-----------------|
| **Cell of origin (production/secretion)** | K cells (duodenum/upper jejunum) | L cells (increasing number towards the distal small intestines, colon and rectum) |
| **Prohormone** | Pro-GIP | Proglucagon |
| **Prohormone convertase** | PC 1/3 | PC1/3 |
| **Nutrient secretagogues** | | |
| **Carbohydrates** | | |
| Glucose | ↑↑ | ↑↑ |
| Fructose | ↓↓; ↑0 | ↓0 |
| Protein/amino acids | ↑94 | ↑58 |
| Glutamine | n.r. | |
| **Fat (triglycerides)** | | |
| Fatty acids | ↑↑; Saturated | ↓ Short-chain FFA |
| 2-monoacylglycerol | n.r. | |
| **Secretion mechanisms** | | |
| \( K_{\text{ATP}} \) channels | ↑↑ | ↑↑ |
| Calcium-sensing receptor | + | + |
| Sweet taste receptors | n.r. | + |
| 7 TM G protein-coupled receptors | + | + |
| \( \text{GPR40} \) | + | + |
| \( \text{GPR119} \) | + | + |
| \( \text{GPR120} \) | + | + |
| \( \text{TGR5/GPBAR1} \) | n.r. | |
| \( \text{Farnesoid X receptors} \) | n.r. | |
| **Neurotransmitters** | | |
| Galanin | ↑113 | Gastrin-releasing peptide↑62; Galanin↑113; somatostatin↑114; endocannabinoids↑114 |
| | | Via Gal1 receptor↑113 |
| **Gut hormones** | n.r. | GIP↑63 |
| **Inflammatory stimuli** | | |
| LPS, mediated by Interleukin-1 | ↑64 | LPS, mediated by Interleukin-6 | ↑65,66 |
| **Feedback inhibition by insulin** | ↓59 | n.r. |
| **Secretion in obese subjects** | (↑)↑115 | (↑)↑116 |
| **Secretion in T2DM** | (↑)↑117 or ≈118 | ≈119 or (↑)↑116,120 |
| **Secretion after gastric bypass** | (↑)↑121 | (↑)↑121 |

**Commentary**
- Cells expressing both GIP and GLP-1 have been described as well.\(^{60,81}\)
- “Aberrant” processing to (“pancreatic-type”) glucagon has been described in the gut.\(^{83}\)
- In endocrine pancreatic \( \alpha \)-cells, PC 2 predominates.\(^{85}\)
- All carbohydrates yielding glucose after digestion
- Important stimulus for both GIP and GLP-1
- Longer-lasting elevations in GIP and GLP-1 as compared to carbohydrate
- Via FFAR2 (GPR43)\(^{88}\) and fatty acid transport protein 4\(^{47}\)
- Points to electrical activity
- Artificial sweeteners do not release incretins significantly
- Receptors for free fatty acid(s) (or their derivatives)
- Potentially important after bariatric surgery
- Only in rodents
- GLP-1 and GIP secretion is stimulated by different inflammatory cytokines
- May limit insulin secretion
- Conflicting results due to high inter-individual variations
- Responsible for reduced weight and improved glycaemic control

**Note:** ↑, ↑↑, ↑↑↑, increases slightly, moderately, or substantially; ↓, ↓↓, ↓↓↓, decreases slightly, moderately, or substantially; +, has an influence; −, has no influence.

**Abbreviations:** LPS: Lipopolysaccharide; n.r. not reported.
3.5 Body weight regulation (food/energy intake, energy expenditure)

Particularly GLP-1, but recently also GIP has been found to be involved in the regulation of body weight.

3.5.1 GLP-1

Intracerebroventricular administration of μg amounts of GLP-1 reduces food intake in rodents. GLP-1 administered peripherally reaches certain CNS areas (subfornical organs and area postrema). 

FIGURE 2 “Aberrant” production of glucagon-like peptide-1 (GLP-1) (and glucose-dependent insulinotropic polypeptide [GIP]) in α-cells of the endocrine pancreas and of (pancreatic-type) glucagon in gut L cells: Cell types and prohormone convertases involved and resulting “aberrant” products of proglucagon and proGIP translational processing.

FIGURE 3 Glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptors in the hypothalamus and brainstem involved in the regulation of energy intake (meal initiation and termination) and body weight. PB: Parabrachial nucleus; NTS: Nucleus tractus solitarii; AP: Area postrema; PVH: Para-ventricular hypothalamus; DMH: Dorso-medial hypothalamus; VMH: Ventro-medial hypothalamus; ARC: Arcuate nucleus; POMC/CART: Proopiomelanocortin/cocaine-amphetamine-regulated transcript; NPY: Neuropeptide Y; AgRP: Agouti-related peptide.
TABLE 3 Patterns of effects of GIP receptor agonism or antagonism on energy balance, body weight, and glycaemic control in animal models of obesity and diabetes

| Experimental approach | Model                              | Body weight/energy household | Glycaemic homeostasis | References                  |
|-----------------------|------------------------------------|-----------------------------|-----------------------|-----------------------------|
|                       |                                    |                             |                       |                             |
| Agonism               | Prevention of diet-induced obesity and diabetes | (\(\downarrow\)) (\(\downarrow\)) 0 | \(\uparrow\) \(\downarrow\) | 132-137                     |
|                       | Treatment of pre-existent obesity and diabetes | (\(\downarrow\)) 0 \(\downarrow\) (\(\downarrow\)) 0 | \(\uparrow\) \(\downarrow\) | 138-143                     |
| Antagonism            |                                    |                             |                       |                             |
|                       | Prevention of diet-induced obesity and diabetes | 0 0 \(\downarrow\) (\(\downarrow\)) 0 | 0 0 | 144                           |
|                       | Treatment of pre-existent obesity and diabetes | 0 \(\downarrow\) 0 \(\downarrow\) (\(\downarrow\)) 0 | \(\uparrow\) (\(\downarrow\)) | 132,141,145-152             |

Note: The present table summarizes patterns of effects evident from published studies on this topic compiled in Supplementary Table 1. Prevention of diet-induced obesity describes studies starting with healthy, non-obese animals receiving experimental treatment while receiving a high-fat diet; Treatment of pre-existing obesity describes studies, in which obesity was present due to genetic mutations (ob/ob or db/db mice), or was induced by high-fat diets prior to starting experimental treatment. Agonism summarizes peptide GIP agonists, interventions leading to GIP hypersecretion, or antibody-mediated stimulation of GIP receptors; antagonism summarizes peptide GIP antagonists, interventions against K cells or GIP secretion, or specific antibodies either inactivating circulating GIP or GIP receptors. (\(\downarrow\)), (\(\downarrow\)), (\(\downarrow\)): Trend or significant increment in this parameter (weak, intermediate or strong effect); (\(\downarrow\)), (\(\downarrow\)), (\(\downarrow\)): Trend or significant reduction in this parameter (weak, intermediate or strong effect); 0: no obvious effect. Only patterns that are representative for all published studies in this category have contributed to conclusions summarized in this Table.

and reduces appetite and food intake.\(^5\) GLP-1 receptor agonists reduce body weight.\(^7,8\) The GLP-1 receptor agonist lixisenatide and exenatide, after peripheral administration, reach hypothalamic and brainstem nuclei, which at the same time are equipped with GLP-1 receptors (Figure 3).\(^27,28\) In the arcuate nucleus, GLP-1 receptors are found on neurons also expressing POMC/CART (proopiomelanocortin/cocaine and amphetamine-regulated transcript). POMC/CART neurons are depolarized (activated) by GLP-1 receptor stimulation and inhibit orexigenic NPY/agouti-related peptide neurons,\(^27,28\) which is associated with reduced appetite and a deferred initiation of meals. Both types of neurons project to the lateral parabrachial nucleus, where meal termination is regulated (Figure 3).\(^27,28\) A role for GLP-1 in body weight reduction is well established and has led to the development of GLP-1 receptor agonists for the treatment of type 2-diabetic patients, but also to dedicated development programs for the treatment of obesity and associated disorders.\(^8\) GLP-1 receptor agonists are also found on afferent parasympathetic nerve fibres in the gut (with their nerve endings close to L cells and capillaries draining the mucosa)\(^126,127\) and in the hepato-portal region.\(^128,129\) Stimulation of these receptors participates in metabolic regulation,\(^127-129\) but may also be one mechanism mediating effects of circulating GLP-1 on appetite and food intake. This does not appear to be important when GLP-1 concentrations are in the physiological range.\(^130\)

3.5.2 | GIP

Based on studies in transgenic rodents with a knocked-out GIP receptor, which gain less weight on a high-fat diet, an obesogenic role for GIP has been a popular view, especially considering an anabolic role in adipose tissue favouring triglyceride storage. Consequently, GIP receptor antagonists or other interventions interfering with GIP secretion or action have been explored in animal models of obesity/impaired glucose tolerance (genetic background like ob/ob, db/db [mice], ZDF [rats], or dietary interventions). On the other hand, recent studies have provided evidence for GIP or its receptor agonists preventing diet-induced obesity and reducing body weight in already obese animals (Table S1). Thus, opposing therapeutic measures are claimed to be beneficial for obesity, metabolic syndrome and type 2 diabetes. A recent review by Campbell has summarized these findings and suggests some mechanisms explaining these apparently contradictory approaches,\(^131\) which both have been extensively studied (Table S1). Predominant patterns for therapeutic effects of GIP agonism as well as antagonism in preventing diet-induced obesity and in reducing body weight in pre-existing obesity detected in Table S1 have been summarized as Table 3.

3.6 | Weight-lowering therapy with GIP receptor agonism vs. antagonism

Both GIP receptor agonism and antagonisms have been described to reduce body weight or prevent diet-induced obesity.\(^131\)

3.6.1 | GIP receptor antagonism

In the prevention of diet-induced obesity, some, but not all studies indicate a reduction in body weight gain, more consistently in models with inactivated GIP receptors and immunological interventions compared to pharmacological GIP receptor antagonists. Genetic models also describe a reduction in food intake. No clear pattern is found regarding energy
expenditure. Rather uniformly, glucose tolerance and insulin sensitivity are improved with reduced or absent GIP receptor signalling (Table S1). GIP receptor antagonism is less effective in reducing body weight in pre-existing obesity; however, an improvement in glucose tolerance and insulin sensitivity has typically been described (Table S1).

3.6.2 | GIP receptor agonism

In the prevention of diet-induced obesity, overexpressing GIP in K cells reduces body weight and food intake, and it improves glucose tolerance and insulin sensitivity.\(^\text{144}\) This pattern is remarkably similar to the effect of GIP receptor antagonism in the comparable experimental paradigm (Table S1). In the treatment of pre-existing obesity, GIP receptor agonism in earlier studies (2005-2014) appeared to be ineffective, while more recent studies (2015-2021) consistently found a reduction in body weight in parallel with a reduction in food intake.\(^\text{132,141,153}\) This may be the consequence of employing higher-affinity GIP receptor agonists with slower elimination pharmacokinetics, providing more reliable 24 hours exposure with daily administration. Unfortunately, there is no longer-acting GIP receptor agonist available for human studies. Considering the superior weight loss described with the GIP/GLP-1 receptor co-agonist tirzepatide, joint effects of GIP and GLP-1 receptor stimulation are of interest. After intracerebroventricular injection, synergistic effects have been described.\(^\text{154}\)

No effects of either GIP agonism or antagonism were seen when rodents were fed normal chow (Table S2).

The paradoxical observation that GIP receptor agonism and antagonism sometimes have similar effects on body weight and glucose tolerance has recently been reviewed by Campbell.\(^\text{131}\)

3.7 | Effects on adipose tissue function

Fat cell GIP receptors were shown in human, animal and cell culture models by gene expression and functional assays.\(^\text{155-157}\) GIP was shown to increase glucose uptake and the activity of lipoprotein lipase and of lipogenesis (i.e., the re-esterification of free fatty acids into triglycerides in vitro in isolated fat cells).\(^\text{157-160}\) GIP also supported de novo lipogenesis from glucose as well as lipolysis in in vitro studies.\(^\text{155,161,162}\) GIPR expression increased with the differentiation of adipocytes.\(^\text{159}\) GIP thus supports the lipid storage of adipose tissue that is supported by animal studies showing that a selective deletion of adipose tissue GIPR reduces high-fat diet induced obesity.\(^\text{133,163}\)

Some groups interpret the lipotropic function of GIP as positive, arguing that it may support the expansion of healthy subcutaneous fat depots,\(^\text{164}\) while most studies view GIP as an obesogenic endogenous hormone in adipose tissue.\(^\text{165-166}\) Although the genetic deletion or blockade of GIP receptors prevents high-fat diet induced obesity (vide supra) these studies combine weight gain and high-fat diet, which may elicit independent effects.\(^\text{169}\) High-sucrose diets induce fatty liver in mice, while isomaltulose, which is a slowly cleaved 1,6-linked glucose-fructose dimer, and therefore, releases very little GIP in contrast to the rapidly cleaved GIP-releasing sucrose, prevents triglyceride accumulation in the liver, independent of weight gain and insulin release.\(^\text{168,170}\) Moreover, GIP receptor knock out mice are protected from sucrose- or high glycemic index-induced fatty liver.\(^\text{169-171}\) GIP, therefore, promotes ectopic fat storage in mice, the hallmark of ‘unhealthy’ obesity, and may similarly mediate the unfavourable effects not only of high-fat diets,\(^\text{169}\) but also of rapidly absorbed or high glycemic index–carbohydrates, a characteristic of highly processed foods typical of Western diets.\(^\text{168}\) Although these data clearly show the effect of endogenous GIP, they may not be informative regarding pharmacological agonists or antagonists.\(^\text{133}\) For further information on the therapeutic potential of GIP receptor agonists or antagonists, see Table S1.

Cell culture studies support a proinflammatory action of GIP in adipose tissue. Human stem cell-derived adipocytes secrete cytokines such as IL-6 upon stimulation by GIP.\(^\text{161}\) Cocultures of human macrophages with human fat cells showed increased release of MCP-1 in the presence of GIP\(^\text{172}\), and overexpression of GIP receptors in 3T3-L1 cells induced a Jun N-terminal kinase (JNK) dependent cytokine expression and insulin resistance.\(^\text{173}\) There is some evidence for expression of GIP receptors in stromal vascular adipose tissue in endothelial cells and monocyte/macrophages,\(^\text{172,174,175}\) which were proposed to mutually interact to enhance inflammation.\(^\text{172,174,176}\) A limited, GIP-induced, acute postprandial release of cytokines may, however, represent a physiological response required for the healthy function of adipose tissue.\(^\text{177}\) It may become pathogenic only if exaggerated, as in insulin-resistant obesity.\(^\text{176}\) By contrast, other studies reported increased inflammatory responses upon targeted deletion of GIP in myeloid immune cells suggesting anti-inflammatory functions of endogenous GIP.\(^\text{178,179}\) These differences may be related to the diverging roles of GIP in the immune cell development concerning the myeloid compartment\(^\text{180}\) and in an adipose tissue environment where it triggers differentiation of monocytes to more (M1) or less (M2) inflammatory macrophage phenotypes.\(^\text{172,176}\) However, marked global overexpression of GIP-reduced inflammatory markers in mice and prevented obesity\(^\text{144}\) which confirms the currently unresolved paradox of similar effects of agonists and antagonists of GIP on metabolism.

Figure 4 illustrates the influences of GIP and/or GLP-1 on white adipose tissue cells.

For further information on GIP and GLP-1 effects on insulin sensitivity, see Online Supplement, section 3.

For further information on GIP and GLP-1 effects on bone metabolism and stability, see Online Supplement, section 4.

4 | GIP AND GLP-1 PHYSIOLOGY: HEALTHY HUMAN SUBJECTS

4.1 | Secretion of GIP and GLP-1

Like in animals, the main stimuli for the secretion of GIP from K cells (mainly located in the duodenum and upper jejunum) and GLP-1 (L cells with their density increasing from the lower jejunum to the ileum and further to the colon and rectum) are nutrients like glucose...
and other carbohydrates, amino acids derived from protein digestion and triglycerides. Details are presented in Table 1. A release of GIP and GLP-1 requires the presence of these nutrients in the intestinal lumen and their absorption through enterocytes. The same energy substrates administered intravenously do not change the rate of secretion of GIP or GLP-1. This is not only true in the case of glucose,12 but also with respect to amino acids181 and lipids.182 As outlined in detail elsewhere,12 oral glucose- or meal-stimulated GIP concentrations rise to higher values compared to GLP-1 concentrations.12 Responses to meals high in fat content (or pure lipid meals) last longer than those to readily absorbed monosaccharide or disaccharide solutions. As a rule, it takes approximately 10 to 15 minutes before the plasma concentrations of GIP and GLP-1 rise above basal concentrations after nutrient intake. Peak values are usually observed after 45 to 90 minutes, followed by a progressive decline over a few hours. The fact that the bulk of GLP-1 is synthesized and stored in L cells in the lower gastrointestinal tract has sparked the idea that the upper small intestine signals the lower intestinal GLP-1 release upon contact with nutrients. Entero-hormonal (GIP as the signal63) and neural transmission (intramural plexus, for example, gastrin-releasing peptide as neurotransmitter 62) have been suggested as potential mechanisms. Their role in human physiology, however, has not been substantiated.12 Even in rodents, the main source for the luminal stimulation of GLP-1 secretion appears to be L cells in the upper small intestines.183 Only systemic stimuli (eg, inflammatory cytokines) appear to release GLP-1 from the full length of the gut.183 Circulating concentrations of GIP and/or GLP-1 reached by endogenous secretion from K or L cells are sufficient to stimulate insulin secretion, as long as plasma glucose concentrations are in the permissive range of hyperglycaemia.15

4.2 | Insulin secretion and the incretin effect

In healthy human subjects, GIP184,185 and GLP-115 stimulate insulin secretion in a glucose-dependent manner (as already outlined when describing rodent and porcine experiments). Nevertheless, even with high-physiological concentrations of GIP achieved by exogenous infusion, insulin secretion approached zero at an average plasma glucose concentration of 2.4 mmol/L (43 mg/dl).186 With pharmacological concentrations of GLP-1, the glucose threshold for stimulating insulin secretion has been found to be around 66 mg/dL (3.7 mmol/L)187 in healthy human subjects. The higher plasma glucose concentrations rise, the greater the relative stimulation by GIP186 and GLP-1188 seems to rise. Both GIP and GLP-1 act by potentiating insulin secretion triggered by hyperglycaemia as the primary stimulus. Thus, the plasma glucose concentrations eventually determine the degree of stimulation of insulin secretion in subjects exposed to GIP and/or GLP-1.187,189 The exact characteristics of glucose-dependence have never been compared head-to-head between GIP and GLP-1.

Two approaches have been used to estimate the relative importance of GIP and GLP-1 as mediators of the incretin effect: Earlier studies have attempted to match plasma concentrations of GIP and GLP-1 to those measured after oral glucose intake, and have measured insulin, C-peptide and calculated insulin secretion rates with physiological plasma glucose concentration profiles maintained by ‘isoglycaemic’ clamp procedures.15 Since GIP and GLP-1 concentrations during exogenous administration and after oral glucose loads roughly were matched, a major role for GIP and a minor role for GLP-1 in mediating the incretin effect were concluded.15 This was in line with the higher concentrations measured for GIP as compared to GLP-115 (as is usually observed).12
Now, specific high-affinity peptide antagonists at the GIP (GIP [3-30]) and GLP-1 (exendin [9-39]) are available which allow the near-complete blockade of biological effects of endogenously released GIP and GLP-1, respectively.\textsuperscript{190,191} Using this novel methodology, Gasbjerg et al.\textsuperscript{16} have confirmed the assumption that the contribution of GIP to mediating the incretin effect after oral glucose in healthy human subjects is far greater than that of GLP-1.\textsuperscript{17} Similar results have been found after mixed meals.\textsuperscript{192} Thus, GIP has been established as the major physiological incretin hormone. This conclusion has sometimes not been emphasized appropriately, given the obvious therapeutic potential of GLP-1.

### 4.3 Glucagon secretion

In fasting human subjects, GLP-1 transiently suppresses glucagon secretion,\textsuperscript{187,193} with the consequence that—in the absence of counter-regulatory measures—hepatic glucose production is reduced as well as plasma glucose concentrations.\textsuperscript{193} However, in response to hypoglycaemia, glucagon concentrations increase as much as they would in the absence of GLP-1.\textsuperscript{187} Overall, the effect of GLP-1 on glucagon secretion depends on ambient glycaemia: At or below 5 mmol/L (90 mg/dL) plasma glucose, GLP-1 may even stimulate glucagon, while at euglycaemia\textsuperscript{187} or hyperglycaemia, glucagon is suppressed by GLP-1.\textsuperscript{186,187} One of the major differences between GIP and GLP-1 is their influence on glucagon secretion: GIP has the potential to increase glucagon in the absence of hypoglycaemia.\textsuperscript{194}

When quantifying the incretin effect by comparing insulin secretory responses to oral and ‘isoglycaemic’ intravenous glucose, glucagon is suppressed more with intravenous glucose than with oral glucose.\textsuperscript{195,196} The explanation could be a stimulation of glucagon secretion by GIP\textsuperscript{195} and GLP-2\textsuperscript{197} after oral glucose, which is absent during intravenous glucose administration.

### 4.4 Food (energy) intake and energy expenditure

Since therapeutic effects of either GLP-1 or GIP on body weight are discussed, the question arises, whether physiological concentrations of both incretin hormones, alone or in combination, may affect appetite, satiety, prospective food consumption, and, eventually, food (and, therefore) energy intake or, alternatively, energy expenditure (Figure 3). Pharmacological doses and/or concentrations of GLP-1 do reduce appetite and prospective food intake and increase satiety and a feeling of fullness in healthy human volunteers.\textsuperscript{5} To the best of our knowledge, truly physiological plasma concentrations of GLP-1 have never been shown to modify energy intake.\textsuperscript{198} The GLP-1 receptor antagonist exendin [9-39], however, has even reduced energy intake in obese subjects, a finding hardly compatible with an effect of physiological GLP-1 on reducing appetite and energy intake.\textsuperscript{199} Therefore, a reduction in food intake seems to be a consequence of pharmacological rather than physiological doses/concentrations of GLP-1. This may, nevertheless, be an important prerequisite for beneficial therapeutic actions of GLP-1 receptor agonists in type 2 diabetes, obesity and its related conditions.

Regarding GIP, effects on appetite and food intake have only recently been claimed based on animal studies identifying GIP receptors on hypothalamic neurons in the CNS of mice, the optogenetic activation of which reduced food intake.\textsuperscript{46} Peripherally administered GIP has been described to have similar effects.\textsuperscript{132} In human obese volunteers, it has not been possible to reduce appetite or food intake with exogenous GIP, even at pharmacological quantities.\textsuperscript{200} Rather, GIP counteracted the food reduction observed with exogenous GLP-1 when administered in combination.\textsuperscript{200} An effect of endogenously released GIP on appetite, satiety, fullness and prospective food consumption has not been found, when employing the GIP receptor antagonist GIP [3-30 amide].\textsuperscript{16,192} and ad libitum food intake has not been reported to change with either GIP\textsuperscript{201} or GLP-1 receptor antagonist treatment,\textsuperscript{16,192} nor with their combination.\textsuperscript{16} Therefore, the preclinical findings of GIP mediating reduced food intake and, potentially, weight reduction, lack confirmation in human studies. Also, while the uptake of peripherally administered GLP-1\textsuperscript{125} and GLP-1 receptor agonists liraglutide and semaglutide\textsuperscript{27,28} into the relevant brain areas have been firmly established, such studies are lacking for GIP or GIPR agonists. With the current information at hand, it is impossible to conclude whether these study results indicate a relevant species difference between rodents and human subjects.

Acute effects of GIP and/or GLP-1 on energy expenditure appear to be negligible, both when responses to (high dose) exogenous administration\textsuperscript{200} or to endogenously secreted GIP and/or GLP-1 (using antagonists GIP [3-30 amide] and/or exendin [9-39])\textsuperscript{192} were analysed.

Under conditions where treatment with either GIP or GLP-1 (or their receptor agonists) leads to weight reductions, another question arises: A reduction in body weight predominantly affects adipose tissue mass, however, a slight reduction in lean body (ie, skeletal muscle) mass is usually observed as well. The latter is strongly connected with resting energy expenditure, so that a reduction in muscle mass will almost always be associated with a reduction in resting energy expenditure. A reduction in resting energy expenditure counteracts weight loss or requires a more negative energy balance to maintain the weight loss induced by a given calorie restriction.\textsuperscript{202} While some evidence for such a mechanism has been suggested in the case of GLP-1 receptor agonists reducing body weight,\textsuperscript{28} it has not been studied in detail, whether GIP or GLP-1 agonism might interfere with adaptations of energy expenditure leading to increasing or decreasing body weight. Such a mechanism could be important for a potential influence of GIP and/or GLP-1 agonism on body weight, even in the absence of simple effects on food/energy intake or energy expenditure.

In summary, GLP-1 and its receptor agonists reduce food intake and body weight when used in pharmacological doses/concentrations. Similar effects of GIP have been described in rodent studies, but contradictory findings have been reported from studies in human volunteers. This discrepancy could indicate important interspecies differences and should be resolved with further research. There is no
obvious change in (resting) energy expenditure in response to GIP or GLP-1 receptor stimulation contributing to effects on body weight or composition.

4.5 Gastric emptying and intestinal mobility and dependent gastro-intestinal functions

Gastric emptying is slowed by physiological and pharmacological doses/concentrations of GLP-1,203–205 at higher doses leading to a complete standstill of gastric emptying.204,205 GLP-1 receptor agonists also retard gastric emptying.206,207 On the other hand, GIP has no effects on gastric emptying.208 Several aspects related to effects of GLP-1 and GLP-1 receptor agonists on gastric emptying are worth mentioning: (a) Retarded gastric emptying leads to a slower, potentially overall reduced, plasma concentration increment in substrates originating from gastric contents, among them glucose and triglycerides.204,205,209 Since post-meal rises in plasma glucose are important determinants of insulin secretory responses, insulin secretion is reduced with lesser glycaemic excursions caused by decelerated gastric emptying.204,209,210 This leads to the paradoxical effect that the incretin hormone (this role is defined by a net stimulation of insulin secretion57) GLP-1 reduces insulin secretory responses, since the effects on gastric emptying outweigh the direct insulinotropic effect as a result of lower increments in plasma glucose concentrations.204 This has led to considerations questioning an important incretin role for GLP-1,211 further strengthening the leading role for GIP as a mediator of the incretin effect in healthy human volunteers. (b) The deceleration of gastric emptying is subject to tachyphylaxis.212,213 Maintaining GLP-1 or GLP-1 receptor agonist concentrations in the effective range will lead to a reduction in effects on gastric emptying over time. This tachyphylaxis occurs already after a few hours of exposure to GLP-1,212 and takes several weeks to months before constantly elevated GLP-1 receptor agonist concentrations near-completely lose their influence on gastric emptying.206,214 This, however, only happens in the case of long-acting GLP-1 receptor agonists, while short-acting ones (eg, exenatide twice daily), which lead to intermittent exposure to effective concentrations, are not subject to tachyphylaxis.206,214

Deceleration of gastric emptying by GLP-1 secondarily reduces some gastrointestinal function that require stimulation by intestinal hormones, the release of which depends on trans-pyloric delivery of gastric contents. An example is gastric acid secretion stimulated by gastrin or pancreatic exocrine secretion stimulated by secretin and cholecystokinin.203 In addition to the effect on gastric emptying, GLP-1215 and GLP-1 receptor agonists216,217 reduce intestinal motility and may, thus, affect the absorption of nutrients.

Taken together, the lack of net stimulation of post-meal insulin secretory responses and the secondary inhibition of gastrointestinal functions through a deceleration of gastric emptying provide suggestive evidence for a role of GLP-1 in the ‘ileal brake’; thus, providing a stop signal for eating, digestion and absorption of ingested nutrients, and propulsive peristalsis in the case of diarrhoea, when nutrients reach lower sections of the gut, because they could not be absorbed in the proper place. This would also be very much compatible with the quantitative distribution of L cells, which are increasingly found towards the lower gut.218 An incretin function would not provide a convincing teleological explanation for this pattern.

Pharmacological concentrations of GIP increased the interval between migrating motor complexes in dogs, while physiological doses were without effect on intestinal motility.219

4.6 Adipose tissue metabolism

In healthy lean humans, GIP did not alter the local metabolism in the adipose tissue when infused alone but it enhanced insulin-induced hydrolysis of triacylglycerol (TAG), glucose uptake and adipose tissue blood flow while reducing free fatty acid output resulting in increased TAG accumulation during hyperinsulinaemic, hyperglycemic clamps.220 Additional studies comparing GIP with saline infusion or lipids emulsions confirmed that GIP did not alter TAG clearance in the absence of insulin and did not alter energy metabolism, hunger or appetite.220 Further studies targeting the interaction of GIP and insulin by inhibiting insulin secretion with somatostatin confirmed the insulin-dependent effects of GIP on adipose tissue blood flow and metabolism.221 Finally, the effects of GIP in adipose tissue were confirmed using the selective GIP [3-30] NH2-antagonist.222

Obesity appears to induce resistance for the actions of GIP in adipose tissue. The GIP receptor density appears to decrease in humans with obesity and may increase again after weight loss.172,174,175 Indeed, reduced activity of GIP was reported in adipose tissue of obese subjects, which improved upon weight loss.43,223,224 Somewhat variable results were reported in insulin-resistant or obese subjects and type 2 diabetes patients. TAG accumulation increased significantly during hyperinsulinemia, euglycaemic clamps in participants with type 2 diabetes, but not in non-diabetic subjects, whether lean or obese while similar decreases of free fatty acids were seen in all groups.225

The proinflammatory endocrine activity of adipose tissue in obesity is intricately linked to insulin resistance.176 Infusion of GIP was shown to increase the expression of cytokines such as IL-6 and chemokines such as MCP-1 and others in vivo in humans.172,174,226 GIPR polymorphisms and circulating levels of GIP were associated with increased levels of the cytokine osteopontin, and an increased risk of CVD.165,174 Mechanistically, GIP was proposed to release endothelin-1 (ET-1) from endothelial cells, which then increased osteopontin in humans.174

5 GIP and GLP-1 Pathophysiology: Type 2 Diabetes

5.1 Secretion of GIP and GLP-1

Early studies have indicated that in patients with type 2 diabetes, post-oral glucose load or post-meal increments in plasma
concentrations of GIP were higher than in non-diabetic control subjects. Conversely, GLP-1 rises after meals were found to be reduced in type 2 diabetes. With more data available, meta-analyses were performed, which overall did not show systematic differences between type 2-diabetic patients and normal glucose-tolerant subjects for GIP and GLP-1. The reason for diverging results probably lies in the great inter-individual variability in incretin hormone responses, some of which can be explained by genetic determination. A population-based study with large sample size, however, has described minor reductions in GLP-1 responses in subjects with impaired oral glucose or diabetes mellitus, and similar reduction in those with high body-mass index.

5.2 GIP-induced insulin secretion and consequences for the incretin effect (GIP “resistance”) Although GIP was isolated and characterized around 1970, and its glucose-dependent insulinotropic action in healthy human subjects became evident in 1976, it took until 1988 to compare effects between patients with (type 1 and type 2) diabetes mellitus and healthy controls. The insulinotropic effectiveness under hyperglycaemic clamp conditions was substantially reduced in both types of diabetes. The interpretation was somewhat hampered by the use of GIP corresponding to the porcine amino acid sequence, which resulted in uncertainties regarding the equivalence of endogenous (human) and exogenous (porcine) GIP concentrations due to differential binding of porcine and human GIP to the antibodies employed in the radioimmunoassays. In 1993, the same finding was confirmed with GIP of the human amino acid sequence. This finding has been confirmed with various protocols, GIP dosages, and plasma glucose concentration profiles. Sometimes, the substantially reduced ability of GIP to stimulate insulin secretion even at hyperglycaemia has been called GIP resistance.

There is no doubt that the greatly impaired insulinotropic action of GIP is the major reason for the reduced incretin effect described in patients with type 2 diabetes. In 1986, Nauck et al. extended previous findings by Perley and Kipnis employing state-of-the-art glucose clamp techniques to achieve “isoglycaemia” between glucose profiles after oral glucose and during intravenous glucose infusions. This was later confirmed.

The situation is quite different in the case of insulinotropic GLP-1 effects in patients with type 2 diabetes: Much of the ability to stimulate insulin secretion at hyperglycaemia is preserved in type 2 diabetes, and pharmacological dosages/concentrations of exogenous GLP-1, not too far from physiological concentrations, reduce plasma glucose substantially, up to a full normalization of plasma glucose in the fasting state. Only when carefully studying dose-response relationships between GLP-1 concentrations and insulin secretory responses under hyperglycaemic clamp conditions, a relative impairment in insulinotropic effects of GLP-1 is found for type 2-diabetic patients. The difference in insulinotropic effects elicited by GIP vs. GLP-1 at hyperglycaemia in subjects with type 2 diabetes (Figure 5) is the main reason for ascribing an obvious therapeutic potential to GLP-1, but not to GIP.

While the differential effects on insulin secretion of GIP and GLP-1 have been described almost 30 years ago, relatively little is known about the mechanisms that explain both the impaired insulinotropic effect of GIP and the preserved insulinotropic effect of GLP-1. Two hypotheses compete: (a) A reduced β-cell mass may not allow to detect major differences in insulin secretory responses to a strong stimulus (oral glucose: hyperglycaemia plus incretin hormones) versus a weaker stimulus (intravenous glucose: only hyperglycaemia), because the weak stimulus already leads to the maximum possible insulin secretory response. This view has been challenged by the demonstration of a dose-response relationship between oral glucose load and the incretin effect even in subjects with type 2 diabetes, however, mainly caused by an excessive rise in post-load glycaemic responses with higher oral glucose loads. In healthy control subjects,
the post-load glycaemic rises only slightly increased with higher doses.\textsuperscript{239} (b) Alternative explanations assume a specific reduction in the expression of GIP receptors or other components of GIP post-receptor signal-transduction in animals and patients with diabetes mellitus.\textsuperscript{243} In line with this assumption, the expression of GIP receptors in rodents has been found reduced after inducing hyperglycaemia.\textsuperscript{244,245} A phenomenon that was partially reversible by reducing glycaemia.\textsuperscript{246} GIP receptors in ß-cells are expressed dependent on intact peroxisome proliferator-activated receptor γ signalling.\textsuperscript{247} This could point to influences of other aspects of the diabetic state, like ectopic lipid deposition or inflammation concerning the endocrine pancreas, on GIP receptor expression. However, GIP receptor expression in the human endocrine pancreas does not appear to be substantially reduced in specimens from type 2 diabetes patients (S. Ueberberg, J. Wefers, M.A. Nauck, J.J. Meier, unpublished observations).

5.3 | Glucagon secretion

GIP can stimulate glucagon secretion in type 2-diabetic subjects at fasting glycaemia, during hypoglycaemia, and during hyperglycaemic clamp studies.\textsuperscript{3,248} In contrast, GLP-1 suppresses glucagon during hyperglycaemia,\textsuperscript{3,4} but not at a normal fasting plasma glucose concentrations.\textsuperscript{4} GLP-1 receptor agonists have been tested during insulin-induced hypoglycaemia and do not suppress counter-regulatory rises in glucagon,\textsuperscript{249} as in healthy subjects.\textsuperscript{187} When comparing the suppression of glucagon in response to oral and “isoglycaemic” intravenous glucose, the latter provides the greater degree of suppression,\textsuperscript{196} perhaps as the consequence of concomitant GIP and GLP-2 release with oral, but not parenteral glucose administration. The ability of GLP-1 agonism to reduce glucagon secretion, putatively associated with reduced hepatic glucose production and plasma glucose concentrations, has reinforced the therapeutic potential for GLP-1, but not for GIP.

5.4 | Gastric emptying

In type 2 diabetes, the deceleration of gastric emptying by GLP-1 occurs with liquid and solid meals\textsuperscript{205,209} as described for non-diabetic subjects.\textsuperscript{204} This said, the metabolic consequences probably are graver, since glucose absorbed from the gut will lead to higher increments in plasma glucose concentrations due to the impaired insulin secretion and action, which is typical for this condition. While it has often been assumed that inhibitory effects of GLP-1 receptor stimulation on gastric and intestinal motility are responsible for nausea, vomiting and abdominal cramps, which are typical adverse events in the treatment with GLP-1 receptor agonists,\textsuperscript{250} the complete standstill of gastric emptying induced by high doses/concentrations of exogenous GLP-1 is not usually accompanied by abdominal symptoms.\textsuperscript{204,205,209} So-called “gastrointestinal” side effects are most likely caused by a direct interaction of GLP-1 receptor agonists with the CNS (brainstem).

The deceleration of gastric emptying is an important mechanism of action reducing post-meal glycaemic rises during the therapy of type 2 diabetes with short-acting GLP-1 receptor agonists like exenatide or lixisenatide, while tachyphylaxis to this particular effect limits its impact when treating with long-acting GLP-1 receptor agonists like liraglutide.\textsuperscript{206}

6 | GLP-1 AND GIP: THERAPEUTIC POTENTIAL FOR TYPE 2 DIABETES, OBESITY, AND FATTY LIVER DISEASE

6.1 | GLP-1 receptor agonists

The ability of GLP-1 and its receptor agonists to stimulate insulin secretion, to suppress glucagon secretion, to decelerate gastric emptying, to reduce appetite, to increase satiety and to decrease food (energy) intake and thus, to cause weight loss, provides a convincing rationale for viewing GLP-1 as a parent compound for therapeutics. While the primary indication for GLP-1 receptor agonists has been type 2 diabetes,\textsuperscript{7,8} they are currently explored for the treatment of obesity,\textsuperscript{251,252} the prevention of obesity-associated diabetes mellitus,\textsuperscript{253} cardiovascular disorders (SELECT; ClinicalTrials.gov identification number NCT03574597) and fatty liver disease.\textsuperscript{254}

6.2 | GIP receptor agonists

In the absence of long-acting GIP receptor agonists for human studies, the therapeutic potential can only indirectly be assessed from the superior therapeutic effectiveness of the GIP/GLP-1 receptor co-agonist tirzepatide.\textsuperscript{255} These studies also suggest the potential for relevant synergism between GIP and GLP-1 receptor agonism.

For further information on interactions between the incretin hormones GIP and GLP-1, see Online Supplement, section 5.

6.3 | Synergistic effects of GIP and GLP-1 on insulin secretion

Insulinotropic effects have been additive in cultured rat insulinoma cells,\textsuperscript{256} in healthy human volunteers,\textsuperscript{15} and in type 2-diabetic patients\textsuperscript{257} (Figure 5) in the sense that the combined administration of GIP and GLP-1 stimulates insulin secretion like the sum of what is observed with the administration of single agents. However, in type 2 diabetic patients, GIP does not contribute at all to the overall effect of the combination, for the reasons outlined above. Rather, the combination of GIP and GLP-1 tends to be less insulinotropic compared to the sum of the individual effects of GIP and GLP-1 administered separately (Figure 5).
table 4 Effects of glucagon-like peptide (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) or their receptor agonists on cardiovascular functions. Data from human mechanistic studies are selected preferentially, but animal data are presented where human data have not been reported

| Organ                        | Effect(s) on                                      | GLP-1 (7-36 amide) or (7-37) | GIP (or GIP receptor agonists) |
|------------------------------|--------------------------------------------------|------------------------------|--------------------------------|
|                              |                                                  | Biological effect | Evaluation | Biological effect | Evaluation |
| Heart                        | Left-ventricular function                        | -                            | +           | -                | 0          |
|                              | Congestive heart failure:                         | LVEF ↓, VO₂ max. ↓, 6 min   | +           | Not reported     | 0          |
|                              | 6 min walk distance ↑ 261 (not confirmed at lower dose of GLP-1 262) |                |             |                  |            |
|                              | Cardioprotection (preserved function in response to ischemia/myocardial stunning) | LVEF ↓, regional contractility ↑ 263,264 | +           | Germline or cardiomyocyte-selective loss of GIP receptor improves survival and reduces adverse ventricular remodelling after experimental MI in mice; acute GIP receptor agonism without effect 26 | (-)        |
|                              | Preserved LV function during coronary balloon occlusion 265,266 |                |             |                  |            |
|                              | ↓ regional wall motility ↑ (72 h after acute myocardial infarction 266) |                |             |                  |            |
|                              | Cardiac hypertrophy/fibrosis                      | ↑ 267 (angiotensin II and pressure-overload-induced hypertrophy in mice) | +           |                  | +          |
|                              | Heart rate                                        | ↑ 269 (+)                  | (-)         |                  | -          |
|                              | Arterial blood vessels                            | Human endothelial cells: New vessel formation ↑ (high concentrations of GLP-1) 270, NO production 271 | +           | No effect on NO production 271 | 0          |
|                              | Angiogenesis, endothelial cell proliferation      | Human endothelial cells: Nitric oxide synthase 272 | +           | Canine portal vein endothelial cells: NO production 175, vasodilation, 275 but canine hepatic arterial endothelial cells: endostatin-1 175, vasoconstriction 275 | +/-        |
|                              | Endothelium-derived vasodilation (NO production)  | Acetyl choline-induced vasodilation ↑ (healthy subjects 273 and patients with T2DM and stable CAD 274) | +           | Abdominal subcutaneous adipose tissue blood flow↑ (abolished by GIP receptor antagonist) 222 | +          |
|                              | Regional blood flow                               | New vessel formation from human endothelial cells improved by high doses of GLP-1 270 | +           |                  |            |
|                              |                                                  | Exenatide stimulated proliferation of human coronary artery endothelial cells 276 | +           |                  |            |
|                              | Atherosclerosis (plaque generation, progression, rupture) | ↓ Apo E-/- mice 277 (GLP-1 receptor agonists liraglutide and semaglutide) | +           | ↓ (lesion size, foam cell formation) Apo E-/- mice 259,260; low GIP predicts peripheral artery disease in human subjects 259 | +          |
|                              | Blood pressure                                    | Systolic blood pressure     | Transient ↑ (pharmacological dose) 278, ≈ physiological dose 279 | Transient ↑ (pharmacological dose) 22,201 | -/+ |
|                              |                                                  | Natriuretic peptides        | ANP 278,280 | Pro-ANP: No effect 281 | 0          |
|                              | Glomerular filtration                             | ↑ (acute response) 282      | (+)         | Not reported     | 0          |
|                              | Albumin excretion                                 | No immediate effects        | 0           | Not reported     | 0          |
| Metabolic milieu             | Hyperglycaemia                                    | Plasma glucose ↓ 4          | ++          | No effect in type 2 diabetes 235 | 0          |
|                              | Fasting lipoproteins/lipids                       | Non-esterified fatty acids ↓ transient 6 | +           | Non-esterified fatty acids 283 | 0          |
|                              |                                                  |                              |             | High GIP associated with LDL cholesterol ↓ and HDL cholesterol ↓ 284 | (-)        |

(Continues)
**6.4 | Effects of GIP and GLP-1 combined on glucagon secretion**

The question of whether and how GIP and GLP-1 in combination affect glucagon secretion is a relevant one, given the fact that GIP rather stimulates, and GLP-1 rather suppresses glucagon secretion. Data in healthy animals or subjects are not available. One study in type 2-diabetic patients confirms the glucagon suppression with GLP-1 but does not yield increases in glucagon with GIP. However, the combination does no longer reduce glucagon concentrations. This indicates an interaction between GIP and the suppression in glucagon secretion observed with GLP-1 alone. However, tirzepatide, a dual GIP/GLP-1 receptor agonist, suppresses fasting glucagon more than the selective GLP-1 receptor agonist dulaglutide, even after adjusting for ambient plasma glucose concentrations.

**6.5 | Effects of GIP and GLP-1 combined on energy intake or expenditure and body weight**

The question, whether GIP and GLP-1 may have additive or synergistic effects on parameters eventually influencing body weight, is related to the question, whether GIP receptor stimulation by tirzepatide (GIP/GLP-1 receptor co-agonist) contributes to the superior weight loss observed in patients with type 2 diabetes. Evidence for the induction of weight loss through an inhibition of appetite and hunger and, consequently, food/energy intake is limited to mouse studies. Indeed, in support of such an assumption, one study found greater effects for a combination of intracerebroventricular GIP and GLP-1, while the single agents did not significantly affect food intake or body weight. However, in obese human subjects, exogenous GIP at pharmacological dosage was without effect on measures of appetite, satiety, prospective food consumption and calorie intake at the occasion of an ad libitum meal, while GIP added to GLP-1 even counteracted the effect of reduced appetite and food intake.

For further information on GIP and GLP-1 effects in the central nervous system, see Online Supplement, section 6 (Table S4).

**7 | GLP-1 AND GIP: BIOLOGICAL EFFECTS AND THERAPEUTIC POTENTIAL IN THE CARDIO-VASCULAR SYSTEM**

Dedicated cardiovascular outcomes studies with GLP-1 receptor agonists undoubtedly have proven the therapeutic potential of GLP-1 effects in the cardiovascular system, which can be summarized as a multifaceted, beneficial influence on cardiovascular function (more fully covered in Nauck et al. 2017) as well as an inhibitory on the process of atherosclerotic plaque development, progression, and rupture. For comparison with similar findings regarding GIP, some of these results are summarized in Table 4. Regarding potential benefits vs. harm, almost all these individual effects have to be evaluated positively.

Regarding GIP, information on cardiovascular effects is sparse. Nevertheless, a recent review summarized our current knowledge on GIP actions in on heart and blood vessel function (Heimbürger et al. 2020). GIP, like GLP-1 receptor agonists, raises heart rate. Vasodilation and blood flow appear to be regulated in a tissue-specific manner (enhanced regarding the portal vein and in subcutaneous adipose tissue as appropriate for a post-prandial situation). Animal models have shown anti-atherosclerotic activity of GIP. GIP may reduce oxidative stress in human endothelial cells and inflammatory cytokine release in visceral adipose tissue. Overall, a number of unknowns remain, and would need to be studied to clarify the overall role of GIP receptor stimulation in and for the cardiovascular system. Our overall evaluation of the role of GIP agonism is less beneficial than for the unanimously positive role of GLP-1 agonisms with...
8 | OUTLOOK/OPEN RESEARCH QUESTIONS

The development of incretin-based medications has prompted two decades of scientific efforts to elucidate details of the mechanisms behind therapeutic actions of GLP-1 receptor agonists, which has yielded a large body of evidence, which still continues to grow. Interest in GIP as a therapeutic compound has been revived by the superior glucose- and body weight-lowering effectiveness of GIP/GLP-1 co-agonists, like tirzepatide. A spectrum of GIP actions suggested by these findings (a substantial glucose-lowering effect in type 2 diabetic patients through augmenting insulin secretion and increasing insulin sensitivity; a reduction in appetite leading to further weight loss) are at odds with previously published data describing a substantially reduced insulinotropic activity of GIP in subjects with type 2 diabetes and the hypothesized “obesogenic” role of GIP due to its effects on triglyceride storage in adipose tissue. Some of these discrepancies may be the consequence of lacking tools to study long-term consequences of GIP receptor stimulation in human subjects. A long-acting GIP receptor agonist, as has successfully been developed for rodent studies, is urgently needed also for human studies. Whether such a compound will have a therapeutic potential of its own, is an open question. Together with the already available GIP receptor antagonists, we would command a toolbox allowing the clarification of those questions which have hitherto remained unanswered.

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CONFLICT OF INTEREST

M.A.N. has been member on advisory boards or has consulted with AstraZeneca, Boehringer Ingelheim, Eli Lilly & Co., GlaxoSmithKline, Menarini/Berlin Chemie, Merck, Sharp & Dohme, and NovoNordisk. He has received grant support from AstraZeneca, Eli Lilly & Co., Menarini/Berlin Chemie, Merck, Sharp & Dohme and NovoNordisk. DRQ and JW have nothing to declare. AHFP served on advisory boards for Sanofi, Novo-Nordisk, Abbott, Berlin Chemie/Menarini, Boehringer Ingelheim, Novartis, Eli Lilly Germany. He received Grant support from Abbott, Beneo, Novartis, Boehringer Ingelheim. He served on speaker’s bureau of Servier, Eli Lilly Germany, Abbott, Berlin Chemie, Sanofi, AstraZeneca, Beneo, Amgen, Wildt-Stiftung.

AUTHOR CONTRIBUTIONS

All authors searched and analysed retrieved literature, prepared tables and figures, and drafted sections of the text, and revised the draft manuscript for critical intellectual content. All authors jointly decided to submit the final manuscript for publication.

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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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